

Lipid Prodrugs of Agomelatine

Priority Claim

This application claims priority to U.S. Provisional Application Serial No. 63/612,242 entitled “LIPID PRODRUGS OF AGOMELATINE” filed December 19, 2023, which is incorporated herein by reference in its entirety.

Field of Invention

[0001] The present disclosure relates generally to lipid prodrugs of agomelatine with enhanced oral bioavailability and safety profiles and uses thereof.

Background

[0002] Depression and anxiety disorders are some of the most common mental health disorders afflicting adults in the modern era. The World Health Organization estimates that approximately 4-5% of the adult population suffers from a depressive or anxiety disorder.

[0003] A number of antidepressants and anti-anxiety medications exist in the art. A majority of these impact the levels of serotonin and/or norepinephrine in the presynaptic cleft by inhibiting reuptake of said monoamine neurotransmitters. Drug classes that fall under this category are selective serotonin uptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), serotonin antagonist and reuptake inhibitors (SARIs), serotonin modulators and stimulators (SMSs), tri- and tetra-cyclic antidepressants. Additional drug classes include monoamine oxidase inhibitors (MAOIs) and noradrenergic and specific serotonergic antidepressants (NaSSAs) (Harmer CJ *et al.*, Lancet Psychiatry 2017).

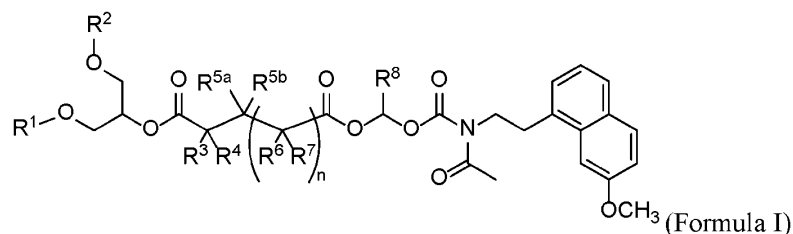
[0004] Many of these medications are associated with numerous side effects, including mania, sexual dysfunction, emotional blunting, weight gain, weight loss, and/or bone loss, amongst others. These symptoms can be debilitating, and lead to poor adherence or discontinuation. Further, tachyphylaxis can require sequential increases in dosing or transitioning a patient onto a different drug class – both of which can exacerbate or alter the side effect profile (Braund TA *et al.*, Translational Psychiatry 2021; Targum SD, Innovations in Clinical Neuroscience 2014).

[0005] There remains an unmet need to develop improved compounds and methods for the treatment of depression and anxiety disorders.

Summary of Invention

[0006] In contrast to SSRIs, SNRIs, SARIs, and other classes of drugs that act as antidepressants and anti-anxiety medications, Agomelatine has a unique mechanism of action that differs from the currently available classes. Agomelatine is a potent MT₁ and MT₂ receptor agonist and a 5-HT_{2C} antagonist which has known therapeutic value in the treatment of certain depressive disorders. However, there are serious liver toxicity concerns that restrict its therapeutic use and therefore its development as an antidepressant or anti-anxiety treatment in humans has faced numerous setbacks due to issues associated with its safety profile (Norman TR and Olver JS, Expert Opinion on Pharmacotherapy, 2019; Pladevall-Vila M *et al.*, CNS Drugs, 2019). The agomelatine prodrugs disclosed herein have been developed to capture the unique therapeutic potential of agomelatine by providing compounds with advantageous pharmacological properties (increased bioavailability) while minimizing safety concerns and side effects (reducing liver toxicity, improving tolerability).

[0007] In one aspect, disclosed herein are lipid prodrugs of agomelatine represented by Formula I:



wherein R¹ and R² are each independently hydrogen or a residue of a C₂-C₂₈ fatty acid;

R³ and R⁴ are each independently hydrogen or C₁-C₄ alkyl;

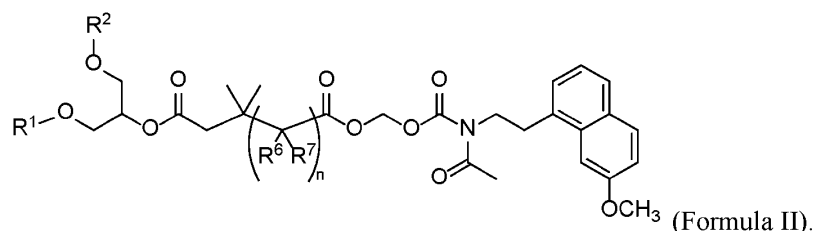
R^{5a} and R^{5b} are each independently hydrogen, C₁-C₄ alkyl, or are taken together with the carbon to which they are attached form a C₃-C₈ cycloalkyl;

R⁶ and R⁷ are each independently at each occurrence hydrogen or C₁-C₄ alkyl;

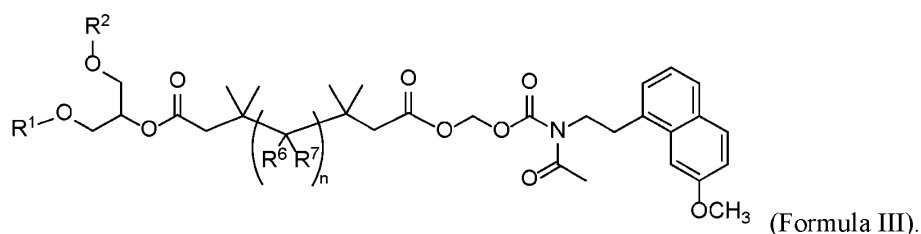
n is 1-10; and

R⁸ is hydrogen or C₁-C₁₀ alkyl.

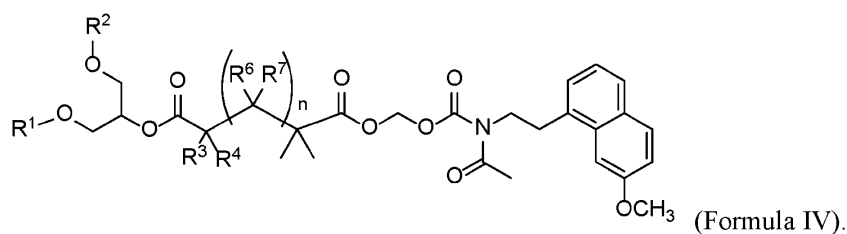
[0008] In one aspect, disclosed herein are lipid prodrugs of agomelatine represented by Formula II:



[0009] In one aspect, disclosed herein are lipid prodrugs of agomelatine represented by Formula III:



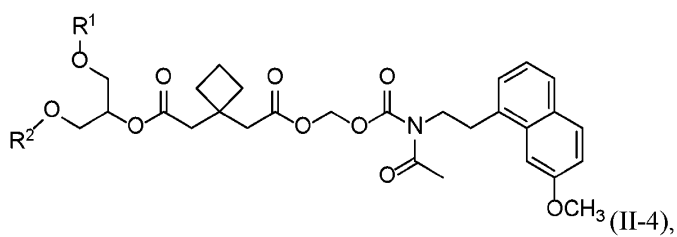
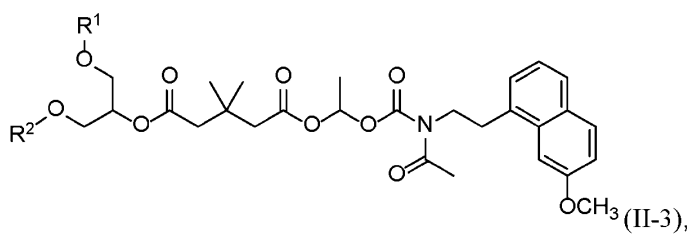
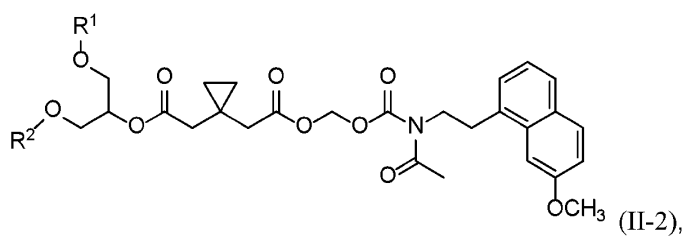
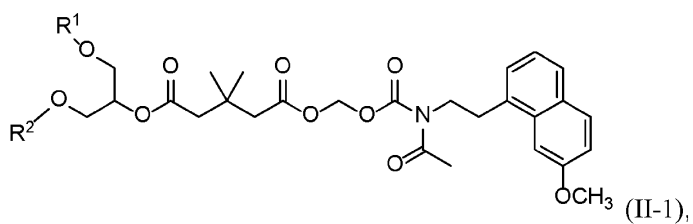
[0010] In one aspect, disclosed herein are lipid prodrugs of agomelatine represented by Formula IV:

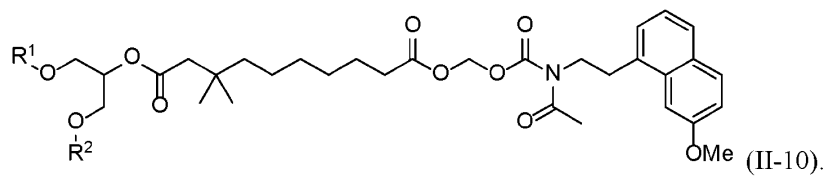
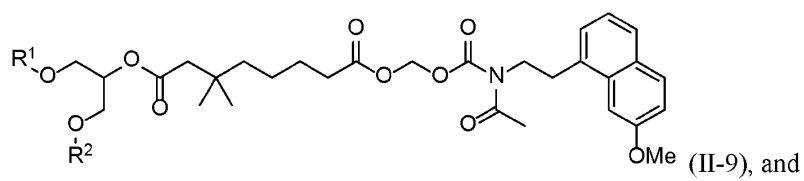
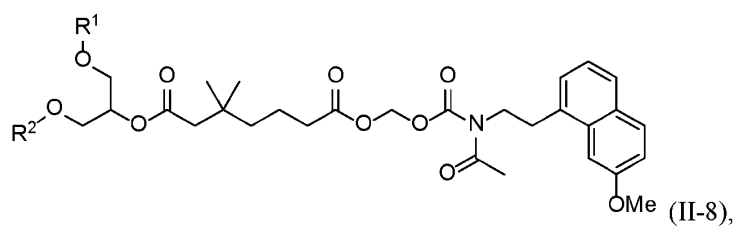
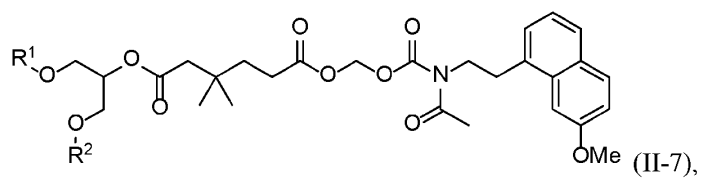
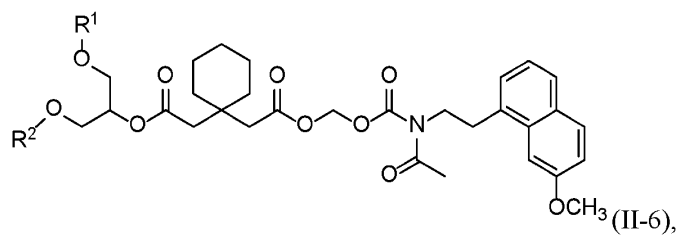
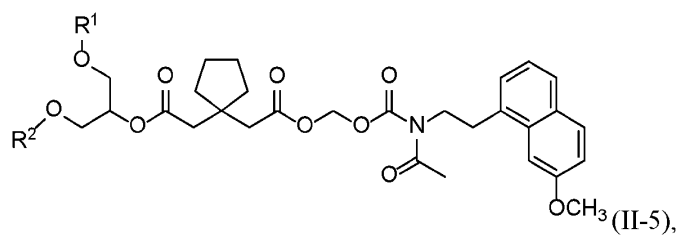


[0011] In some embodiments, R^8 is hydrogen or methyl. In some embodiments, R^8 is hydrogen. In some embodiments, R^8 is methyl. In some embodiments, R^3 and R^4 are each independently hydrogen or methyl. In some embodiments, R^3 and R^4 are each hydrogen. In some embodiments, R^{5a} and R^{5b} are each hydrogen, methyl or taken together to form a cyclopropyl. In some embodiments, n is 1-10. In some embodiments, n is 1-6. In some embodiments, n is 1. In some embodiments, R^6 and R^7 are each independently at each occurrence hydrogen or methyl. In some embodiments, R^6 and R^7 are each hydrogen. In some embodiments, at least one of R^1 and R^2 is a

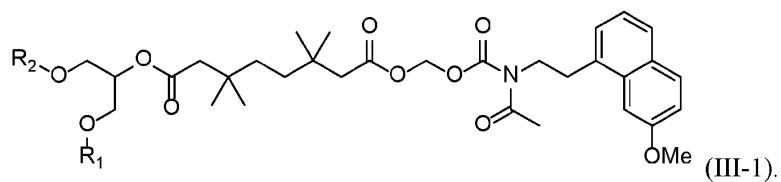
residue of a C₂-C₂₈ fatty acid. In some embodiments, R¹ and R² are each independently a residue of a C₂-C₂₈ fatty acid. In some embodiments, R¹ and R² are each independently a residue of a C₄-C₁₈ fatty acid. In some embodiments, R¹ and R² are each independently a residue of a C₈ fatty acid.

[0012] Specific embodiments of compounds having the structure Formula II include, but are not limited to:

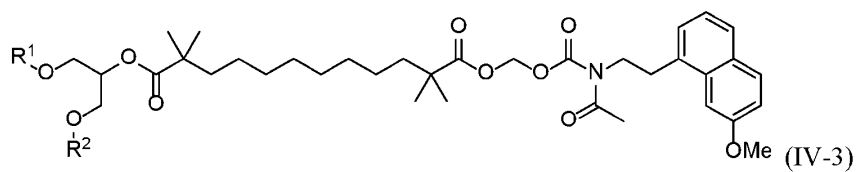
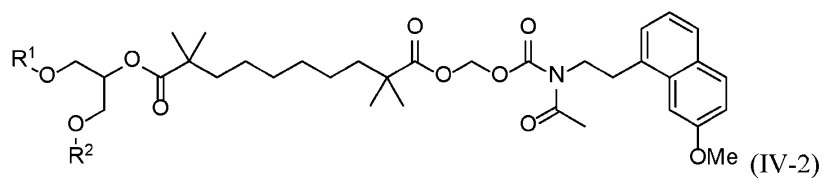
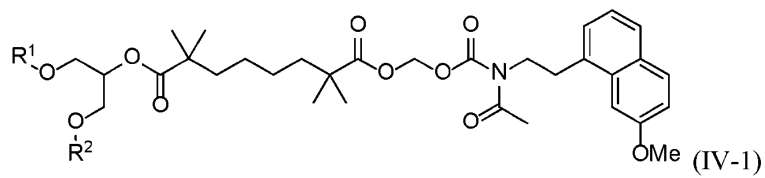


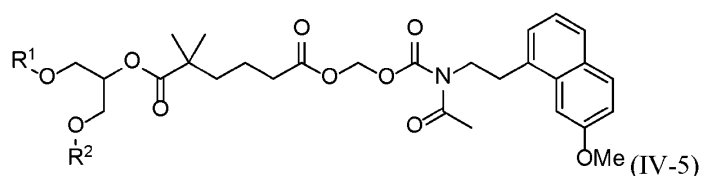
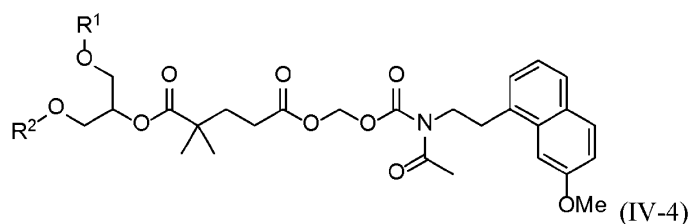


[0013] A specific embodiment of compounds having the structure Formula III includes compound (III-1):



[0014] Specific embodiments of compounds having the structure Formula IV include, but are not limited to:





[0015] In one aspect, disclosed herein is a pharmaceutical composition comprising a disclosed compound of Formula I, Formula II, Formula III, and Formula IV and a pharmaceutically acceptable carrier.

[0016] In one aspect, a method of treating a disorder in a subject, wherein the disorder is a bipolar and related disorder, a depressive disorder, an anxiety disorder, or a trauma- and stressor-related disorder, comprises administering a therapeutically effective amount of a compound as described in any compound of Formula I, Formula II, Formula III, and Formula IV or a pharmaceutical composition of the compound to effectively treat the disorder in the subject.

[0017] In one aspect, a compound as described in any of Formula I, Formula II, Formula III, and Formula IV for use in treating a disorder in a subject, wherein the disorder is a bipolar and related disorder, a depressive disorder, an anxiety disorder, or a trauma- and stressor-related disorder.

[0018] In some embodiments, any one of Compounds II-1, II-2, II-7, II-8, II-9, II-10, III-1, IV-1, IV-2, IV-3, IV-4, or IV-5 are administered to a subject QD. In some embodiments, any one of Compounds II-1, II-2, II-7, II-8, II-9, II-10, III-1, IV-1, IV-2, IV-3, IV-4, or IV-5 are administered to a subject QHS.

[0019] In one aspect, the disorder is a bipolar and related disorder. The bipolar disorder can be bipolar I disorder or bipolar II disorder.

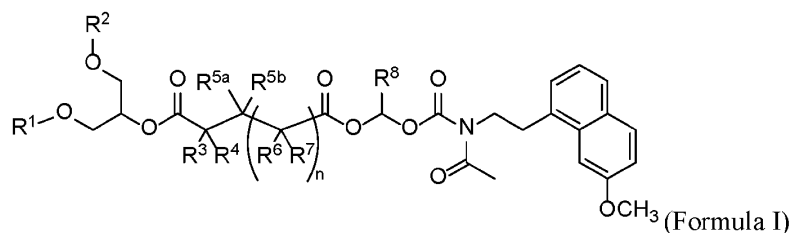
[0020] In one aspect, the disorder is a depressive disorder. The depressive disorder can be a major depressive disorder (MDD), persistent depressive disorder (PDD), or an unspecified mood disorder.

[0021] In one aspect, the disorder is an anxiety disorder. The anxiety disorder can be a separation anxiety disorder, a specific phobia, a social anxiety disorder, a panic disorder, or a generalized anxiety disorder (GAD).

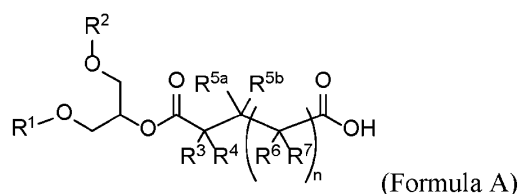
[0022] In one aspect, the disorder is a trauma- and stressor-related disorders. The trauma- and stressor-related disorder can be a posttraumatic stress disorder (PTSD), acute stress disorder, or adjustment disorder.

[0023] In certain aspects, the subject is a pediatric subject, an adolescent subject, an adult subject, or a geriatric subject.

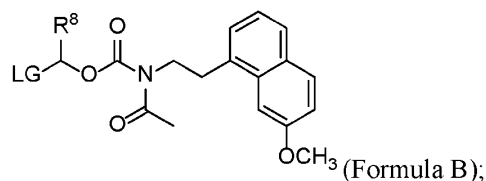
[0024] In one aspect, disclosed herein is a method of making a compound of Formula I:



the method comprising reacting a compound of Formula A



or a salt thereof, with a compound of Formula B



wherein R^1 and R^2 are each independently a residue of a C_2 - C_{28} fatty acid;

R^3 and R^4 are each independently hydrogen or C_1 - C_4 alkyl;

R^{5a} and R^{5b} are each independently hydrogen, C_1 - C_4 alkyl, or are taken together with the carbon to which they are attached form a C_3 - C_8 cycloalkyl;

R^6 and R^7 are each independently at each occurrence hydrogen or C_1 - C_4 alkyl;

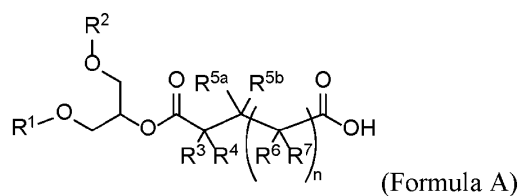
n is 1-10;

R^8 is hydrogen or C_1 - C_{10} alkyl; and

LG is a leaving group.

[0025] In some embodiments, the method further comprises purifying the compound of Formula I.

[0026] In one aspect, disclosed herein is a compound of Formula A:



or a salt thereof, wherein:

R^1 and R^2 are each independently a residue of a C_2 - C_{28} fatty acid;

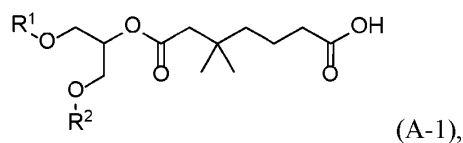
R^3 and R^4 are each independently hydrogen or C_1 - C_4 alkyl;

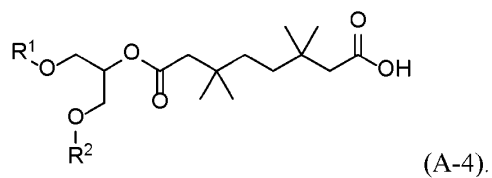
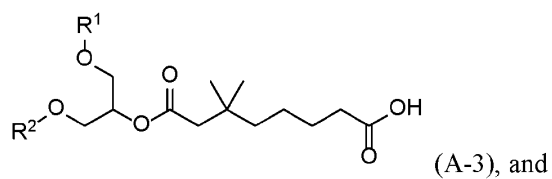
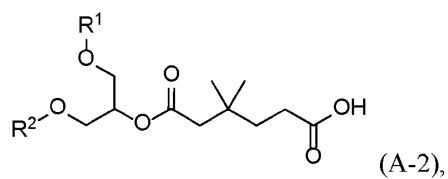
R^{5a} and R^{5b} are each independently hydrogen, C_1 - C_4 alkyl, or taken together with the carbon to which they are attached form a C_3 - C_8 cycloalkyl;

R^6 and R^7 are each independently at each occurrence hydrogen or C_1 - C_4 alkyl; and

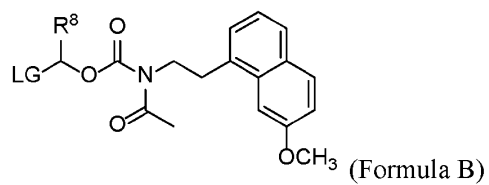
n is 1-10.

[0027] Specific embodiments of compounds having the structure Formula A include, but are not limited to:





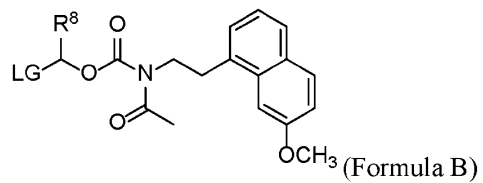
[0028] In one aspect, disclosed herein is a compound of Formula B:



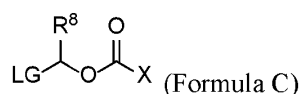
wherein R⁸ is hydrogen; and

LG is a leaving group.

[0029] In one aspect, disclosed herein is a method of making a compound of Formula B:



the method comprising the step of reacting agomelatine or a salt thereof with a compound of Formula C



wherein R^8 is hydrogen;

X is halo; and

LG is a leaving group.

[0030] In some embodiments, the agomelatine salt is an alkali metal salt. In some embodiments, the salt is a lithium salt. In some embodiments, the LG is chloro- and/or wherein X is chloro-.

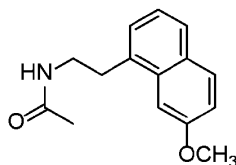
Detailed Description

[0031] Disclosed herein are lipid prodrugs of agomelatine (AGM) which provide enhanced oral bioavailability of agomelatine. The prodrugs disclosed herein are lipid mimetic compounds that behave similarly to natural triglycerides, enabling transport through the lymphatic system prior to reaching systemic circulation, effectively circumventing first-pass metabolism. Accordingly, the lipid prodrugs of agomelatine (AGM) disclosed herein avoid first-pass metabolism and result in enhanced oral bioavailability of AGM. The prodrugs of the instant disclosure are transported to the lymph at substantially higher levels than agomelatine alone. For example, the disclosed lipid prodrugs resulted in significant increases in lymphatic transport (26-77%); 700-1800X greater than agomelatine alone.

[0032] Further, the prodrugs of the instant disclosure, when administered orally, provide increased systemic exposure of agomelatine, as measured by plasma AUC. Thus, the prodrugs of agomelatine can be orally administered to a subject, resulting in increased systemic exposure of agomelatine. Representative Formula I compounds tested exhibited AUC values ranging from 104 to 288 nmol*h/L. In contrast, when agomelatine alone was administered orally, no agomelatine was detected in the plasma (ND = not detected).

[0033] Accordingly, disclosed herein are lipid prodrugs of agomelatine (AGM) which provide enhanced oral bioavailability of agomelatine. Agomelatine has antidepressant and anti-anxiety activity with a unique mechanism of action as compared to other drugs in the art. While a majority of these drugs (e.g., SSRIs and SNRIs) impact monoamine uptake, agomelatine primarily impacts melatonin receptors MT_1 and MT_2 . Agomelatine further acts as an antagonist of $5-HT_{2C}$. It is

predicted that its efficacy is due in large part to a synergistic effect between its agonist and antagonist properties. Agomelatine has the following structure:



[0034] While agomelatine is readily absorbed when administered orally, up to 90% of agomelatine is metabolized by cytochrome P450 isoenzymes in the liver (Freiseleben SD and Furczyk K, J Mol Psychiatry, 2015). This results in an estimated overall oral bioavailability of agomelatine of 0.9-4% (Norman TR and Olver JS, Expert Opinion on Pharmacotherapy, 2016 and AusPAR report for Valdoxan, 2010). Agomelatine has been approved for the treatment of major depressive disorder (MDD) in certain jurisdictions, namely Europe and Australia, and Generalized Anxiety Disorder (GAD) in Australia. Following its approval, longitudinal studies identified liver toxicity concerns in some patients receiving agomelatine. This led to the European Medicines Agency issuing restrictive prescription warnings for patients that may be susceptible or prone to liver damage (CHMP Assessment Report for Valdoxan). It further requires that the liver function of patients receiving agomelatine be monitored. Patients receiving Valdoxan (agomelatine) undergo liver function tests prior to starting treatment, and at 3, 6, 12, and 24 weeks. Treatment is discontinued, or not initiated, if transaminase levels exceed 3X the upper limit of normal. This monitoring presents a burdensome requirement that can contribute to reduced compliance and increased discontinuation. These limitations can further impact overall prescriptions as agomelatine may be deemed unsuitable for patients at risk of liver damage. Efforts to develop agomelatine in the US market were discontinued.

[0035] Without being bound by any particular theory, it is expected that a prodrug of agomelatine that is capable of averting first-pass metabolism would reduce the risk of hepatic damage associated with agomelatine. The lipid prodrugs of the instant disclosure allow for agomelatine to be transported by the lymph, thus avoiding first-pass metabolism in the intestine and/or liver. In bypassing first-pass metabolism, the lipid prodrugs afford high oral bioavailability of agomelatine.

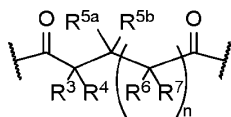
Definitions

[0036] As used herein, the terms “treatment”, “treat”, and “treating” refer to reversing, alleviating, delaying the onset of, mitigating, or inhibiting the progression of a disease, or one or more symptoms thereof. In some embodiments, the compounds disclosed herein treat an anxiety disorder, a depressive disorder, a mood disorder and/or one or more symptoms thereof. For example, when these terms are used with respect to the treatment of anxiety, “treating anxiety” includes both alleviating existing anxiety and preventing anxiety, as well as managing anxiety. Additionally or alternatively, when these terms are used with respect to the treatment of depression, “treating depression” includes both alleviating existing depression and preventing depression, as well as managing depression associated with one or more depressive disorders.

[0037] As used herein, the terms “subject” and/or “patient” refer to a mammalian subject, including a human subject. In some embodiments, the subject is a human subject. In some embodiments, the subject suffers from a disease, disorder, or condition in which systemic exposure of agomelatine is beneficial. Systemic exposure of agomelatine may be achieved by the administration of any of the lipid prodrugs of agomelatine described herein. In some embodiments, the subject suffers from an anxiety disorder, a depressive disorder, or a mood disorder, for example generalized anxiety disorder (GAD) or major depressive disorder (MDD).

[0038] As used herein, the term “self-immolative group” defines a chemical moiety that forms a scissile bond with the linker and a stable bond with the pharmaceutical agent, wherein the bond with the pharmaceutical agent becomes labile upon cleavage of the linker. Examples of self-immolative groups include, but are not limited to acetals, carboxyacetals, carboxy(methylacetals), para-hydroxybenzyl carbonyls, flipped esters, and trimethyl locks. A number of suitable self-immolative groups are suitable for use in the instant disclosure and are known in the art as described, for example, in C.A. Blencowe *et al.* 2011 and F. Kratz *et al.* 2008.

[0039] As used herein, the term “linker” refers to the portion of the lipid prodrug that connects the self-immolative group to a glyceride portion of the lipid prodrug. The linker of Formula I is



represented by:

where R³ and R⁴ are each independently hydrogen or C₁-C₄ alkyl;

R^{5a} and R^{5b} are each independently hydrogen, C₁-C₄ alkyl, or are taken together with the carbon to which they are attached form a C₃-C₈ cycloalkyl;

R⁶ and R⁷ are each independently at each occurrence hydrogen or C₁-C₄ alkyl; and

n is 1-10 or n is 1-6. It should be understood that, when n is greater than 1, each instance of R⁶ and R⁷, at each occurrence, are independently hydrogen or C₁-C₄ alkyl. In some instances, R³, R⁴, R^{5a}, R^{5b}, R⁶ and R⁷ are hydrogen or methyl.

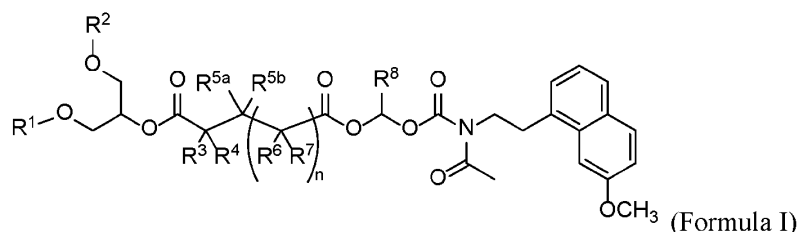
[0040] As used herein, the term “alkyl”, either alone or in reference to compounds, denotes straight chain or branched alkyl. Prefixes such as C₁-C₂₈ are used to denote the number of carbon atoms within the alkyl group (e.g., 1 to 28). Examples of straight chain and branched chain alkyl include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, *t*-butyl, *n*-pentyl, hexyl, heptyl, 5-methylheptyl, 5-methylhexyl, octyl, nonyl, decyl, undecyl, and dodecyl.

[0041] As used herein, the term “pharmaceutically acceptable carriers” refers to non-toxic carriers, excipients, adjuvants, or vehicles, or combinations thereof, that do not destroy the pharmacological activity of the agent with which it is formulated. Pharmaceutically acceptable carriers suitable for use include, but are not limited to, ion exchangers, alumina, stearates, lecithins, serum proteins, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, glyceride mixtures, surfactants, lipids, water, salts, or electrolytes.

[0042] Unless otherwise stated, structures depicted herein are meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational) forms of the structure: for example, the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures are within the scope of the disclosed compounds and uses thereof.

Lipid Prodrugs of Agomelatine

[0043] Disclosed herein are lipid prodrugs of agomelatine (AGM) that avoid first-pass metabolism and result in enhanced oral bioavailability. Accordingly, in one aspect disclosed herein are compounds of Formula (I):



wherein

R^1 and R^2 are each independently hydrogen or a residue of a C_2 - C_{28} fatty acid;

R^3 and R^4 are each independently hydrogen or C_1 - C_4 alkyl;

R^{5a} and R^{5b} are each independently hydrogen, C_1 - C_4 alkyl, or are taken together with the carbon to which they are attached form a C_3 - C_8 cycloalkyl;

R^6 and R^7 are each independently at each occurrence hydrogen or C_1 - C_4 alkyl;

n is 1-10; and

R^8 is hydrogen or C_1 - C_{10} alkyl.

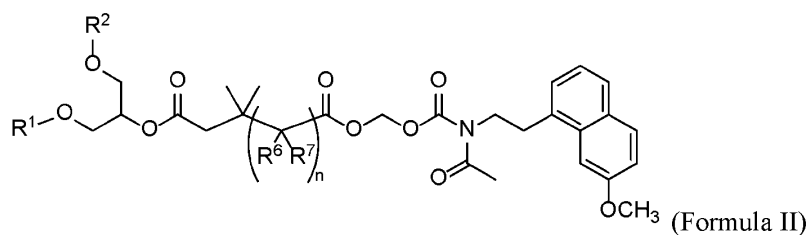
[0044] As used herein, the residue of a fatty acid refers to the acyl portion of the fatty acid. A residue of palmitic acid refers to, for example, the acyl portion of palmitic acid, *i.e.*, $-C(O)C_{15}H_{31}$. In some embodiments of Formula (I), R^1 and R^2 are residues of octanoic acid, *i.e.*, $-C(O)C_7H_{15}$. In some embodiments of Formula (I), R^1 and R^2 are residues of oleic acid, *i.e.*, $-C(O)C_{17}H_{35}$.

[0045] It is understood that $-C(O)C_{15}H_{31}$ includes straight-chained palmitates and derivatives thereof comprising said molecular formula, that $-C(O)C_7H_{15}$ includes *n*-octanoate, branched octanoates (*e.g.*, isooctanoate) and derivatives thereof comprising said molecular formula, and that $-C(O)C_{17}H_{35}$ includes oleates and derivatives thereof comprising said molecular formula.

[0046] In some embodiments, the residue of a fatty acid is saturated. In some embodiments, the residue of a fatty acid is unsaturated. In some embodiments, the saturated fatty acid is a saturated straight-chain fatty acid or a saturated branched chain fatty acid. In some embodiments, the unsaturated fatty acid is a monounsaturated fatty acid or a polyunsaturated fatty acid. In some embodiments, the residue of the fatty acid has a C_2 - C_{28} chain. In some embodiments, the residue of the fatty acid has a C_2 - C_{28} , C_4 - C_{28} , C_6 - C_{28} , C_8 - C_{28} , C_2 - C_{24} , C_4 - C_{24} , C_6 - C_{24} , C_8 - C_{24} , C_2 - C_{22} , C_4 - C_{22} , C_6 - C_{22} , C_8 - C_{22} , C_2 - C_{20} , C_4 - C_{20} , C_6 - C_{20} , C_8 - C_{20} , C_2 - C_{18} , C_4 - C_{18} , C_6 - C_{18} , C_8 - C_{18} , C_2 - C_{16} , C_4 - C_{16} , C_6 - C_{16} , C_8 - C_{16} , C_2 - C_{14} , C_4 - C_{14} , C_6 - C_{14} , C_8 - C_{14} , C_2 - C_{12} , C_4 - C_{12} , C_6 - C_{12} , C_8 - C_{12} , C_2 - C_{10} , C_4 - C_{10} , C_6 - C_{10} , C_8 - C_{10} , C_2 - C_8 , C_4 - C_8 , or C_5 - C_8 chain. In some embodiments, R^1 and R^2 are the same

fatty acids. In some embodiments, R^1 and R^2 are different fatty acids. Fatty acids, and residues thereof, that are suitable for use in the compounds disclosed herein are further described in WO2016/023082 and US Patent No. 11,311,512, incorporated herein by reference.

[0047] In some embodiments, a lipid prodrug of agomelatine (AGM) is represented by Formula II:



wherein

R^1 and R^2 are each independently hydrogen or a residue of a C_2 - C_{28} fatty acid;

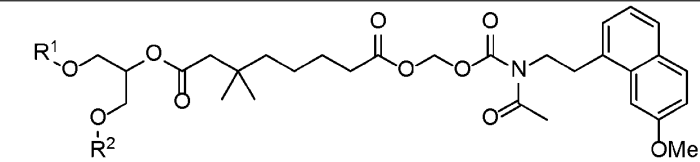
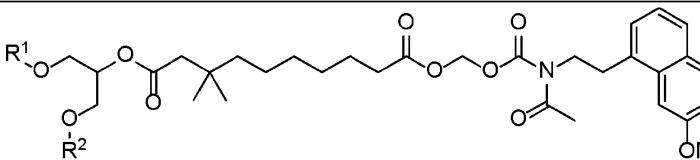
R^6 and R^7 are each independently at each occurrence hydrogen or C_1 - C_4 alkyl; and

n is 1-10.

[0048] In some embodiments, compounds represented by Formula (II) is one of the below compounds, wherein R^1 and R^2 are as defined above:

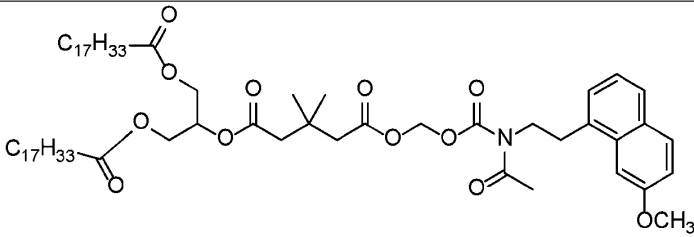
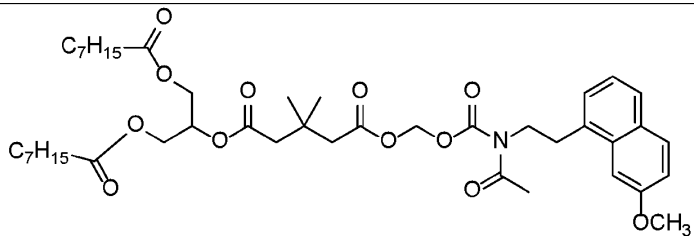
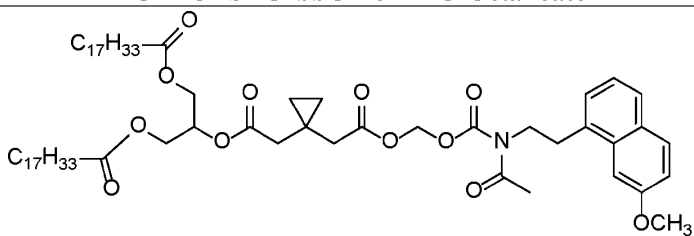
Compound	Structure
II-1	AGM-CASI-C5bbGMe-2-TG
II-2	AGM-CASI-C5bcPr-2-TG

II-3	AGM-CMSI-C5bbGMe-2-TG
II-4	AGM-CASI-C5bcBu-2-TG
II-5	AGM-CASI-C5bcPn-2-TG
II-6	AGM-CASI-C5bcHx-2-TG
II-7	AGM-CASI-C6bbGMe-2-TG
II-8	AGM-CASI-C7bbGMe-2-TG

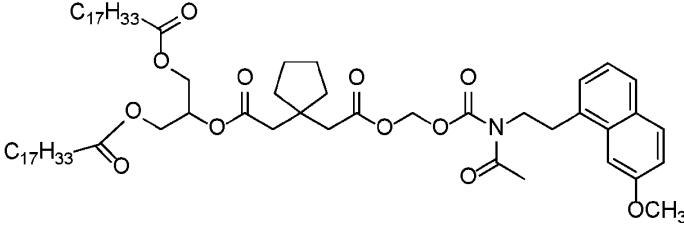
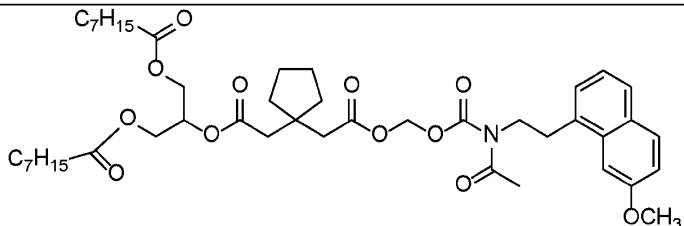
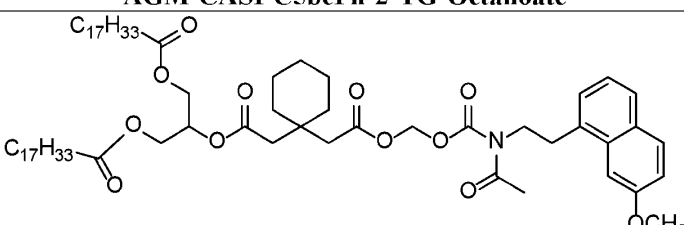
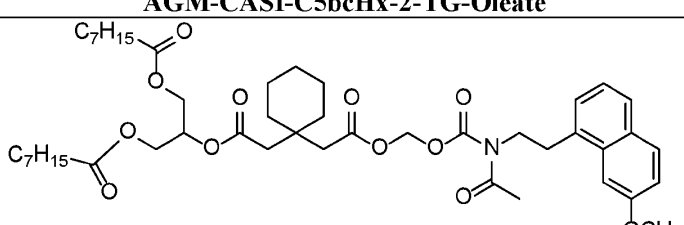
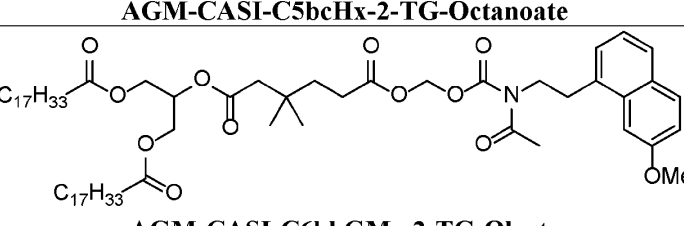
II-9	 AGM-CASI-C8bbGMe-2-TG
II-10	 AGM-CASI-C10bbGMe-2-TG

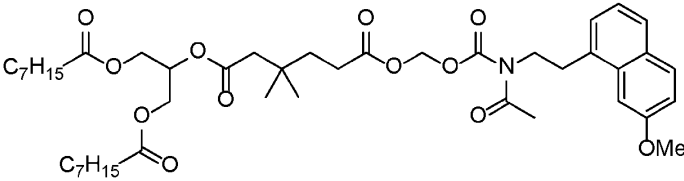
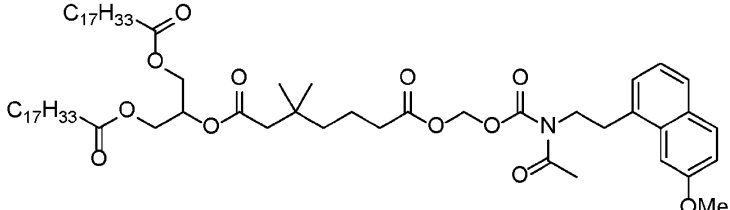
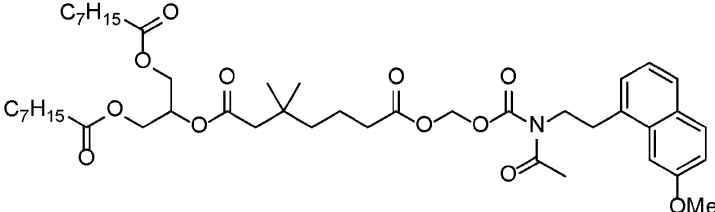
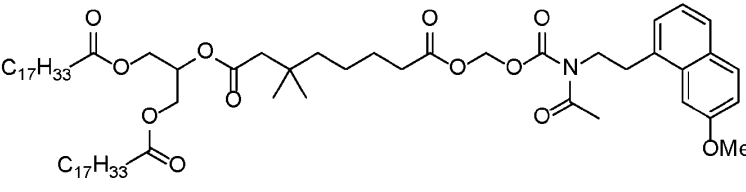
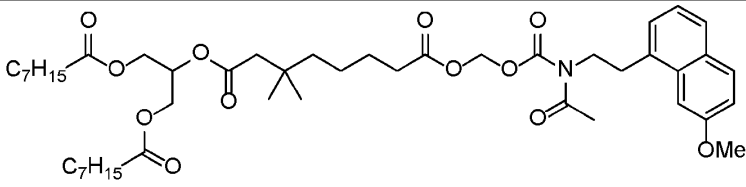
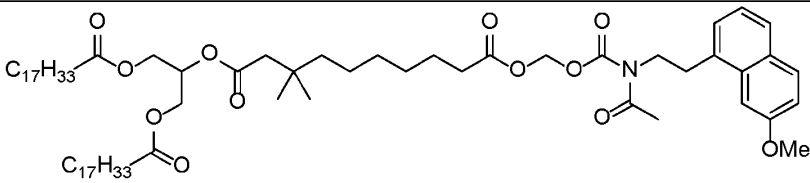
[0049] In one aspect, disclosed herein are compounds of Formula (II) as shown in **Table 1**:

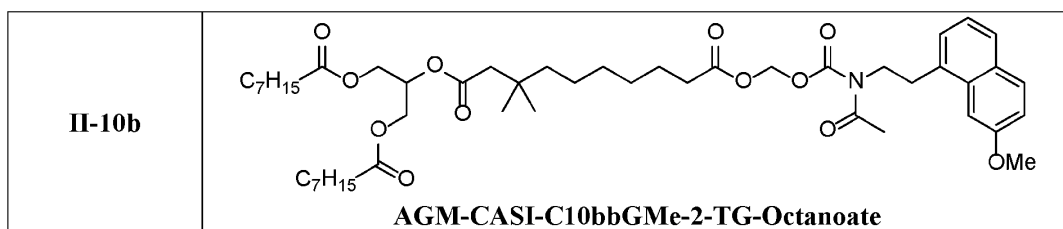
Table 1: Exemplary Compounds – Formula II

Compound	Structure
II-1a	 AGM-CASI-C5bbGMe-TG-Oleate
II-1b	 AGM-CASI-C5bbGMe-2-TG-Octanoate
II-2a	 AGM-CASI-C5bcPr-2-TG-Oleate

II-2b	Chemical structure of AGM-CASI-C5bcPr-2-TG-Octanoate. It features a central 1,2,3-trimethyl-1,3-propanediol core. The left hydroxyl group is esterified with octanoic acid (C₇H₁₅COOH). The right hydroxyl group is esterified with a 2-(4-methoxyphenyl)propanoate derivative. The central carbon is substituted with a cyclopropylmethyl group and a 2-(4-methoxyphenyl)propanoate derivative.
II-3a	Chemical structure of AGM-CMSI-C5bbGMe-2-TG-Oleate. It features a central 1,2,3-trimethyl-1,3-propanediol core. The left hydroxyl group is esterified with oleic acid (C₁₇H₃₃COOH). The right hydroxyl group is esterified with a 2-(4-methoxyphenyl)propanoate derivative. The central carbon is substituted with a 2-(4-methoxyphenyl)propanoate derivative and a 2-(4-methoxyphenyl)propanoate derivative.
II-3b	Chemical structure of AGM-CMSI-C5bbGMe-2-TG-Octanoate. It features a central 1,2,3-trimethyl-1,3-propanediol core. The left hydroxyl group is esterified with octanoic acid (C₇H₁₅COOH). The right hydroxyl group is esterified with a 2-(4-methoxyphenyl)propanoate derivative. The central carbon is substituted with a 2-(4-methoxyphenyl)propanoate derivative and a 2-(4-methoxyphenyl)propanoate derivative.
II-4a	Chemical structure of AGM-CASI-C5bcBu-2-TG-Oleate. It features a central 1,2,3-trimethyl-1,3-propanediol core. The left hydroxyl group is esterified with oleic acid (C₁₇H₃₃COOH). The right hydroxyl group is esterified with a 2-(4-methoxyphenyl)propanoate derivative. The central carbon is substituted with a 2-(4-methoxyphenyl)propanoate derivative and a 2-(4-methoxyphenyl)propanoate derivative.
II-4b	Chemical structure of AGM-CASI-C5bcBu-2-TG-Octanoate. It features a central 1,2,3-trimethyl-1,3-propanediol core. The left hydroxyl group is esterified with octanoic acid (C₇H₁₅COOH). The right hydroxyl group is esterified with a 2-(4-methoxyphenyl)propanoate derivative. The central carbon is substituted with a 2-(4-methoxyphenyl)propanoate derivative and a 2-(4-methoxyphenyl)propanoate derivative.

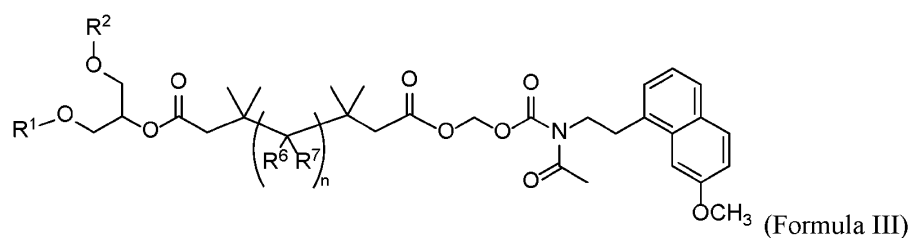
II-5a	 AGM-CASI-C5bcPn-2-TG-Oleate
II-5b	 AGM-CASI-C5bcPn-2-TG-Octanoate
II-6a	 AGM-CASI-C5bcHx-2-TG-Oleate
II-6b	 AGM-CASI-C5bcHx-2-TG-Octanoate
II-7a	 AGM-CASI-C6bbGMe-2-TG-Oleate

II-7b	 Chemical structure of AGM-CASI-C6bbGMe-2-TG-Octanoate. It features a central glycerol backbone esterified with two octanoate groups (C₇H₁₅) and a long chain containing a branched ester and a 4-methoxyphenyl group. AGM-CASI-C6bbGMe-2-TG-Octanoate
II-8a	 Chemical structure of AGM-CASI-C7bbGMe-2-TG-Oleate. It features a central glycerol backbone esterified with two oleate groups (C₁₇H₃₃) and a long chain containing a branched ester and a 4-methoxyphenyl group. AGM-CASI-C7bbGMe-2-TG-Oleate
II-8b	 Chemical structure of AGM-CASI-C7bbGMe-2-TG-Octanoate. It features a central glycerol backbone esterified with two octanoate groups (C₇H₁₅) and a long chain containing a branched ester and a 4-methoxyphenyl group. AGM-CASI-C7bbGMe-2-TG-Octanoate
II-9a	 Chemical structure of AGM-CASI-C8bbGMe-2-TG-Oleate. It features a central glycerol backbone esterified with two oleate groups (C₁₇H₃₃) and a long chain containing a branched ester and a 4-methoxyphenyl group. AGM-CASI-C8bbGMe-2-TG-Oleate
II-9b	 Chemical structure of AGM-CASI-C8bbGMe-2-TG-Octanoate. It features a central glycerol backbone esterified with two octanoate groups (C₇H₁₅) and a long chain containing a branched ester and a 4-methoxyphenyl group. AGM-CASI-C8bbGMe-2-TG-Octanoate
II-10a	 Chemical structure of AGM-CASI-C10bbGMe-2-TG-Oleate. It features a central glycerol backbone esterified with two oleate groups (C₁₇H₃₃) and a long chain containing a branched ester and a 4-methoxyphenyl group. AGM-CASI-C10bbGMe-2-TG-Oleate



[0050] In some embodiments, the compound of Formula I is II-1b. In some embodiments, the compound of Formula I is II-2b. In some embodiments, the compound of Formula I is II-7b. In some embodiments, the compound of Formula I is II-8b. In some embodiments, the compound of Formula I is II-8b. In some embodiments, the compound of Formula I is II-9b. In some embodiments, the compound of Formula I is II-10b.

[0051] In some embodiments, a lipid prodrug of agomelatine (AGM) is represent by Formula III:



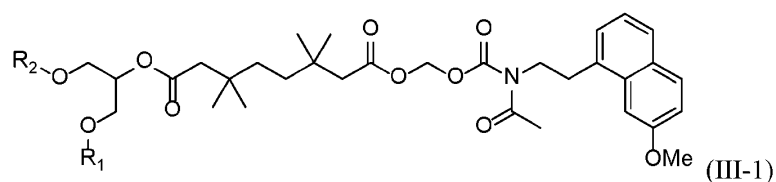
wherein

R^1 and R^2 are each independently hydrogen or a residue of a C_2 - C_{28} fatty acid;

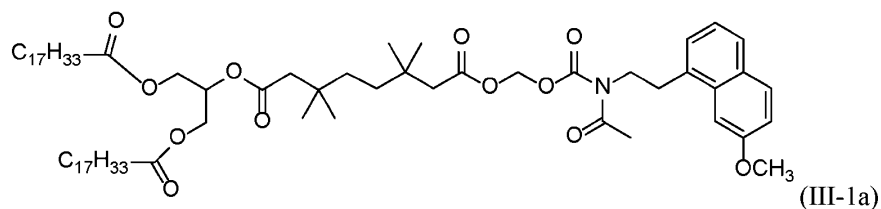
R^6 and R^7 are each independently at each occurrence hydrogen or C_1 - C_4 alkyl; and

n is 1-10.

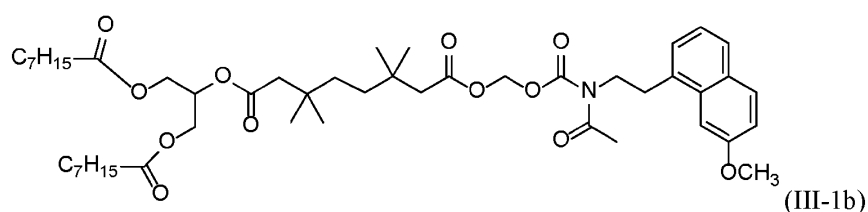
[0052] A specific embodiment of compounds having the structure Formula III is compound (III-1):



Examples of compound (III-1) include, but are not limited to:

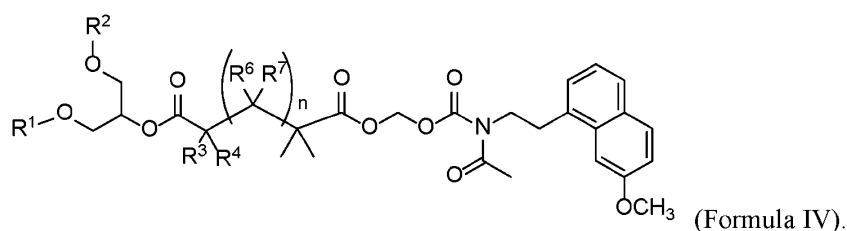


AGM-CASI-C8b'b'bbGMe-2-TG-oleate



AGM-CASI-C8b'b'bbGMe-2-TG-octanoate

[0053] In one aspect, disclosed herein are lipid prodrugs of agomelatine represented by Formula IV:



wherein

R^1 and R^2 are each independently hydrogen or a residue of a C_2 - C_{28} fatty acid;

R^3 and R^4 are each independently hydrogen or C_1 - C_4 alkyl;

R^6 and R^7 are each independently at each occurrence hydrogen or C_1 - C_4 alkyl; and

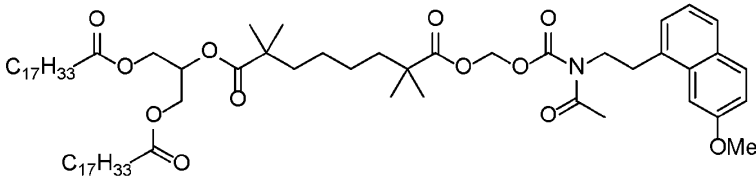
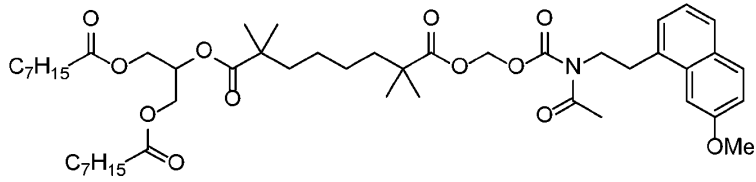
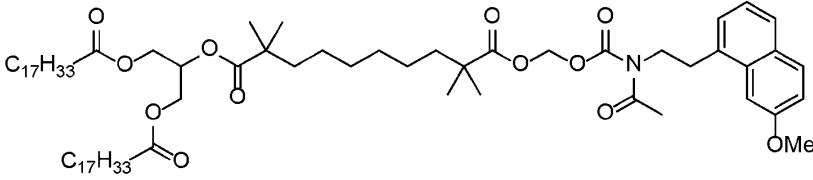
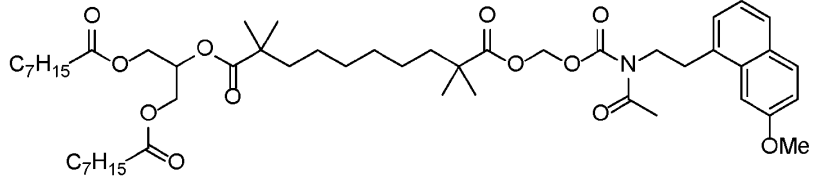
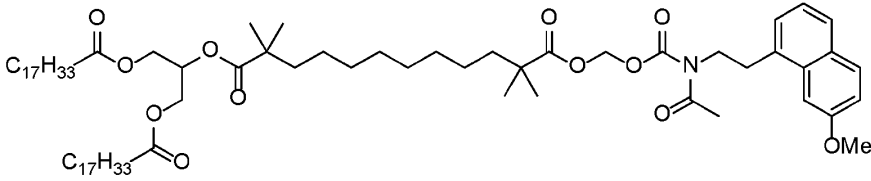
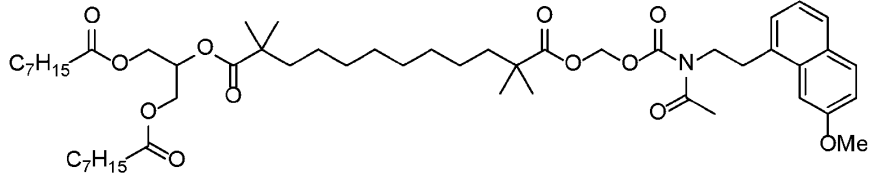
n is 1-10.

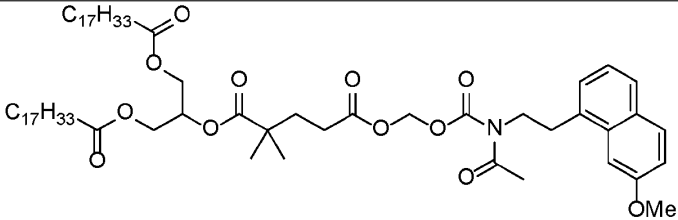
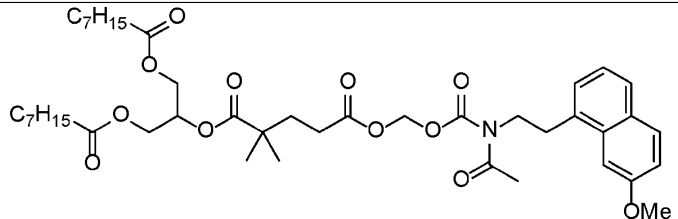
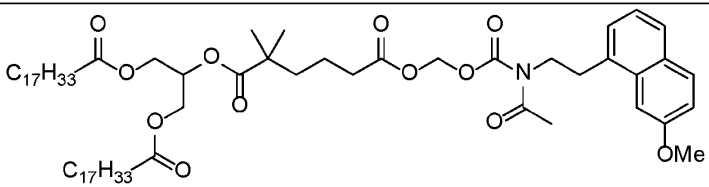
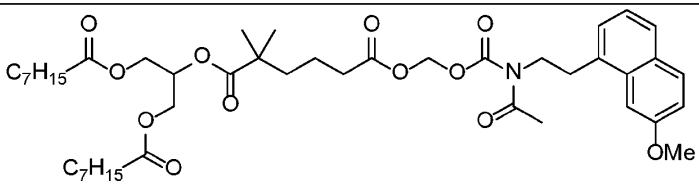
[0054] In some embodiments, compounds represented by Formula (VI) is one of the below compounds, wherein R^1 and R^2 are as defined above:

Compound	Structure
IV-1	AGM-CASI-C8a'a'aaGMe-2-TG
IV-2	AGM-CASI-C10a'a'aaGMe-2-TG
IV-3	AGM-CASI-C12a'a'aaGMe-2-TG
IV-4	AGM-CASI-C5aaGMe-2-TG
IV-5	AGM-CASI-C6aaGMe-2-TG

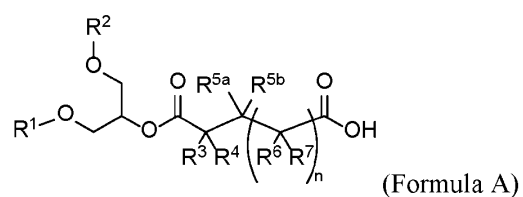
[0055] In one aspect, disclosed herein are compounds of Formula (IV) as shown in **Table 2**:

Table 2: Exemplary Compounds – Formula IV

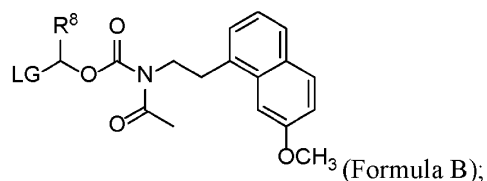
Compound	Structure
IV-1a	 AGM-CASI-C8a'a'aaGMe-2-TG-Oleate
IV-1b	 AGM-CASI-C8a'a'aaGMe-2-TG-Octanoate
IV-2a	 AGM-CASI-C10a'a'aaGMe-2-TG-Oleate
IV-2b	 AGM-CASI-C10a'a'aaGMe-2-TG-Octanoate
IV-3a	 AGM-CASI-C12a'a'aaGMe-2-TG-Oleate
IV-3b	 AGM-CASI-C12a'a'aaGMe-2-TG-Octanoate

IV-4a	 AGM-CASI-C5aaGMe-2-TG-Oleate
IV-4b	 AGM-CASI-C5aaGMe-2-TG-Octanoate
IV-5a	 AGM-CASI-C6aaGMe-2-TG-Oleate
IV-5b	 AGM-CASI-C6aaGMe-2-TG-Octanoate

[0056] In one aspect, a compound of Formula I can be prepared by reacting a compound of Formula A:



or a salt thereof, with a compound of Formula B:



wherein R^1 and R^2 are each independently a residue of a C_2 - C_{28} fatty acid;

R^3 and R^4 are each independently hydrogen or C_1 - C_4 alkyl;

R^{5a} and R^{5b} are each independently hydrogen, C_1 - C_4 alkyl, or are taken together with the carbon to which they are attached form a C_3 - C_8 cycloalkyl;

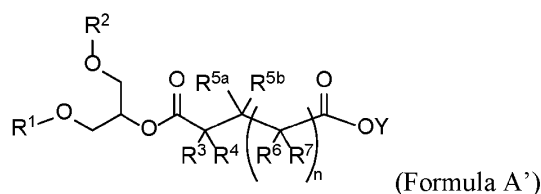
R^6 and R^7 are each independently at each occurrence hydrogen or C_1 - C_4 alkyl;

n is 1-10;

R^8 is hydrogen or C_1 - C_{10} alkyl; and

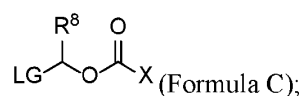
LG is a leaving group.

[0057] Where the compound of Formula A is a salt, such a compound may be prepared with or without isolation and may be represented by Formula A':



wherein Y is an alkali metal (*e.g.*, Li, Na) or an ammonium group optionally substituted with one or more alkyl groups (*e.g.*, NH_4 , NR_4 , NH_2R_2 , NH_3R , or NHR_3 , where R is C_1 - C_{10} alkyl).

[0058] A compound of Formula B can be prepared by reacting agomelatine or a salt thereof with a compound of Formula C:

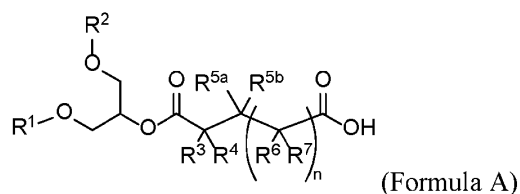


wherein R^8 is hydrogen;

X is halo; and

LG is a leaving group.

[0059] In one aspect, disclosed herein is a compound of Formula A:



or a salt thereof, wherein:

R^1 and R^2 are each independently a residue of a C_2 - C_{28} fatty acid;

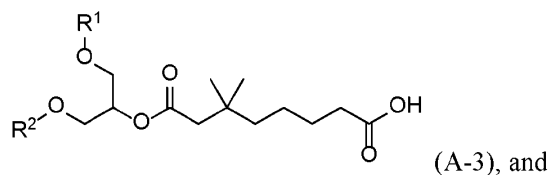
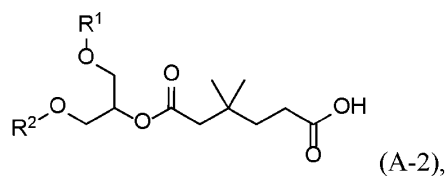
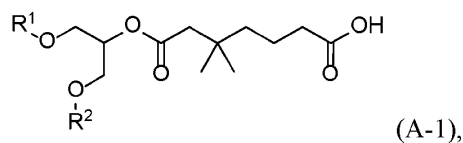
R^3 and R^4 are each independently hydrogen or C_1 - C_4 alkyl;

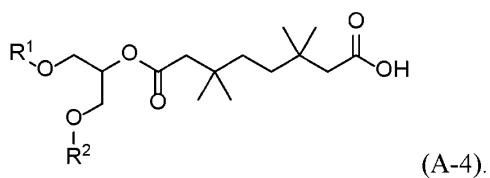
R^{5a} and R^{5b} are each independently hydrogen, C_1 - C_4 alkyl, or taken together with the carbon to which they are attached form a C_3 - C_8 cycloalkyl;

R^6 and R^7 are each independently at each occurrence hydrogen or C_1 - C_4 alkyl; and

n is 1-10.

[0060] Specific embodiments of compounds having the structure Formula A include, but are not limited to:

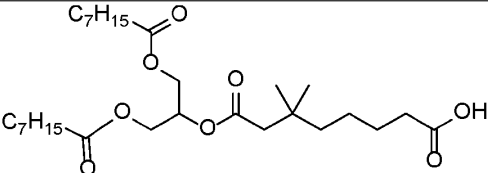
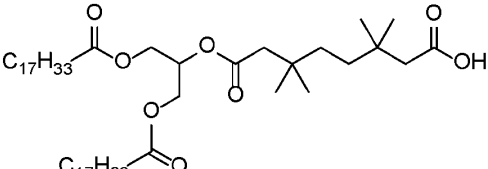
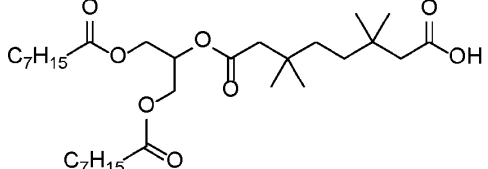




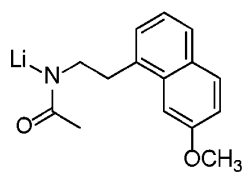
[0061] In one aspect, disclosed herein are compounds of Formula (A) as shown in **Table 3**:

Table 3: Exemplary Compounds – Formula A

Compound	Structure
A-1a	C7bbGMe-Acid-2-TG-Oleate
A-1b	C7bbGMe-Acid-2-TG-Octanoate
A-2a	C6bbGMe-Acid-2-TG-Oleate
A-2b	C6bbGMe-Acid-2-TG-Octanoate
A-3a	C8bbGMe-Acid-2-TG-Oleate

A-3b	 C8bbGMe-Acid-2-TG-Octanoate
A-4a	 C8b'b'bbMe-acid-2-TG-Oleate
A-4b	 C8b'b'bbMe-acid-2-TG-Octanoate

[0062] As used herein, leaving group (LG) is as defined by the International Union of Pure and Applied Chemistry (IUPAC), referring to an atom or group of atoms that detaches from the main or residual part of a substrate during a reaction or elementary step of a reaction. In some embodiments, the leaving group is chloro-. In some embodiments, the salt of agomelatine is an alkali metal, for example lithium. In this regard, a lithium salt of agomelatine may be prepared by treating agomelatine with a strong lithium base such as lithium diisopropylamide (LDA). Such a lithium salt may be generated either with or without isolation and may be presented by the following structure:



[0063] The lipid prodrugs disclosed herein afford high lymphatic transport and subsequent systemic exposure of agomelatine when administered orally. Example 3 demonstrates that the prodrugs of the instant disclosure are transported to the lymph at substantially higher levels than

agomelatine alone. Further, Example 6 demonstrates that the prodrugs of the instant disclosure, when administered orally, provide increased systemic exposure of agomelatine. Thus, the prodrugs of agomelatine can be orally administered to a subject in need thereof, resulting in increased systemic exposure of agomelatine. In some embodiments, the subject in need thereof has an anxiety disorder, a depressive disorder, and/or a mood disorder. In some embodiments, the anxiety disorder is generalized anxiety disorder (GAD). In some embodiments, the depressive or mood disorder is major depressive disorder (MDD). In some embodiments, the depressive or mood disorder is bipolar and related disorders.

Uses of Agomelatine Prodrugs

[0064] The lipid prodrugs of agomelatine disclosed herein are suitable for the treatment of bipolar and related disorders, depressive disorders, anxiety disorders, trauma- and stressor-related disorders, which are described in the Diagnostic and Statistical Manual of Mental Disorders, 5th Ed. Text Revision (DSM-5-TR), as well as other mood disorders. Examples of bipolar and related disorders include, but are not limited to, bipolar I disorder and bipolar II disorder. Examples of depressive disorders include, but are not limited to, major depressive disorder (MDD), persistent depressive disorder (PDD), and unspecified mood disorder. Examples of anxiety disorders include, but are not limited to, separation anxiety disorder, specific phobia, social anxiety disorder, panic disorder, and generalized anxiety disorder (GAD). Examples of trauma- and stressor-related disorders include, but are not limited to, posttraumatic stress disorder (PTSD), acute stress disorder, and adjustment disorders. As will be understood by those skilled in the art, certain of the aforementioned disorders may also be characterized as mood disorders in previous versions of the DSM or elsewhere (e.g., major depressive disorder, bipolar I and II disorders, and persistent depressive disorder, etc.). It is further understood that the aforementioned disorders may include various disorder subtypes and/or specifiers listed in the DSM-5-TR. As a non-limited example, MDD may be present with seasonal pattern, commonly referred to as seasonal affective disorder. In some embodiments, a subject may have more than one of the aforementioned disorders at the same time.

[0065] The lipid prodrugs of agomelatine disclosed herein are suitable for treating a pediatric subject, an adolescent subject, or an adult subject. As used herein, “pediatric subject” refers to a subject between the ages of 0 (birth) and 11 years of age. As used herein, “adolescent subject”

refers to a subject between 12 years of age and 21 years of age. As used herein, “adult subject” refers to a subject between 22 and 64 years of age. As used herein, “geriatric subject” refers to a subject 65 years or older.

[0066] Accordingly, in some embodiments the subject with MDD may be a pediatric subject, an adolescent subject, an adult subject, or a geriatric subject. In some embodiments, the subject with PDD may be a pediatric subject, adolescent subject, an adult subject, or a geriatric subject. In some embodiments, the subject with bipolar disorder may be a pediatric subject, an adolescent subject, an adult subject, or a geriatric subject. In some embodiments, the subject with GAD may be a pediatric subject, an adolescent subject, an adult subject, or a geriatric subject. In some embodiments, the subject with social anxiety disorder may be a pediatric subject, an adolescent subject, an adult subject, or a geriatric subject. In some embodiments, the subject with separation anxiety disorder may be a pediatric subject, an adolescent subject, an adult subject, or a geriatric subject. In some embodiments, the subject with one or more phobias may be a pediatric subject, adolescent subject, an adult subject, or a geriatric subject.

Methods of Treatment

[0067] The lipid prodrugs of agomelatine disclosed herein are suitable for the treatment of bipolar and related disorders, depressive disorders, anxiety disorders, trauma- and stressor-related disorders, which are described in the Diagnostic and Statistical Manual of Mental Disorders, 5th Ed. Text Revision (DSM-5-TR), as well as other mood disorders. Examples of bipolar and related disorders include, but are not limited to, bipolar I disorder and bipolar II disorder. Examples of depressive disorders include, but are not limited to, major depressive disorder (MDD), persistent depressive disorder (PDD), and unspecified mood disorder. Examples of anxiety disorders include, but are not limited to, separation anxiety disorder, specific phobia, social anxiety disorder, panic disorder, and generalized anxiety disorder (GAD). Examples of trauma- and stressor-related disorders include, but are not limited to, posttraumatic stress disorder (PTSD), acute stress disorder, and adjustment disorders. As will be understood by those skilled in the art, certain of the aforementioned disorders may also be characterized as mood disorders in previous versions of the DSM or elsewhere (e.g., major depressive disorder, bipolar I and II disorders, and persistent depressive disorder, etc.). It is further understood that the aforementioned disorders may include various disorder subtypes and/or specifiers listed in the DSM-5-TR. As a non-limiting example,

MDD may be present with seasonal pattern, commonly referred to as seasonal affective disorder. In some embodiments, a subject may have more than one of the aforementioned disorders at the same time.

[0068] The subject may be a pediatric subject, an adolescent subject, or an adult subject. As used herein, “pediatric subject” refers to a subject between the ages of 0 (birth) and 11 years of age. As used herein, “adolescent subject” refers to a subject between 12 years of age and 21 years of age. As used herein, “adult subject” refers to a subject between 22 and 64 years of age. As used herein, “geriatric subject” refers to a subject 65 years or older.

[0069] Accordingly, in some embodiments the subject with MDD may be a pediatric subject, an adolescent subject, an adult subject, or a geriatric subject. In some embodiments, the subject with PDD may be a pediatric subject, adolescent subject, an adult subject, or a geriatric subject. In some embodiments, the subject with bipolar disorder may be a pediatric subject, an adolescent subject, an adult subject, or a geriatric subject. In some embodiments, the subject with GAD may be a pediatric subject, an adolescent subject, an adult subject, or a geriatric subject. In some embodiments, the subject with social anxiety disorder may be a pediatric subject, an adolescent subject, an adult subject, or a geriatric subject. In some embodiments, the subject with separation anxiety disorder may be a pediatric subject, an adolescent subject, an adult subject, or a geriatric subject. In some embodiments, the subject with one or more phobias may be a pediatric subject, adolescent subject, an adult subject, or a geriatric subject.

[0070] In one aspect, the disclosed lipid prodrugs of agomelatine are suitable for oral administration to a human subject in need thereof. In some aspects, the prodrugs disclosed herein afford the administration of agomelatine to a subject in need thereof with reduced liver toxicity (also referred to as hepatotoxicity). Liver toxicity can be monitored using biomarkers associated with liver function. Biomarkers of liver function include alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), and bilirubin (BR). Elevated levels of one or more liver biomarkers is considered indicative of liver toxicity and/or abnormal liver function and are further described in the Common Terminology Criteria for Adverse Events v 3.0 (CTCAE) published on August 9th, 2006 by the National Cancer Institute, which is incorporated herein by reference in its entirety.

[0071] Liver biomarkers (*e.g.*, ALT, AST, bilirubin, ALP, and GGT) are benchmarked to a normal range of values, which can vary based on laboratory, assay, and patient population, but can be readily determined by a skilled practitioner. A biomarker can be within normal limits (WNL) or above the upper limit of normal (ULN). The extent to which a respective biomarker is above the ULN is associated with the grade of liver injury, as summarized in **Table 4**.

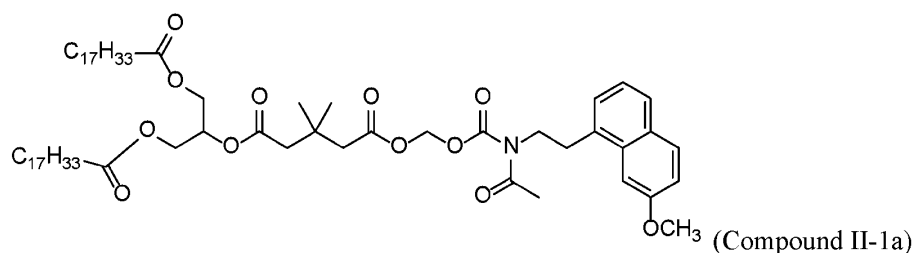
Table 4: Liver Biomarker Levels and Toxicity

Biomarker	Grade Classification				
	0	1	2	3	4
ALT	WNL	>ULN – 2.5X ULN	>2.5-5.0X ULN	>5.0-20X ULN	>20X ULN
AST	WNL	>ULN – 2.5X ULN	>2.5-5.0X ULN	>5.0-20X ULN	>20X ULN
Bilirubin	WNL	>ULN – 1.5X ULN	>1.5-3.0X ULN	>3.0-10X ULN	>10X ULN
ALP	WNL	>ULN-2.5X ULN	>2.5-5.0X ULN	>5.0-20X ULN	>20X ULN
GGT	WNL	>ULN-2.5X ULN	>2.5-5.0X ULN	>5.0-20X ULN	>20X ULN

[0072] A liver biomarker classified as grade 0 is within normal limits and is indicative of normal liver function. A liver biomarker classified as grades 1, 2, 3, or 4, is indicative of abnormal liver function. In one aspect, the lipid prodrugs disclosed herein can be administered to a subject in need thereof, in which one or more liver biomarkers are classified as grade 0 following administration of the prodrug. In another aspect, the lipid prodrugs disclosed herein can be administered to a subject in need thereof, in which one or more liver biomarkers are classified as grade 0 or grade 1 following administration of the prodrug. In some embodiments, the lipid prodrugs, following administration to a subject in need thereof, do not result in a liver biomarker classified as grade 2, 3, or 4. In some embodiments, the lipid prodrugs, following administration to a subject in need thereof, do not result in one or more liver biomarkers exceeding 3X the ULN. In some embodiments, the lipid prodrugs, following administration to a subject in need thereof, do not result in ALT exceeding 3X the ULN. In some embodiments, the lipid prodrugs, following administration to a subject in need thereof, result in one or more liver biomarker levels within the normal limit. In other embodiments, the lipid prodrugs, following administration to a subject in need thereof, result in one or more liver biomarkers levels being between 1-2.5X or 1-2.99X the upper limit of normal.

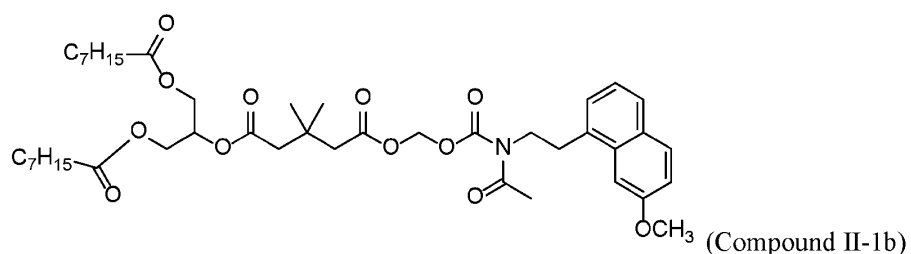
[0073] In contrast to agomelatine, the lipid prodrugs disclosed herein have advantageous pharmacological properties that greatly reduce the hepatotoxicity associated with the therapeutic use of agomelatine. Accordingly, administration of the disclosed lipid prodrugs to a human subject can reduce or eliminate the need to monitor liver function during the course of treatment. In some embodiments, the lipid prodrugs can be administered to a human subject without a need to monitor liver function during the course of treatment. In some embodiments, the lipid prodrugs can be administered to a human subject without a need to monitor one or more liver biomarkers during the course of treatment. In some embodiments, the lipid prodrugs can be administered to a human subject with monitoring of liver function as clinically indicated. In other embodiments, the lipid prodrugs can be administered to a human subject with a pre-existing hepatic impairment.

[0074] The disclosed lipid prodrugs are designed to release agomelatine (AGM) once in systemic circulation. Accordingly, the amount of administered compound can be expressed in molar equivalents of agomelatine (AGMeq), which refers to the total amount of AGM present in an amount or formulation after accounting for the molecular weight of the prodrug. For example, Compound II-1a (AGM-CASI-C5bbGMe-2-TG-oleate):



has a molecular weight of 1062.48 g/mol. AGM has a molecular weight of 243.31 g/mol. Accordingly, 2.1 mg of Compound II-1a is about 0.5 mg (2.1 μ mol) of AGMeq and 65.2 mg of Compound II-1a is about 15 mg (62 μ mol) of AGMeq.

[0075] As an additional example, Compound II-1b (AGM-CASI-C5bbGMe-2-TG-octanoate):



has a molecular weight of 785.97 g/mol. AGM has a molecular weight of 243.31 g/mol. Accordingly, 1.6 mg of Compound II-1b is about 0.5 mg (2.1 μ mol) of AGMeq and 48 mg of Compound II-1b is about 15 mg AGMeq (62 μ mol).

[0076] The compounds of Formula I, Formula II, Formula III, and Formula IV may be administered to a subject once per day (QD). In some embodiments, the compounds of Formula I, Formula II, Formula III, and Formula IV may be administered to a subject once per day at night (QHS). In some embodiments, any one of Compounds II-1, II-2, II-7, II-8, II-9, II-10, III-1, IV-1, IV-2, IV-3, IV-4, or IV-5 are administered to a subject QD. In some embodiments, any one of Compounds II-1, II-2, II-7, II-8, II-9, II-10, III-1, IV-1, IV-2, IV-3, IV-4, or IV-5 are administered to a subject QHS.

Formulations

[0077] The lipid prodrugs disclosed herein may be prepared as a composition with one or more pharmaceutically acceptable carriers as are known in the art. To aid in delivery, the lipid prodrugs may be formulated in a lipid-based formulation.

[0078] Lipid formulations may contain lipids and/or surfactants, optionally with co-solvents, and are generally categorized into 4 types. Type I formulations include lipids which require digestion, such as mono-, di-, and triglycerides and combinations thereof. Type II formulations are water-insoluble self-emulsifying drug delivery systems (SEDDS) which contain lipids in addition to water insoluble surfactants. Type III formulations are SEDDS or self-microemulsifying drug delivery systems (SMEDDS) which contain lipids in addition to water-soluble surfactants and/or co-solvents. Type IV formulations contain predominantly hydrophilic surfactants and co-solvents such as PEG and propylene glycol.

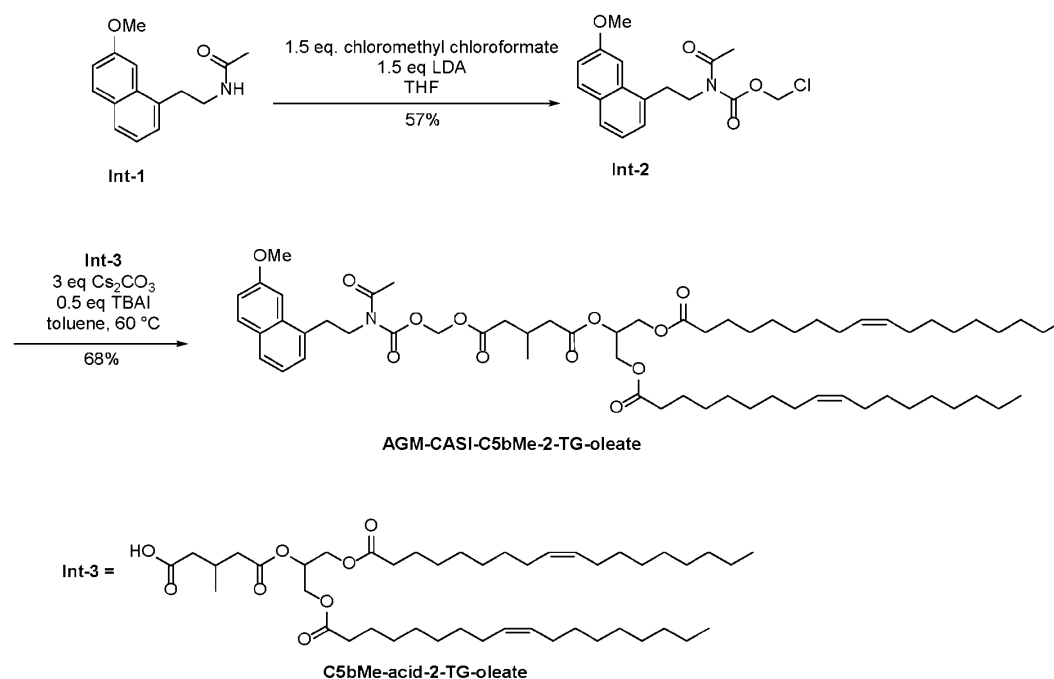
[0079] An exemplary SEDDS formulation is 30% w/w soybean oil, 30.5% w/w Maisine-CC, 31.5% w/w Kolliphor EL (a polyethoxylated castor oil surfactant prepared by reacting 35 moles of ethylene oxide per mole of castor oil, available from BASF Corp.), and 7.4% w/w ethanol. Alternatively, an exemplary SEDDS formulation is 25% w/w sesame oil, 27% w/w Peceol (glycerol monooleate, available from Gattefosse), 48% w/w Kolliphor EL.

[0080] In some embodiments, the lipid prodrugs are administered as an oral dosage form. The oral dosage form can be any orally acceptable dosage form, including but not limited to capsules, tablets, suspensions, or solutions as are known in the art.

Examples

Example 1: Synthesis of Agomelatine Lipid Prodrugs

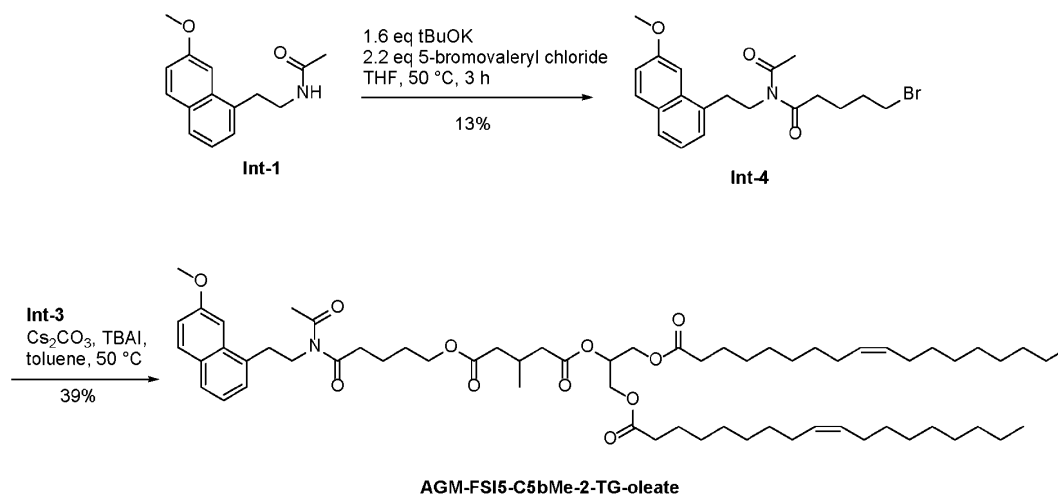
AGM-CASl-C5bMe-2-TG-Oleate



[0081] *Synthesis of Int-2.* LDA in THF/heptane/ethylbenzene (2M, 30.8 mL, 61.6 mmol) was added to a solution of agomelatine (**Int-1**; 10.0 g, 41.1 mmol) in tetrahydrofuran (THF; 200 mL) at -78 °C under argon. The reaction mixture was stirred for 1 hour while maintaining temperature. Chloromethyl chloroformate (7.95 g, 61.7 mmol, 5.48 mL) was added dropwise. The mixture was warmed to room temperature (RT) and stirred for 16 hours. The reaction was quenched with water (200 mL) and organics extracted with ethyl acetate (2 x 250 mL). The combined organic layers were washed with brine (200 mL), dried over sodium sulfate, and reduced under vacuum to afford crude **Int-2**. Crude **Int-2** was purified by normal phase purification (Biotage Isolera LS, 330 g SiliaSep Cartridge) using a 0-20% ethyl acetate in heptane eluent over 10 column volumes (CV)

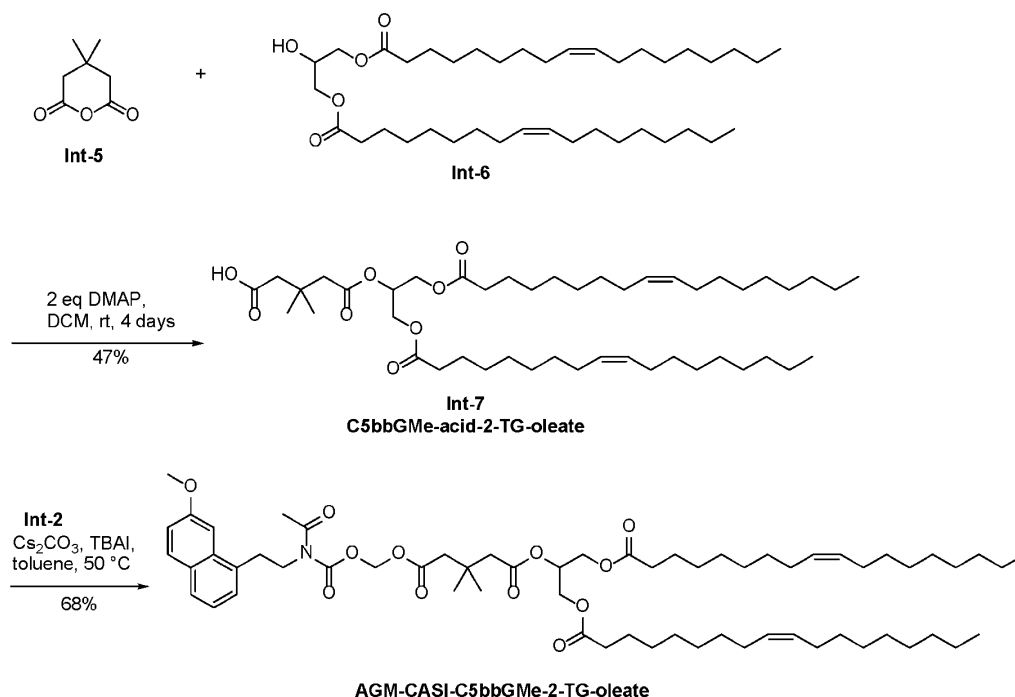
to afford pure **Int-2** (7.92 g, 57.2% yield) as a white solid. ^1H NMR (400 MHz, CDCl_3): δ 7.76 (d, J = 8.9 Hz, 1H), 7.68 (d, J = 7.9 Hz, 1H), 7.60 (d, J = 2.3 Hz, 1H), 7.35 - 7.31 (m, 1H), 7.29 - 7.23 (m, 1H), 7.17 (dd, J = 2.4, 8.9 Hz, 1H), 5.73 (s, 2H), 4.12 - 4.01 (m, 5H), 3.30 - 3.22 (m, 2H), 2.59 (s, 3H). UPLC-MS: (BEH-C18 Short Base 2-95%) R_t = 1.10 min (99.6%), MS (ESIpos): m/z = $[\text{M}+\text{H}]^+$ not observed.

[0082] *Synthesis of AGM-CASI-C5bMe-2-TG-oleate.* Cs_2CO_3 (6.72 g, 20.6 mmol) and TBAI (1.27 g, 3.44 mmol) were added to a solution of **Int-2** (5.15 g, 6.87 mmol) and **Int-3** (2.31 g, 6.87 mmol) in toluene (200 mL). **Int-3** can be prepared as described in WO 2021/159021 (see paragraphs 328 to 334). The reaction was heated to 60 $^\circ\text{C}$ and stirred for 3 hours, after which it was allowed to cool to RT. Water (50 mL) was added, and the organics were extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over sodium sulfate, and concentrated to afford crude **AGM-CASI-C5bMe-2-TG-oleate**. The crude product was purified by normal phase purification (Biotage Isolera, 120 g SiliaSep cartridge) using a 0-5% ethyl acetate in heptane eluent over 5 CVs, 5% isocratic over 2 CVs, 5-15% over 3 CVs, 15% isocratic over 2 CVs, and 15-100% over 10 CVs to afford pure **AGM-CASI-C5bMe-2-TG-oleate** (4.91 g, 68.1% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 7.75 (d, J = 9.0 Hz, 1H), 7.68 (d, J = 0.9 Hz, 1H), 7.64 (d, J = 0.5 Hz, 1H), 7.33 (d, J = 6.5 Hz, 1H), 7.28 (dd, J = 6.6, 8.1 Hz, 1H), 7.16 (dd, J = 2.5, 9.0 Hz, 1H), 5.80 (s, 2H), 5.40 - 5.23 (m, 5H), 4.28 (ddd, J = 2.0, 4.3, 11.9 Hz, 2H), 4.11 (dd, J = 6.3, 12.0 Hz, 2H), 4.06 - 4.04 (m, 5H), 3.24 - 3.20 (m, 2H), 2.57 (s, 3H), 2.53 - 2.27 (m, 9H), 2.01 (q, J = 6.4 Hz, 8H), 1.61 - 1.57 (m, 4H), 1.29 - 1.26 (m, 40H), 1.06 (d, J = 6.5 Hz, 3H), 0.88 (t, J = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ 173.4, 172.9, 171.3, 170.9, 158.3, 153.3, 133.5, 133.2, 130.21, 130.15, 129.8, 129.3, 127.8, 127.3, 123.3, 118.7, 102.6, 80.7, 69.4, 62.1, 55.7, 45.1, 40.6, 40.3, 34.1, 32.8, 32.1, 29.91, 29.85, 29.7, 29.5, 29.32, 29.26, 29.2, 27.4, 27.3, 27.2, 27.1, 25.0, 22.8, 19.7, 14.3. UPLC-MS: (XB BEH 300 C4 20-95%): R_t = 7.19 min., 80.9% (UV), 98.8% (ELSD). MS (ESIpos): m/z = 1066.3 $[\text{M}+\text{NH}_4]^+$.

AGM-FSI5-C5bMe-2-TG-Oleate – Comparative Compound

[0083] *Synthesis of Int-4.* Potassium *tert*-butoxide (738 mg, 6.57 mmol) was added to a stirring solution of agomelatine (**Int-1**; 1.00 g, 4.11 mmol) in tetrahydrofuran (25 mL). The suspension was heated at 50 °C for 30 minutes, after which 5-bromovaleryl chloride (1.80 g, 9.04 mmol, 1.21 mL) was added dropwise. The reaction was heated at 50 °C for 3 hours and then allowed to cool to RT overnight. The mixture was diluted with ethyl acetate (15 mL) and washed with water (15 mL) and brine (15 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated to afford crude **Int-4**. The crude **Int-4** was purified by normal phase purification (Biotage Isolera, 4 g SiliaSep cartridge) using a 0-30% ethyl acetate in heptane eluent to afford a yellow oil (751 mg). Residual 5-bromovaleric acid was removed by resuspending the material in dichloromethane (DCM, 50 mL) and washing with 2M sodium carbonate solution (2 x 50 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated to afford **Int-4** (223 mg, 13.4% yield) as a yellow gum which solidified on standing. ¹H NMR (400 MHz, CDCl₃): δ 7.76 (d, J = 8.9 Hz, 1H), 7.73 - 7.67 (m, 1H), 7.63 (d, J = 2.3 Hz, 1H), 7.30 - 7.24 (m, 2H + CDCl₃), 7.18 (dd, J = 2.4, 8.9 Hz, 1H), 4.05 (s, 3H), 4.01 - 3.95 (m, 2H), 3.39 (t, J = 6.5 Hz, 2H), 3.32 - 3.25 (m, 2H), 2.66 (t, J = 7.0 Hz, 2H), 2.40 (s, 3H), 1.90 - 1.81 (m, 2H), 1.81 - 1.71 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 175.7, 173.5, 158.4, 133.4, 133.1, 130.4, 129.4, 127.61, 127.59, 123.3, 118.8, 102.6, 55.8, 45.8, 37.1, 33.4, 32.2, 26.7, 23.5. UPLC-MS: (BEH-C18 Short Base 2-95%): R_t = 1.15 min (89.1%), MS (ESIpos): m/z = [M+H]⁺ not observed; MS (ESIneg): m/z = [M-H]⁻ not observed.

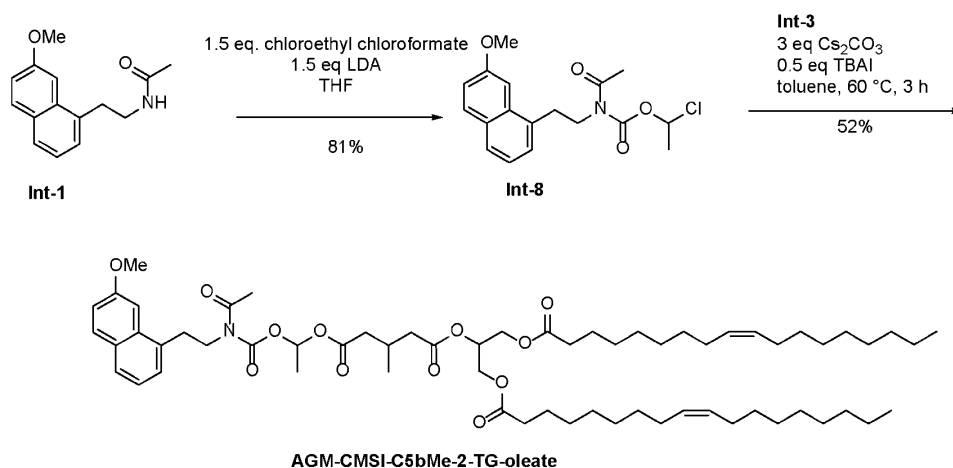
[0084] *Synthesis of AGM-FSI5-C5bMe-2-TG-Oleate.* Cs_2CO_3 (387 mg, 1.19 mmol) was added to a stirring solution of **Int-3** (297 mg, 396 μmol) in toluene (5 mL). The solution was stirred for 10 minutes, after which **Int-4** (172 mg, 396 μmol) and TBAI (73.1 mg, 198 μmol) was added. The reaction was heated at 50 °C for 4 hours. Heating was then stopped, and the mixture allowed to cool to RT. The mixture was diluted with ethyl acetate (40 mL) and washed with water (40 mL) and brine (50 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated to afford crude **AGM-FSI5-C5bMe-2-TG-Oleate** as a pale yellow oil. The crude product was purified by normal phase purification (Biotage Isolera, 12 g SiliaSep Cartridge) using a 0-20% ethyl acetate in heptane eluent over 30 CVs to afford pure **AGM-FSI5-C5bMe-2-TG-Oleate** (177 mg, 38.7% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 7.76 (d, J = 8.9 Hz, 1H), 7.73 - 7.66 (m, 1H), 7.64 (d, J = 2.3 Hz, 1H), 7.30 - 7.23 (m, 2H + CDCl_3), 7.17 (dd, J = 2.4, 8.9 Hz, 1H), 5.42 - 5.19 (m, 5H), 4.38 - 4.23 (m, 2H), 4.13 (dd, J = 6.0, 12.0 Hz, 2H), 4.08 (t, J = 6.2 Hz, 2H), 4.04 (s, 3H), 4.02 - 3.93 (m, 2H), 3.33 - 3.23 (m, 2H), 2.68 (t, J = 7.0 Hz, 2H), 2.52 - 2.35 (m, 6H), 2.33 - 2.18 (m, 6H), 2.08 - 1.94 (m, 8H), 1.75 - 1.53 (m, 8H + water), 1.28 (br d, J = 11.9 Hz, 40H), 1.02 (d, J = 6.5 Hz, 3H), 0.92 - 0.84 (m, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ 175.7, 173.44, 173.40, 172.3, 171.5, 158.4, 133.4, 133.1, 130.4, 130.2, 129.9, 129.4, 127.6, 123.3, 118.8, 102.6, 69.2, 64.2, 62.2, 55.8, 45.7, 40.8, 37.5, 34.1, 33.4, 32.1, 29.91, 29.85, 29.81, 29.7, 29.5, 29.32, 29.27, 29.24, 28.2, 27.5, 27.4, 27.3, 26.7, 25.0, 22.8, 21.4, 19.8, 14.3. UPLC-MS: (XB BEH 300 C4 20-95%): R_t = 7.20 min., 77.9% (UV), 98.2% (ELSD); MS(ESIpos): m/z = 1075.4 $[\text{M}+\text{H}]^+$, 1092.4 $[\text{M}+\text{NH}_4]^+$.

AGM-CASI-C5bbGMe-2-TG-Oleate (II-1a)

[0085] *Synthesis of Int-7.* DMAP (1.77 g, 14.5 mmol) was added to a solution of 3,3-dimethylglutaric anhydride (**Int-5**, 2.06 g, 14.5 mmol) and **Int-6** (5.98 g, 9.63 mmol) in DCM (120 mL). The mixture was stirred at RT for 4 days, after which it was diluted with dichloromethane (200 mL) and washed with water (300 mL) and brine (300 mL). The DCM layer was dried over sodium sulfate, filtered, and concentrated to afford crude **Int-7** as a colorless oil. Crude **Int-7** was purified by normal phase purification (Biotage Isolera, 120 g SiliaSep cartridge) using a 0-10% methanol in DCM eluent over 20 CVs to afford pure **Int-7** (3.42 g, 46.5% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 5.38 – 5.27 (m, 5H), 4.29 (dd, J = 4.2, 11.9 Hz, 2H), 4.14 (dd, J = 6.1, 11.9 Hz, 2H), 2.48 – 2.45 (m, 4H), 2.30 (t, J = 7.5 Hz, 4H), 2.10 – 1.98 (m, 8H), 1.62 – 1.57 (m, 4H), 1.38 – 1.21 (m, 40H), 1.14 (s, 6H), 0.88 (t, J = 6.4 Hz, 6H); exchangeable CO₂H proton not observed. ¹³C NMR (100 MHz, CDCl₃): δ 173.4, 173.0, 171.1, 130.2, 129.9, 69.2, 69.0, 62.3, 45.1, 44.94, 44.85, 34.1, 32.7, 32.1, 29.91, 29.85, 29.7, 29.6, 29.5, 29.32, 29.26, 29.23, 27.8, 27.4,

27.3, 25.0, 22.8, 14.3. UPLC-MS: (XB BEH 300 C4 20-95%): R_t = 6.46 minutes, 95.1% (UV), 100.0% (ELSD). MS (ESIpos): m/z = 781.2 $[M+NH_4]^+$; MS (ESIneg): m/z = 762.0 $[M-H]^-$

[0086] *Synthesis of AGM-CASI-C5bbGMe-2-TG-Oleate (II-1a)*. CS_2CO_3 (4.30 g, 13.2 mmol) and TBAI (811 mg, 2.20 mmol) was added to a solution of **Int-2** (1.47 g, 4.39 mmol) and **Int-7** (3.35 g, 4.39 mmol) in toluene (40 mL) at RT. The mixture was heated to 50 °C and stirred for 2 hours. The mixture was then diluted with ethyl acetate (200 mL), washed with NH_4Cl (200 mL), and washed with brine (200 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated to afford crude **AGM-CASI-C5bbGMe-2-TG-Oleate (II-1a)**. Crude product was purified by normal phase purification (Biotage Isolera, 120 g SiliaSep Cartridge) using a 0-20% ethyl acetate in heptane eluent over 16 CVs to afford pure **AGM-CASI-C5bbGMe-2-TG-Oleate (II-1a)** (3.19 g, 68.4% yield) as a colorless oil. 1H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 8.9 Hz, 1H), 7.70 - 7.63 (m, 2H), 7.35 - 7.30 (m, 1H), 7.29 - 7.22 (m, 1H), 7.15 (dd, J = 2.4, 8.9 Hz, 1H), 5.80 (s, 2H), 5.38 - 5.21 (m, 5H), 4.26 (dd, J = 4.3, 11.9 Hz, 2H), 4.11 (dd, J = 6.0, 12.0 Hz, 2H), 4.07 - 4.00 (m, 5H), 3.30 - 3.16 (m, 2H), 2.57 (s, 3H), 2.53 (s, 2H), 2.46 (s, 2H), 2.30 - 2.26 (m, 4H), 2.00 (q, J = 6.6 Hz, 8H), 1.66 - 1.54 (m, 4H), 1.36 - 1.23 (m, 40H), 1.13 (s, 6H), 0.91 - 0.85 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.3, 172.9, 170.8, 170.4, 158.3, 153.3, 133.5, 133.2, 130.20, 130.15, 129.8, 129.3, 127.8, 127.3, 123.3, 118.7, 102.6, 80.6, 69.2, 62.2, 55.7, 45.1, 45.0, 44.4, 34.1, 32.8, 32.7, 32.0, 29.9, 29.8, 29.7, 29.6, 29.5, 29.3, 29.24, 29.21, 27.7, 27.4, 27.30, 27.0, 24.9, 22.8, 14.2. UPLC-MS: (XB BEH 300 C4 20-95%): R_t = 7.26 minutes, 99.5% (UV), 100.0% (ELSD); MS(ESIpos): m/z 1080.4 $[M+NH_4]^+$.

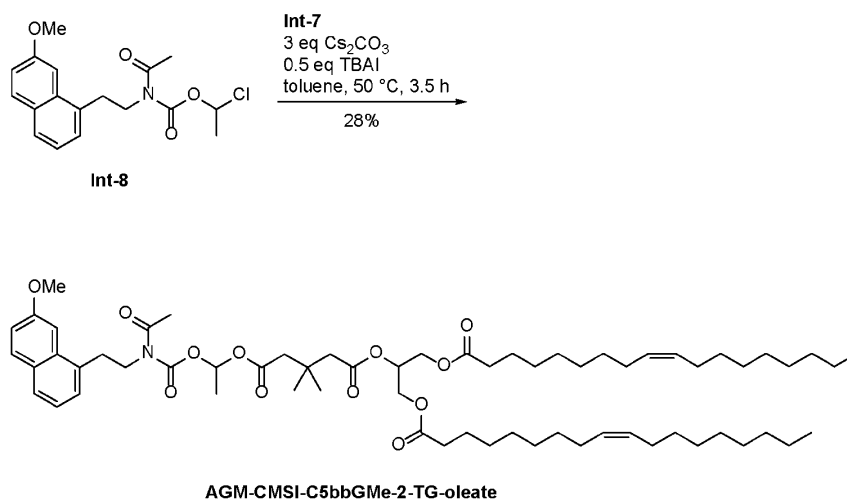
AGM-CMSI-C5bMe-2-TG-Oleate

[0087] *Synthesis of Int-8.* LDA in THF/heptane/ethylbenzene (2M, 3.08 mL, 6.16 mmol) was added to a solution of agomelatine (**Int-1**; 1.00 g, 4.11 mmol) in tetrahydrofuran (10 mL) at -78 °C under argon. The reaction was stirred for 1 hour while maintaining temperature. 1-chloroethyl chloroformate (882 mg, 6.17 mmol, 672 μ L) was added dropwise to the solution. The mixture was warmed to RT and stirred for 16 hours. The reaction was then quenched with water (50 mL) and the organics were extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over sodium sulfate, and concentrated to afford crude **Int-8**. Crude product was purified by normal phase purification (Biotage Isolera, 100 g Biotage Sfar cartridge) using a 0-30% ethyl acetate in heptane eluent over 14 CVs to afford pure **Int-8** (1.17 g, 81.4% yield) as a white solid. ^1H NMR (400 MHz, CDCl_3): δ 7.76 (d, J = 8.9 Hz, 1H), 7.69 (d, J = 7.9 Hz, 1H), 7.63 (d, J = 2.6 Hz, 1H), 7.32 – 7.25 (m, 2H), 7.17 (dd, J = 2.5, 9.1 Hz, 1H), 6.55 (q, J = 5.8 Hz, 1H), 4.14 – 4.00 (m, 5H), 3.31 – 3.22 (m, 2H), 2.59 (s, 3H), 1.80 (d, J = 5.9 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 172.9, 158.3, 152.4, 133.5, 133.3, 130.3, 129.4, 127.7, 127.4, 123.3, 118.5, 102.8, 83.1, 55.8, 45.1, 32.9, 27.1, 25.2.

[0088] *Synthesis of AGM-CMSI-C5bMe-2-TG-Oleate.* Cs_2CO_3 (261 mg, 801 μ mol) and TBAI (50.0 mg, 135 μ mol) was added to a solution of **Int-3** (200 mg, 267 μ mol) and **Int-8** (94.0 mg, 269 μ mol) in toluene (4 mL) at RT. The mixture was then heated at 60 °C for 3 hours, cooled to RT, diluted with ethyl acetate (20 mL), washed with water (20 mL), and brine (20 mL). The

organic layer was dried over sodium sulfate, filtered, and concentrated to afford **AGM-CMSI-C5bMe-2-TG-Oleate** as a crude yellow oil. The crude product was purified by normal phase purification (Biotage Isolera, 12 g SiliaSep cartridge) using a 0-20% ethyl acetate in heptane eluent over 18 CVs to afford the desired product (146.6 mg, 51.7% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 7.74 (d, J = 8.9 Hz, 1H), 7.67 (m, 1H), 7.63 (d, J = 2.0 Hz, 1H), 7.29 – 7.23 (m, 2H), 7.16 (dd, J = 2.4, 9.0 Hz, 1H), 6.86 (q, J = 5.5 Hz, 1H), 5.37 – 5.32 (m, 4H), 5.24 (m, 1H), 4.30 – 4.25 (m, 2H), 4.14 – 4.10 (m, 2H), 4.05 – 3.98 (m, 5H), 3.23 (t, J = 8.1 Hz, 2H), 2.55 (s, 3H), 2.47 – 2.38 (m, 3H), 2.30 – 2.24 (m, 6H), 2.05 – 1.98 (m, 8H), 1.67 – 1.55 (m, 4H), 1.49 (d, J = 5.4 Hz, 3H), 1.31 – 1.24 (m, 40H), 1.03 – 1.01 (m, 3H), 0.88 (t, J = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ 173.4, 173.0, 171.3, 170.34, 170.30, 158.3, 152.6, 133.5, 133.4, 130.3, 130.2, 129.9, 129.4, 127.6, 127.3, 123.3, 118.6, 102.8, 90.5, 69.3, 62.2, 55.8, 45.1, 40.6, 40.4, 34.1, 32.8, 32.1, 29.91, 29.85, 29.81, 29.7, 29.51, 29.47, 29.32, 29.26, 29.23, 27.4, 27.32, 27.28, 27.24, 27.1, 25.0, 22.8, 19.66, 19.62, 19.60, 14.3, 14.2. UPLC-MS: (XB BEH 300 C4 20-95%): R_t = 7.21 minutes, 93.6% (UV), 100.0% (ELSD). MS (ESIpos): m/z = 1080.6 $[\text{M}+\text{NH}_4]^+$.

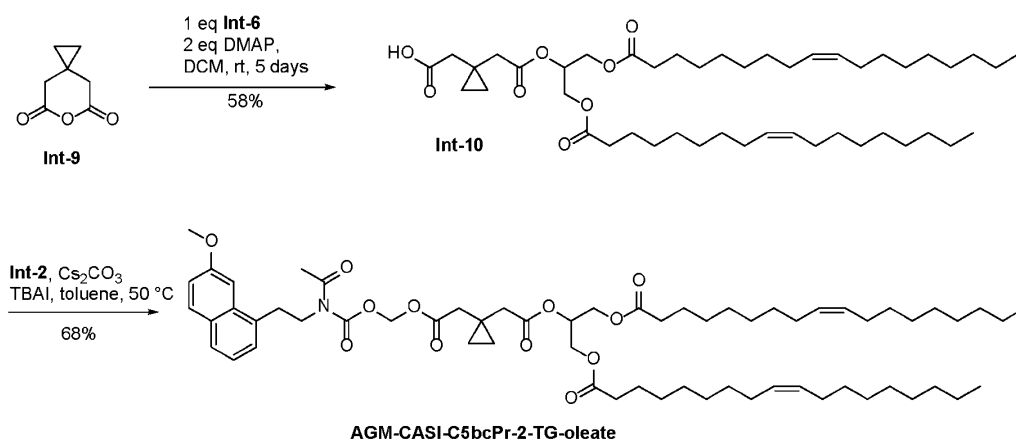
AGM-CMSI-C5bbGMe-2-TG-Oleate (II-3a)



[0089] *Synthesis of AGM-CMSI-C5bbGMe-2-TG-Oleate (II-3a).* Cs_2CO_3 (168 mg, 515 μmol) and TBAI (31.7 mg, 85.8 μmol) was added to a solution of **Int-8** (60.0 mg, 172 μmol) and **Int-7** (131 mg, 172 μmol) in toluene (5 mL). The mixture was heated at 50 $^\circ\text{C}$ for 3.5 hours, after

which it was diluted with ethyl acetate (30 mL), washed with water (30 mL) and washed with brine (30 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated to afford crude **AGM-CMSI-C5bbGMe-2-TG-Oleate (II-3a)** as a yellow oil. The crude product was purified by normal phase purification (Biotage Isolera, 25 g SiliaSep Cartridge) using a 0-20% ethyl acetate in heptane eluent over 30 CVs to afford pure **AGM-CMSI-C5bbGMe-2-TG-Oleate (II-3a)** (51.5 mg, 27.9% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 7.74 (d, J = 8.9 Hz, 1H), 7.68 – 7.64 (m, 2H), 7.29 – 7.23 (m, 2H), 7.16 (dd, J = 2.3, 8.9 Hz, 1H), 6.86 (q, J = 5.4 Hz, 1H), 5.38 – 5.32 (m, 4H), 5.24 – 5.21 (m, 1H), 4.29 – 4.23 (m, 2H), 4.11 (dd, J = 6.0, 11.9 Hz, 2H), 4.09 – 3.96 (m, 5H), 3.23 (t, J = 8.2 Hz, 2H), 2.55 (s, 3H), 2.51 – 2.39 (m, 4H), 2.30 – 2.25 (m, 4H), 2.10 – 1.96 (m, 8H), 1.65 – 1.54 (m, 4H), 1.49 (d, J = 5.5 Hz, 3H), 1.38 – 1.21 (m, 40H), 1.11 (s, 6H), 0.88 (t, J = 6.4 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 173.3, 173.0, 170.8, 169.8, 158.3, 152.6, 133.5, 133.4, 130.2, 130.1, 129.8, 129.3, 127.6, 127.3, 123.3, 118.5, 102.8, 90.3, 69.1, 62.2, 55.7, 45.02, 45.01, 44.7, 34.1, 32.8, 32.7, 32.0, 29.9, 29.8, 29.7, 29.5, 29.3, 29.23, 29.21, 27.61, 27.55, 27.4, 27.3, 27.0, 24.9, 22.8, 19.6, 14.2. UPLC-MS: (XB BEH 300 C4 20-95%): R_t = 7.26 minutes, 99.7% (UV), 100.0% (ELSD). MS (ESIpos): m/z = 1094.6 [M+NH₄]⁺.

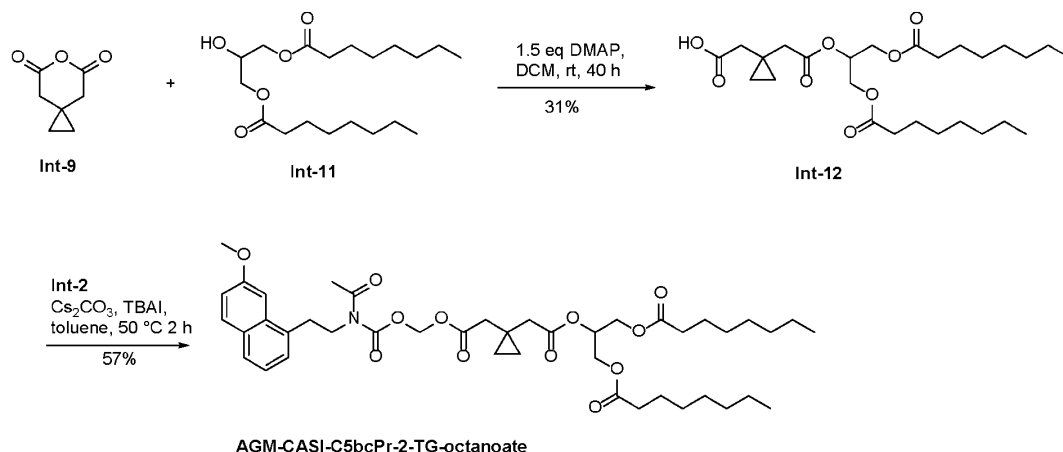
AGM-CASI-C5bcPr-2-TG-Oleate (II-2a)



[0090] *Synthesis of Int-10.* DMAP (1.50 g, 12.3 mmol) was added to a solution of 6-oxaspiro[2.5]octane-5,7-dione (**Int-9**; 1.69 g, 12.1 mmol) and **Int-6** (5.00 g, 8.05 mmol) in DCM (60 mL). The mixture was stirred at RT for 5 days and then concentrated to afford crude **Int-10**.

Crude product was purified by normal phase purification (Biotage Isolera, 120 g SiliaSep cartridge) using a 40-60% ethyl acetate in heptane eluent over 15 CVs to afford pure **Int-10** (3.57 g, 58.3% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 5.46 - 5.22 (m, 5H), 4.31 (dd, J = 4.3, 11.9 Hz, 2H), 4.18 - 4.11 (m, 2H), 2.46 (s, 2H), 2.45 (s, 2H), 2.31 (t, J = 7.5 Hz, 4H), 2.07 - 1.97 (m, 8H), 1.68 - 1.56 (m, 4H), 1.37 - 1.22 (m, 40H), 0.92 - 0.83 (m, 6H), 0.57 (s, 4H). 80H expected 79H observed, exchangeable CO_2H proton not observed. ^{13}C NMR (100 MHz, CDCl_3): δ 177.2, 173.4, 171.4, 130.2, 129.9, 69.3, 62.2, 41.1, 40.8, 34.2, 32.1, 29.91, 29.85, 29.7, 29.5, 29.31, 29.26, 29.24, 27.4, 27.3, 25.0, 22.8, 14.3, 14.2, 12.4. UPLC-MS (XB BEH300 C4 20to95%): R_t = 6.32 minutes, 100.0% (UV), 99.9% (ELSD); MS(ESIpos): m/z = 779.1 $[\text{M}+\text{H}]^+$, MS(ESIneg): m/z = 760.1 $[\text{M}-\text{H}]^-$.

[0091] *Synthesis of AGM-CASI-C5bcPr-2-TG-oleate (II-2a)*. Cs_2CO_3 (1.79 g, 5.48 mmol) and TBAI (337 mg, 913 μmol) was added to a solution of **Int-2** (613 mg, 1.83 mmol) and **Int-10** (1.39 g, 1.83 mmol) in toluene (30 mL). The mixture was stirred at 50 $^\circ\text{C}$ for 3 hours, allowed to cool, and then diluted with ethyl acetate (100 mL). The organic layer was washed with water (100 mL) and brine (2x 100 mL), dried over magnesium sulfate, filtered, and concentrated to afford crude **AGM-CASI-C5bcPr-2-TG-oleate (II-2a)** as a yellow gum. Crude product was purified by normal phase purification (Biotage Isolera, 80 g SiliaSep Cartridge) using a 0-20% ethyl acetate in heptane eluent to afford pure **AGM-CASI-C5bcPr-2-TG-oleate (II-2a)** (1.32 g, 68.0% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 7.74 (d, J = 8.9 Hz, 1H), 7.67 (d, J = 7.9 Hz, 1H), 7.64 (d, J = 2.3 Hz, 1H), 7.35 - 7.31 (m, 1H), 7.28 - 7.23 (m, 1H), 7.16 (dd, J = 2.4, 8.9 Hz, 1H), 5.81 (s, 2H), 5.41 - 5.19 (m, 5H), 4.28 (dd, J = 4.4, 11.9 Hz, 2H), 4.11 (dd, J = 5.9, 12.0 Hz, 2H), 4.07 - 4.00 (m, 5H), 3.26 - 3.19 (m, 2H), 2.57 (s, 3H), 2.51 (s, 2H), 2.43 (s, 2H), 2.28 (t, J = 7.6 Hz, 4H), 2.05 - 1.96 (m, 8H), 1.65 - 1.53 (m, 4H), 1.38 - 1.21 (m, 40H), 0.91 - 0.85 (m, 6H), 0.56 (br d, J = 1.8 Hz, 4H). ^{13}C NMR (100 MHz, CDCl_3): δ 173.3, 172.9, 171.2, 170.9, 158.3, 153.3, 133.5, 133.2, 130.21, 130.16, 129.9, 129.3, 127.8, 127.3, 123.3, 118.7, 102.6, 80.7, 69.3, 62.1, 55.7, 45.1, 40.9, 40.7, 34.1, 32.8, 32.0, 29.91, 29.85, 29.7, 29.5, 29.31, 29.26, 29.23, 27.4, 27.3, 27.1, 25.0, 22.8, 14.3, 14.2, 12.4. UPLC-MS: (XB BEH300 C4 20-95%): R_t = 7.20 minutes, 99.8% (UV), 100% (ELSD); MS(ESIpos): 1078.5 $[\text{M}+\text{NH}_4]^+$.

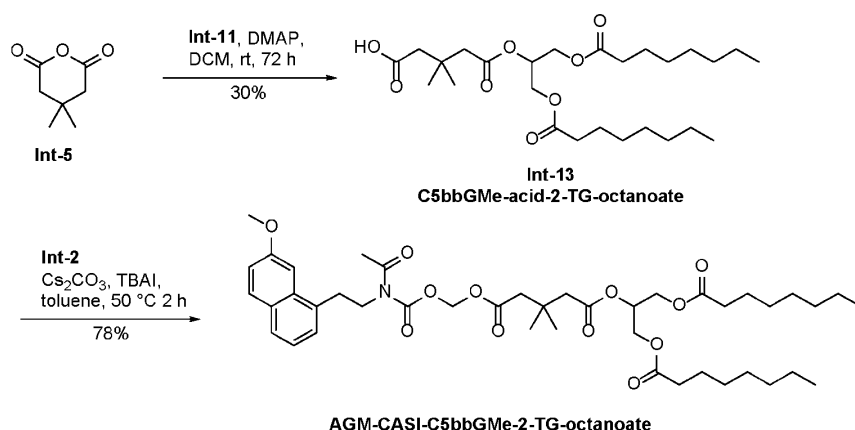
AGM-CASI-C5bcPr-2-TG-Octanoate (II-2b)

[0092] *Synthesis of Int-12.* DMAP (1.36 g, 11.1 mmol) was added to a solution of 6-oxaspiro[2.5]octane-5,7-dione (**Int-9**; 1.53 g, 11.0 mmol) and **Int-11** (2.51 g, 7.30 mmol) in DCM (50 mL). **Int-11** can be synthesized as described in WO 2021/159021 (see paragraphs 545 to 547). The mixture was stirred at RT for 40 hours and concentrated to afford crude **Int-12**. Crude product was purified by normal phase purification (Biotage Isolera, 120 g SiliaSep Cartridge), using a 0-40% ethyl acetate in heptane eluent over 12 CVs to afford pure **Int-12** (1.10 g, 31.1% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 5.27 (quin, *J* = 5.0 Hz, 1H), 4.37 - 4.25 (m, 2H), 4.14 (dd, *J* = 5.9, 11.9 Hz, 2H), 2.51 - 2.40 (m, 4H), 2.31 (t, *J* = 7.5 Hz, 4H), 1.67 - 1.55 (m, 4H), 1.34 - 1.21 (m, 16H), 0.90 - 0.83 (m, 6H), 0.57 (s, 4H). Expected 44H, observed 43H. Exchangeable CO₂H proton not observed. ¹³C NMR (101 MHz, CDCl₃): δ 173.5, 171.5, 171.4, 69.3, 62.2, 41.0, 40.9, 40.8, 34.2, 31.8, 29.2, 29.0, 25.0, 22.7, 14.2, 12.4. UPLC-MS: (XB BEH 300 C4 20-95%): R_t = 3.35 minutes, 92.4% (UV), 100.0% (ELSD); MS(ESIpos): *m/z* = 502.7 [M+H]⁺.

[0093] *Synthesis of AGM-CASI-C5bcPr-2-TG-Octanoate (II-2b).* Cs₂CO₃ (4.03 g, 12.4 mmol) and TBAI (763 mg, 2.07 mmol) were added to a solution of **Int-2** (1.39 g, 4.13 mmol) and **Int-12** (2.00 g, 4.13 mmol) in toluene (40 mL) at RT. The reaction was heated to 50 °C and stirred for 2 hours. The mixture was then cooled, diluted with ethyl acetate (200 mL), and washed with water (200 mL) and brine (200 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated to afford crude **AGM-CASI-C5bcPr-2-TG-Octanoate (II-2b)** as a yellow oil.

Crude product was purified by normal phase purification (Biotage Isolera, 80 g SiliaSep cartridge), using a 0-25% 1:1 DCM/ethyl acetate in heptane eluent over 20 CVs to afford pure **AGM-CASI-C5bcPr-2-TG-Octanoate (II-2b)** (1.85 g, 57.3% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 7.74 (d, *J* = 8.9 Hz, 1H), 7.71 - 7.57 (m, 2H), 7.39 - 7.30 (m, 1H), 7.30 - 7.23 (m, 1H), 7.15 (dd, *J* = 2.3, 8.9 Hz, 1H), 5.82 (s, 2H), 5.23 (quin, *J* = 5.0 Hz, 1H), 4.29 (dd, *J* = 4.3, 11.9 Hz, 2H), 4.11 (dd, *J* = 5.9, 12.0 Hz, 2H), 4.07 - 3.94 (m, 5H), 3.36 - 3.10 (m, 2H), 2.57 (s, 3H), 2.51 (s, 2H), 2.43 (s, 2H), 2.29 (t, *J* = 7.6 Hz, 4H), 1.65 - 1.54 (m, 4H), 1.35 - 1.21 (m, 16H), 0.87 (t, *J* = 6.7 Hz, 6H), 0.56 (br d, *J* = 2.4 Hz, 4H). ¹³C NMR (101 MHz, CDCl₃): δ 173.4, 172.9, 171.2, 170.8, 158.2, 153.3, 133.4, 133.2, 130.2, 129.2, 127.8, 127.3, 123.3, 118.7, 102.5, 80.6, 69.3, 62.0, 55.7, 45.1, 40.9, 40.6, 34.1, 32.8, 31.7, 29.2, 29.1, 29.0, 27.0, 24.9, 22.7, 14.18, 14.15, 12.3. UPLC-MS: (XB BEH300 C4 20-95%): *R*_t = 5.51 minutes, 99.9% (UV), 100% (ELSD). MS (ESIpos): *m/z* = 802.01 [M+NH₄]⁺.

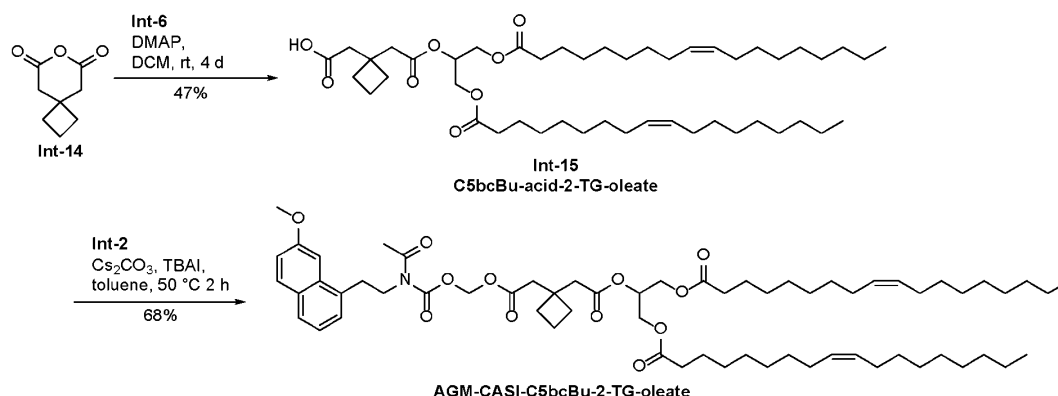
AGM-CASI-C5bbGMe-2-TG-Octanoate (II-1b)



[0094] *Synthesis of Int-13.* DMAP (1.19 g, 9.71 mmol) was added to a solution of 3,3-dimethylglutaric anhydride (**Int-5**; 1.38 g, 9.71 mmol) and **Int-11** (2.23 g, 6.47 mmol) in DCM (40 mL). The mixture was stirred for 3 days at RT, then concentrated to afford crude **Int-13** as an oil. Crude product was purified by normal phase purification (Biotage Isolera, 120 g, SiliaSep cartridge) using a 0-20% ethyl acetate in heptane eluent over 14 CVs to afford pure **Int-13** (951 mg, 30.2% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 5.31 - 5.25 (m, 1H), 4.29 (dd, *J* = 4.2, 12.0 Hz, 2H), 4.14 (dd, *J* = 6.1, 12.0 Hz, 2H), 2.47 (s, 2H), 2.46 (s, 2H), 2.30 (t, *J* =

7.6 Hz, 4H), 1.65 - 1.54 (m, 4H), 1.35 - 1.21 (m, 16H), 1.14 (s, 6H), 0.89 - 0.84 (m, 6H); Exchangeable CO₂H proton not observed. By ¹H NMR, compound contains 20.2% (w/w%) 3,3-dimethylglutaric anhydride and 1.7% (w/w) DCM. UPLC-MS: (XB BEH300 C4 20-95%): R_t = 3.58 minutes, 97.3% (UV), 100.0% (ELSD). MS (ESIpos): m/z = 504.7 [M+NH₄]⁺; MS (ESI_{neg}): m/z = 485.7 [M-H]⁻.

[0095] *Synthesis of AGM-CASI-C5bbGMe-2-TG-Octanoate (II-1b)*. Cs₂CO₃ (1.52 g, 4.65 mmol) and TBAI (287 mg, 776 μmol) was added to a solution of **Int-2** (521 mg, 1.55 mmol) and **Int-13** (950 mg, 1.55 mmol) in toluene (18 mL) at RT. The mixture was heated to 50 °C and stirred for 2 hours. The reaction mixture was cooled, diluted with ethyl acetate (200 mL), and washed with water (200 mL) and brine (200 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated to give crude **AGM-CASI-C5bbGMe-2-TG-Octanoate (II-1b)** as a yellow oil. The crude product was purified by normal phase purification (Biotage Isolera, 80 g SiliaSep Cartridge) using a 0-20% ethyl acetate in heptane eluent over 16 CVs to afford pure **AGM-CASI-C5bbGMe-2-TG-Octanoate (II-1b)** (944 mg, 77.5% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 7.74 (d, *J* = 8.9 Hz, 1H), 7.70 - 7.54 (m, 2H), 7.39 - 7.30 (m, 1H), 7.29 - 7.21 (m, 1H), 7.15 (dd, *J* = 2.4, 9.0 Hz, 1H), 5.80 (s, 2H), 5.29 - 5.17 (m, 1H), 4.26 (dd, *J* = 4.3, 12.0 Hz, 2H), 4.11 (dd, *J* = 6.0, 11.9 Hz, 2H), 4.07 - 3.96 (m, 5H), 3.24 - 3.19 (m, 2H), 2.57 (s, 3H), 2.53 (s, 2H), 2.46 (s, 2H), 2.28 (t, *J* = 7.6 Hz, 4H), 1.62 - 1.53 (m, 4H), 1.32 - 1.20 (m, 16H), 1.12 (s, 6H), 0.90 - 0.84 (m, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 173.4, 172.9, 170.8, 170.4, 158.2, 153.3, 133.4, 133.2, 130.2, 129.2, 127.8, 127.3, 123.3, 118.7, 102.5, 80.5, 69.1, 62.1, 55.7, 45.1, 44.9, 44.4, 34.1, 32.8, 32.7, 31.7, 29.1, 29.0, 27.6, 27.0, 24.9, 22.7, 14.2. UPLC-MS: (XB BEH 300 C4 20-95%): R_t = 5.62 minutes, 99.8% (UV), 100.0% (ELSD). MS (ESIpos): m/z = 804.0 [M+NH₄]⁺.

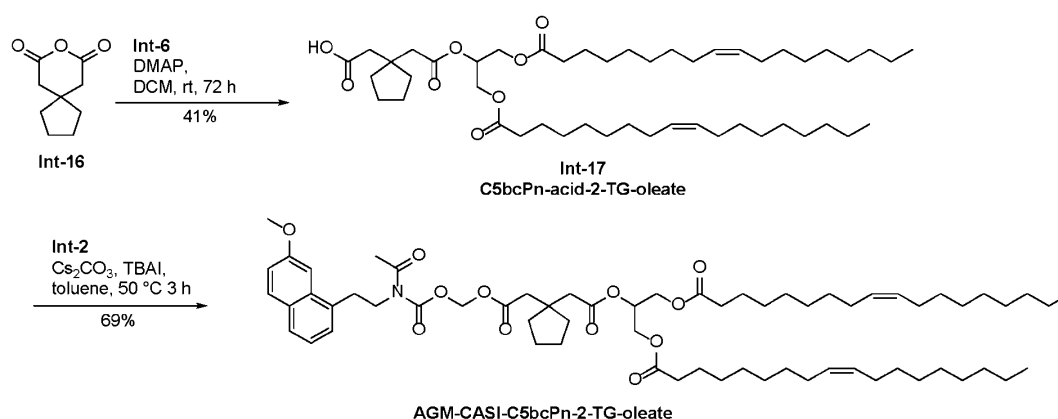
AGM-CASI-C5bcBu-2-TG-Oleate (II-4a)

[0096] *Synthesis of Int-15.* To a solution of 7-oxaspiro[3.5]nonane-6,8-dione (**Int-14**, 374 mg, 2.43 mmol) and **Int-6** (1.00 g, 1.61 mmol) in DCM (20 mL) was added DMAP (296 mg, 2.42 mmol). The mixture was then allowed to stir at room temperature for 4 days. The mixture was diluted with DCM (100 mL) and washed with ammonium chloride (100 mL), water (100 mL) and brine (100 mL). The organic layer was dried over sodium sulfate, filtered, and the filtrate concentrated to give a colorless oil. The crude material was purified by normal phase purification (Biotage Isolera, 80 g SiliCycle cartridge; eluent 0-20% ethyl acetate in heptane over 16 CVs) to give **Int-15** (619 mg, 46.7% yield) as a colorless oil. The material contained 5.61% (w/w%) 7-oxaspiro[3.5]nonane-6,8-dione. ¹H NMR (400 MHz, CDCl₃): δ 5.39 - 5.24 (m, 5H), 4.30 (dd, J = 4.2, 12.0 Hz, 2H), 4.13 (dd, J = 6.0, 12.0 Hz, 2H), 2.71 (s, 4H), 2.30 (t, J = 7.5 Hz, 4H), 2.08 - 1.88 (m, 14H), 1.65 - 1.55 (m, 4H), 1.27 (m, 40H), 0.90 - 0.84 (m, 6H); Exchangeable CO₂H proton not observed. UPLC4-MS: (XB BEH 300 C4 20-95%): R_t = 6.57 minutes, 90.0% (UV), 100% (ELSD). MS (ESIpos): m/z = 793.2 [M+NH₄]⁺.

[0097] *Synthesis of AGM-CASI-C5bcBu-2-TG-Oleate (II-4a).* To a solution of **Int-2** (123 mg, 366 μmol) and **Int-15** (300 mg, 365 μmol) in toluene (6 mL), cesium carbonate (357 mg, 1.10 mmol) and TBAI (68.0 mg, 184 μmol) were added at room temperature. The reaction mixture was heated to 50 °C and was stirred for 2 hours. The reaction mixture was diluted with ethyl acetate (50 mL) washed with water (50 mL) followed by a wash with brine (50 mL). The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford the crude

material as a yellow oil. The material was purified by normal phase purification (Biotage Isolera, 40 g SiliaSep cartridge; eluent 0-20% ethyl acetate in heptane over 24 CV's) to afford **AGM-CASI-C5bcBu-2-TG-Oleate (II-4a)** (268 mg, 68.4% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 7.74 (d, J = 8.9 Hz, 1H), 7.70 - 7.58 (m, 2H), 7.37 - 7.29 (m, 1H), 7.29 - 7.22 (m, 1H), 7.15 (dd, J = 2.3, 8.9 Hz, 1H), 5.80 (s, 2H), 5.46 - 5.27 (m, 4H), 5.26 - 5.16 (m, 1H), 4.26 (dd, J = 4.3, 12.0 Hz, 2H), 4.09 (dd, J = 6.0, 11.9 Hz, 2H), 4.06 - 3.95 (m, 5H), 3.25 - 3.18 (m, 2H), 2.77 (s, 2H), 2.70 (s, 2H), 2.57 (s, 3H), 2.28 (t, J = 7.6 Hz, 4H), 2.09 - 1.83 (m, 14H), 1.65 - 1.53 (m, 4H), 1.37 - 1.17 (m, 40H), 0.91 - 0.83 (m, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 173.4, 173.0, 170.8, 170.5, 158.2, 153.3, 133.4, 133.2, 130.20, 130.15, 129.8, 129.3, 127.8, 127.3, 123.3, 118.7, 102.5, 80.5, 69.1, 62.1, 55.7, 45.1, 42.4, 42.1, 38.2, 34.1, 32.8, 32.2, 32.0, 29.9, 29.8, 29.7, 29.5, 29.32, 29.26, 29.22, 27.4, 27.3, 27.1, 24.9, 22.8, 15.5, 14.3. UPLC4-MS: (XB BEH300 C4 20-95%): R_t = 7.35 minutes, 99.5% (UV), 100% (ELSD). MS (ESIpos): m/z = 1092.4 [M+NH₄]⁺.

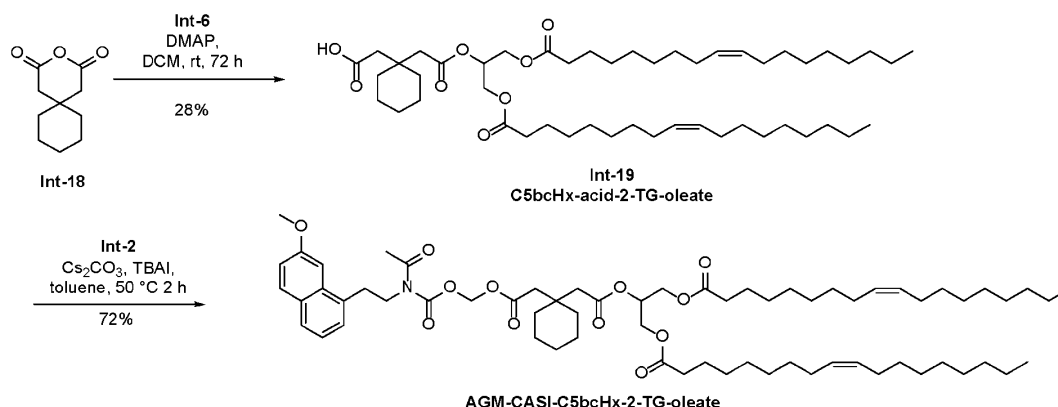
AGM-CASI-C5bcPn-2-TG-Oleate (II-5a)



[0098] *Synthesis of Int-17.* To a solution of 8-oxaspiro[4.5]decane-7,9-dione (**Int-16**, 408 mg, 2.43 mmol) and Int-6 (1.00 g, 1.61 mmol) in DCM (20 mL) was added DMAP (296 mg, 2.42 mmol). The mixture was then allowed to stir at room temperature for 72 hours. The mixture was diluted with DCM (100 mL) and washed with ammonium chloride (100 mL) followed by a wash with water (100 mL) and then with brine (100 mL). The organic layer was dried over sodium sulfate, filtered, and the filtrate concentrated to give a colorless oil. The material was purified by

normal phase purification (Biotage Isolera, 80 g SiliCycle cartridge ; eluent 0-20% ethyl acetate in heptane over 16 CV's) to afford **Int-17** (667 mg, 41.2% yield) as a colorless oil. ^1H NMR indicates the material contains 21.3% (w/w%) 8-oxaspiro[4.5]decane-7,9-dione. ^1H NMR (400 MHz, CDCl_3): δ 5.40 - 5.24 (m, 5H), 4.29 (dd, J = 4.2, 11.9 Hz, 2H), 4.13 (dd, J = 6.1, 11.9 Hz, 2H), 2.58 (s, 4H), 2.30 (t, J = 7.6 Hz, 4H), 2.00 (q, J = 6.4 Hz, 8H), 1.76 (td, J = 3.6, 7.2 Hz, 4H), 1.70 - 1.52 (m, 8H), 1.27 (m, 40H), 0.91 - 0.83 (m, 6H); Exchangeable CO_2H proton not observed. UPLC4-MS: (XB BEH300 C4 20-95%): R_t = 6.71 minutes, 71.0% (UV), 100% (ELSD). MS (ESIpos): m/z = $[\text{M}+\text{NH}_4]^+$ 807.1.

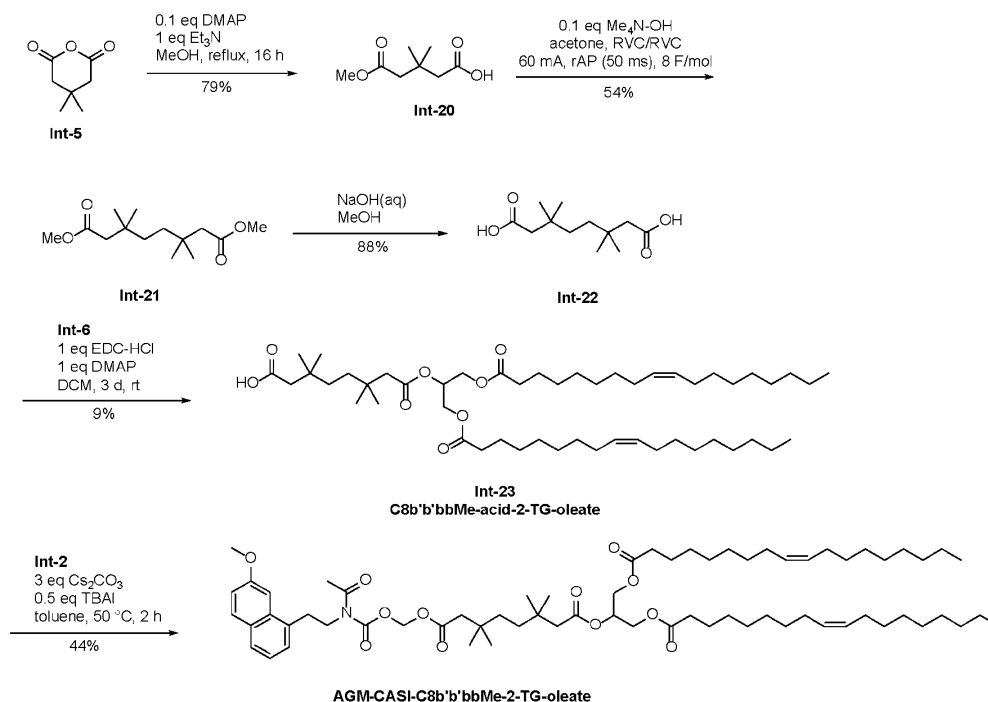
[0099] *Synthesis of AGM-CASI-C5bcPn-2-TG-Oleate (II-5a)*. To a solution of **Int-2** (100 mg, 298 μmol) and **Int-17** (300 mg, 299 μmol) in toluene (6 mL), cesium carbonate (293 mg, 899 μmol) and TBAI (56.0 mg, 152 μmol) were added at room temperature. The reaction mixture was heated to 50 $^\circ\text{C}$ and stirred for 3 hours. The reaction mixture was cooled, diluted with ethyl acetate (50 mL) and washed with water (50 mL) and brine (50 mL). The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford the crude material as a yellow oil. The crude product was purified by normal phase purification (Biotage Isolera, 40 g SiliaSep cartridge; eluent 0-20% ethyl acetate in heptane over 24 CVs) to afford **AGM-CASI-C5bcPn-2-TG-Oleate (II-5a)** (226 mg, 69.3% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 7.74 (d, J = 8.9 Hz, 1H), 7.70 - 7.60 (m, 2H), 7.37 - 7.29 (m, 1H), 7.28 - 7.22 (m, 1H), 7.15 (dd, J = 2.4, 8.9 Hz, 1H), 5.80 (s, 2H), 5.56 - 5.26 (m, 4H), 5.25 - 5.17 (m, 1H), 4.25 (dd, J = 4.3, 11.9 Hz, 2H), 4.10 (dd, J = 6.0, 11.9 Hz, 2H), 4.06 - 3.95 (m, 5H), 3.25 - 3.18 (m, 2H), 2.65 (s, 2H), 2.57 (s, 5H), 2.28 (t, J = 7.6 Hz, 4H), 2.00 (q, J = 6.5 Hz, 8H), 1.69 - 1.51 (m, 12H), 1.38 - 1.18 (m, 40H), 0.87 (t, J = 6.4 Hz, 6H). ^{13}C NMR (101 MHz, CDCl_3): δ 173.4, 173.0, 171.2, 170.8, 158.2, 153.3, 133.4, 133.2, 130.20, 130.15, 129.8, 129.3, 127.8, 127.3, 123.3, 118.7, 102.5, 80.5, 69.0, 62.1, 55.7, 45.1, 43.0, 41.9, 41.6, 38.1, 34.1, 32.8, 32.0, 29.90, 29.85, 29.7, 29.5, 29.33, 29.26, 29.23, 27.4, 27.3, 27.1, 24.9, 24.1, 22.8, 14.3. UPLC4-MS: (XB BEH300 C4 20-95%): R_t = 7.39 minutes, 96.6% (UV), 99.9% (ELSD); MS (ESIpos): m/z = 1106.3 $[\text{M}+\text{NH}_4]^+$.

AGM-CASI-C5bcHx-2-TG-Oleate (II-6a)

[0100] *Synthesis of Int-19.* To a solution of 3-oxaspiro[5.5]undecane-2,4-dione (**Int-18**, 442 mg, 2.43 mmol) and **Int-6** (1.00 g, 1.61 mmol) in DCM (20 mL) was added DMAP (296 mg, 2.42 mmol). The mixture was then allowed to stir at room temperature for 72 hours. The mixture was diluted with DCM (100 mL) and washed with ammonium chloride (100 mL), water (100 mL) and brine (100 mL). The organic layer was dried over sodium sulfate, filtered, and the filtrate concentrated to give a colorless oil. The crude product was purified by normal phase purification (Biotage Isolera, 80 g SiliCycle cartridge; eluent 0-20% ethyl acetate in heptane over 16 CVs) to afford **Int-19** (356 mg, 28% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 5.39 - 5.24 (m, 5H), 4.28 (dd, J = 4.2, 11.9 Hz, 2H), 4.13 (dd, J = 6.1, 11.9 Hz, 2H), 2.59 (s, 2H), 2.57 (s, 2H), 2.30 (t, J = 7.6 Hz, 4H), 2.05 - 1.95 (m, 8H), 1.60 (br t, J = 7.0 Hz, 4H), 1.54 - 1.39 (m, 10H), 1.35 - 1.23 (m, 40H), 0.90 - 0.84 (m, 6H). Exchangeable CO₂H proton not observed. ¹³C NMR (100 MHz, CDCl₃): δ 177.1, 173.4, 171.6, 130.1, 129.8, 69.1, 62.2, 41.4, 41.2, 35.8, 35.5, 34.1, 32.0, 29.9, 29.8, 29.7, 29.6, 29.5, 29.32, 29.25, 29.22, 27.34, 27.29, 25.8, 24.9, 22.8, 21.51, 21.45, 14.3. UPLC4-MS: (XB BEH 300 C4 20-95%): R_t = 6.80 minutes, 96.9% (UV), 99.8% (ELSD). MS (ESIpos): m/z = [M+NH₄]⁺ 821.2.

[0101] *Synthesis of AGM-CASI-C5bcHx-2-TG-Oleate (II-6a).* To a solution of **Int-2** (140 mg, 415 μmol) and **Int-19** (335 mg, 417 μmol) in toluene (6 mL), cesium carbonate (408 mg, 1.25 mmol) and TBAI (78.0 mg, 211 μmol) were added at room temperature. The reaction mixture was heated to 50 °C and was stirred for 2 hours. The reaction mixture was diluted with ethyl

acetate (50 mL) and washed with water (50 mL) and brine (50 mL). The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford the crude material as a yellow oil. The crude product was purified by normal phase purification (Biotage Isolera, 40 g SiliaSep cartridge; eluent 0-20% ethyl acetate in heptane over 24 CVs) to afford **AGM-CASI-C5bcHx-2-TG-Oleate (II-6a)** (332 mg, 72.2% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 7.74 (d, J = 8.9 Hz, 1H), 7.71 – 7.61 (m, 2H), 7.36 – 7.30 (m, 1H), 7.30 – 7.22 (m, 1H), 7.15 (dd, J = 2.4, 8.9 Hz, 1H), 5.81 (s, 2H), 5.45 – 5.26 (m, 4H), 5.26 – 5.13 (m, 1H), 4.24 (dd, J = 4.3, 12.0 Hz, 2H), 4.10 (dd, J = 6.0, 12.0 Hz, 2H), 4.07 – 3.94 (m, 5H), 3.29 – 3.12 (m, 2H), 2.64 (s, 2H), 2.58 (s, 2H), 2.57 (s, 3H), 2.27 (t, J = 7.6 Hz, 4H), 2.10 – 1.89 (m, 8H), 1.62 – 1.55 (m, 4H), 1.52 – 1.36 (m, 10H), 1.27 (br d, J = 7.5 Hz, 40H), 0.87 (t, J = 6.8 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 173.4, 173.0, 171.0, 170.6, 158.2, 153.3, 133.5, 133.2, 130.20, 130.16, 129.9, 129.3, 127.8, 127.3, 123.3, 118.7, 102.5, 80.5, 69.0, 62.2, 55.8, 45.1, 35.8, 35.5, 34.1, 32.8, 32.1, 29.91, 29.86, 29.7, 29.5, 29.34, 29.27, 29.24, 27.4, 27.3, 27.1, 25.8, 24.9, 22.8, 21.5, 14.3. UPLC4-MS: (XB BEH300 C4 20-95%): R_t = 7.44 minutes, 91.7% (UV), 100% (ELSD). MS (ESIpos): m/z = 1120.4 [M+NH₄]⁺.

AGM-CASI-C8b'b'bbMe-2-TG-oleate (III-1a)

[0102] Synthesis of Int-20. To a solution of 3,3-dimethylglutaric anhydride (**Int-5**, 2.00 g, 14.1 mmol) in methanol (25 mL) was added triethylamine (1.42 g, 14.1 mmol, 1.96 mL) and DMAP (172 mg, 1.41 mmol). The mixture was heated at reflux for 16 hours. The mixture was concentrated to remove methanol, then diluted with ethyl acetate (50 mL), and washed with 10% (w/v) aqueous citric acid solution (50 mL), and water (2 x 50 mL). The organic layer was dried over sodium sulfate, filtered, and the filtrate concentrated to afford **Int-20** (2.02 g, 78.7% yield) as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 3.67 (s, 3H), 2.47 (s, 2H), 2.45 (s, 2H), 1.14 (s, 6H). Contains 4.5% w/w ethyl acetate. ¹³C NMR (101 MHz, CDCl₃): δ 177.1, 172.8, 51.6, 45.03, 44.95, 32.7, 27.9.

[0103] Synthesis of Int-21. To a 20 mL ElectraSyn vial equipped with a stirrer bar was added **Int-20** (1.05 g, 6.00 mmol), tetramethylammonium hydroxide pentahydrate (109 mg, 600 μmol), and acetone (14 mL). The vial was then equipped with two RVC electrodes and sealed. The mixture was then sealed and electrolyzed under rAP conditions (parameters: constant current: 60

mA; Alternating frequency: 50 ms (10 Hz), amount of charge 8 F/mol) for 48 hours. The mixture was diluted with ethyl acetate (25 mL), and the RVC electrodes were rinsed with additional ethyl acetate. The mixture was washed with water (20 mL) and brine (20 mL). The organic layer was dried over sodium sulfate and filtered to afford **Int-21** (441 mg, 54.1% yield) as a brown oil. ^1H NMR (400 MHz, CDCl_3): δ 3.64 (s, 6H), 2.19 (s, 4H), 1.28 (s, 4H), 0.97 (s, 12H).

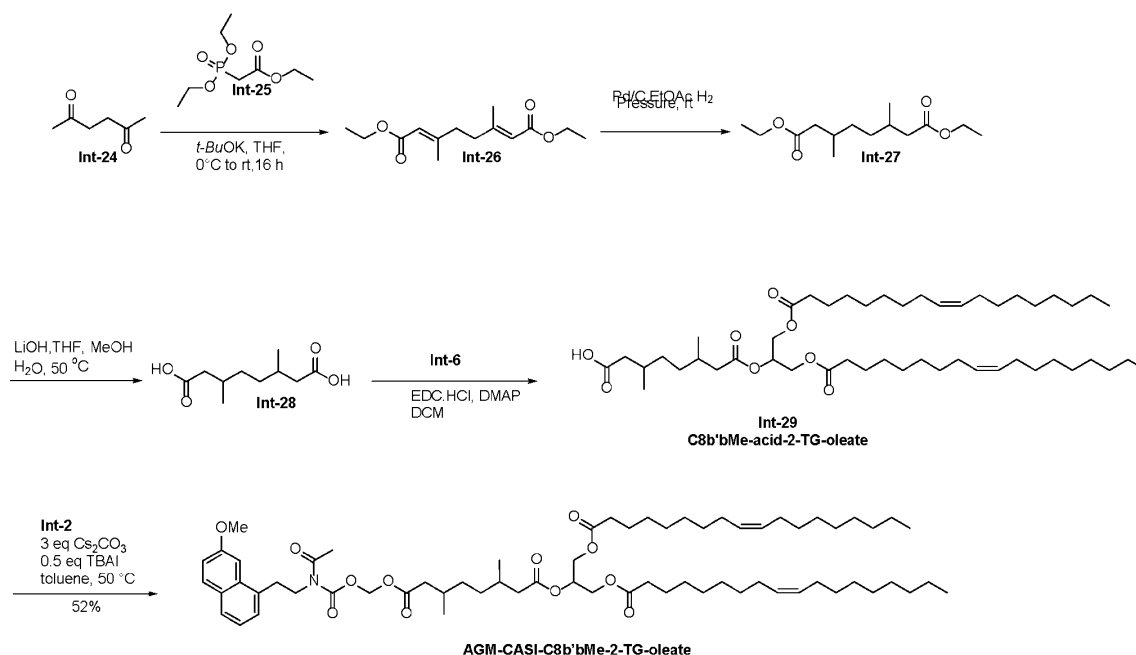
[0104] Synthesis of Int-22. To a solution of **Int-21** (574 mg, 2.22 mmol) in methanol (10 mL) was added sodium hydroxide (aqueous solution) (2 M, 3.33 mL) at room temperature. The mixture was stirred for 16 hours at room temperature. The mixture was concentrated to remove methanol, diluted with water (25 mL), and the basic aqueous mixture washed with DCM (25 mL). The basic aqueous layer was acidified to pH 1 with 2M hydrochloric acid and extracted with ethyl acetate (2 x 20 mL). The combined organic layers were dried over sodium sulfate, filtered, and the filtrate concentrated to afford **Int-22** (450 mg, 88.0% yield) as a beige solid. ^1H NMR (400 MHz, CDCl_3): δ 11.88 (s, 2H), 2.06 (s, 4H), 1.25 (s, 4H), 0.93 (s, 12H). UPLC2-MS: (CSH-C18 Short Acid 2-95%) R_t = 0.79 minutes (98.9%), MS (ESI^{neg}): m/z = [M-H]⁻ 229.2.

[0105] Synthesis of Int-23. To a stirring solution of **Int-22** (450 mg, 1.95 mmol) and **Int-6** (1.21 g, 1.95 mmol) in DCM (20 mL) was added EDC-HCl (375 mg, 1.95 mmol) and DMAP (239 mg, 1.95 mmol). The mixture was stirred at room temperature for 72 hours. The reaction mixture was concentrated. The material was purified by normal phase chromatography (Biotage Isolera, 40 g Biotage Sfar cartridge; eluent 0-20% acetone in heptane over 20 CV's) to afford **Int-23** (155 mg, 8.8% yield) as a colorless oil. UPLC4-MS (XB BEH300 C4 20-95%): R_t = 7.36 minutes, 78.6% (UV), 98.8% (ELSD); MS(ESI^{pos}): m/z = 851.3 [M+NH₄]⁺; MS(ESI^{neg}): m/z = 832.3 [M-H]⁻. ^1H NMR (400 MHz, CDCl_3): δ 5.39 - 5.31 (m, 4H), 5.29 - 5.22 (m, 1H), 4.31 - 4.24 (m, 2H), 4.15 (dd, J = 5.9, 11.9 Hz, 2H), 2.31 (t, J = 7.6 Hz, 4H), 2.23 (s, 2H), 2.22 (s, 2H), 2.04 - 1.97 (m, 8H), 1.64 - 1.57 (m, 54H), 1.35 - 1.24 (m, 44H), 1.02 (s, 6H), 0.98 (s, 6H), 0.90 - 0.85 (m, 6H).

[0106] Synthesis of AGM-CASI-C8b'b'bbMe-2-TG-oleate (III-1a). To a solution of **Int-2** (62.5 mg, 186 μmol) and **Int-23** (155 mg, 186 μmol) in toluene (4 mL) was added cesium carbonate (182 mg, 558 μmol) and TBAI (34.4 mg, 93.1 μmol). The mixture was stirred at 50 °C for 2 hours. The mixture was cooled to room temperature, diluted with ethyl acetate (25 mL) and washed with water (25 mL) and brine (25 mL). The organic layer was dried over sodium sulfate, filtered, and the filtrate concentrated to give a yellow oil. The material was purified by normal phase

chromatography (Biotage Isolera, 25 g Biotage Sfar cartridge; eluent 0-30% ethyl acetate in heptane over 32 CV's) to afford **AGM-CASI-C8b'bMe-2-TG-oleate (III-1a)** (96 mg, 43.7% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 7.74 (d, J = 8.9 Hz, 1H), 7.69 - 7.63 (m, 2H), 7.35 - 7.30 (m, 1H), 7.28 - 7.23 (m, 1H), 7.16 (dd, J = 2.3, 8.9 Hz, 1H), 5.80 (s, 2H), 5.41 - 5.21 (m, 5H), 4.27 (dd, J = 4.3, 11.9 Hz, 2H), 4.13 (dd, J = 6.0, 11.9 Hz, 2H), 4.08 - 4.00 (m, 5H), 3.26 - 3.18 (m, 2H), 2.57 (s, 3H), 2.32 - 2.26 (m, 6H), 2.20 (s, 2H), 2.06 - 1.96 (m, 8H), 1.65 - 1.55 (m, 4H), 1.36 - 1.23 (m, 44H), 1.00 (s, 6H), 0.96 (s, 6H), 0.91 - 0.85 (m, 6H). ^{13}C NMR (101 MHz, CDCl_3): δ 173.4, 172.9, 171.3, 170.8, 158.3, 153.4, 133.5, 133.2, 130.21, 130.16, 129.9, 129.3, 127.8, 127.3, 123.3, 118.7, 102.6, 80.6, 68.9, 62.3, 55.7, 45.7, 45.3, 45.1, 36.2, 34.2, 33.3, 33.2, 32.8, 32.0, 29.91, 29.85, 29.7, 29.5, 29.31, 29.26, 29.23, 27.4, 27.31, 27.25, 27.1, 25.0, 22.8, 14.3. UPLC-MS: (XB BEH 300 C4 20-95%): R_t = 7.45 minutes, 96.0% (UV), 99.9% (ELSD); MS(ESIpos): m/z = 1150.6 $[\text{M}+\text{NH}_4]^+$.

AGM-CASI-C8b'bMe-2-TG-oleate



[0107] *Synthesis of Int-26.* Potassium *tert*-butoxide (295 g, 2.628 mol, 3.0 eq) was slowly added at 0-5 $^\circ\text{C}$ under N_2 atmosphere to a stirred solution of **Int-25** (589.25 g, 2.628 mol, 3.0 eq) in THF

(3500 mL, 35V). The reaction was stirred for 30 minutes, followed by the addition of **Int-24** (100 g, 0.8761 mol, 1.0 eq) at 0-5 °C. After stirring for 10-15 minutes, the reaction cooled to RT and stirred for 16 hours. After reaction completion, ice water (2000 mL, 20V) was added into the reaction mixture at 0 °C, stirred for 30 minutes, and extracted with ethyl acetate (2x 2000 mL). The organic layer was separated and concentrated under reduced pressure to obtain 280 g of crude product. Crude product was combined with 285 g of crude product prepared from a subsequent batch and purified by column chromatography using 100-200 mesh silica gel. Desired product eluted at 5-10% ethyl acetate in hexane. Fractions of desired product were concentrated under vacuum to generate pure **Int-26** (300 g, 67.3% yield). ¹H NMR (400 MHz, CDCl₃) δ 5.72 – 5.69 (m, 2H), 4.15 (q, J = 7 Hz, 4H), 2.30 (s, 4H), 2.18 (s, 6H), 1.30 – 1.27 (t, J = 7.2 Hz, 6H).

[0108] *Synthesis of Int-27*. 10% palladium on carbon (30% w/w, 87 g) was added to a solution of **Int-26** (290 g, 1.1402 mol, 1.0 eq) in ethyl acetate (2900 mL, 10V) and flushed with N₂ gas three times. The reaction mixture was stirred at RT for 24 hours under 20 kg hydrogen pressure in an autoclave. Reaction progress was monitored by TLC and ¹H NMR. After completion of the reaction, the hydrogen gas was slowly released and flushed with nitrogen three times. The reaction mixture was filtered through a pad of Celite® and washed with ethyl acetate (2900 mL, 10V). The filtrate was concentrated under reduced pressure to give crude **Int-27** as a colorless oil (300 g, 100% yield). ¹H NMR (400 MHz, CDCl₃) δ 4.16 (m, 4H), 2.32-2.25 (m, 2H), 2.15-2.05 (m, 2H), 1.94-1.93 (m, 2H), 1.28 (m, 10H), 0.90 (d, J = 6.8 Hz, 6H).

[0109] *Synthesis of Int-28*. A solution of **Int-27** (300 g, 1.1611 mol, 1.0 eq) in THF (1800 mL, 6.0V), water (600 mL, 2.0V) MeOH (600 mL, 2.0V), and LiOH.H₂O (292.33 g, 6.967 mol, 6.0 eq) was prepared at RT. The reaction mixture was warmed to 50 °C and stirred for 3 hours. The progress of the reaction was monitored by TLC. After completion, the reaction was cooled to RT, acidified to pH 4-5 by the addition of 1M HCl, and the organic solvent removed under reduced pressure. The crude residue was diluted with water (3000 mL, 10V) and the aqueous phase extracted with ethyl acetate (3 x 3000 mL). The combined organic layer was dried over sodium sulfate and evaporated under pressure to afford crude **Int-28** as a solid. Crude compound was purified by heptane purification by adding 10V of heptane and stirring for 1 hour. After 1 hour, the solid was filtered out and washed with heptane (2V) prior to drying under vacuum to generate pure **Int-28** as a white solid (200 g, 85.47% yield). ¹H NMR (400 MHz, CDCl₃) δ 2.23-2.19 (m,

2H), 2.18-2.16 (m, 2H), 2.04 – 1.95 (m, 2H), 1.77 (m, 2H), 1.31-1.25 (m, 2H), 1.15-1.12 (m, 2H), 0.88 (s, 6H).

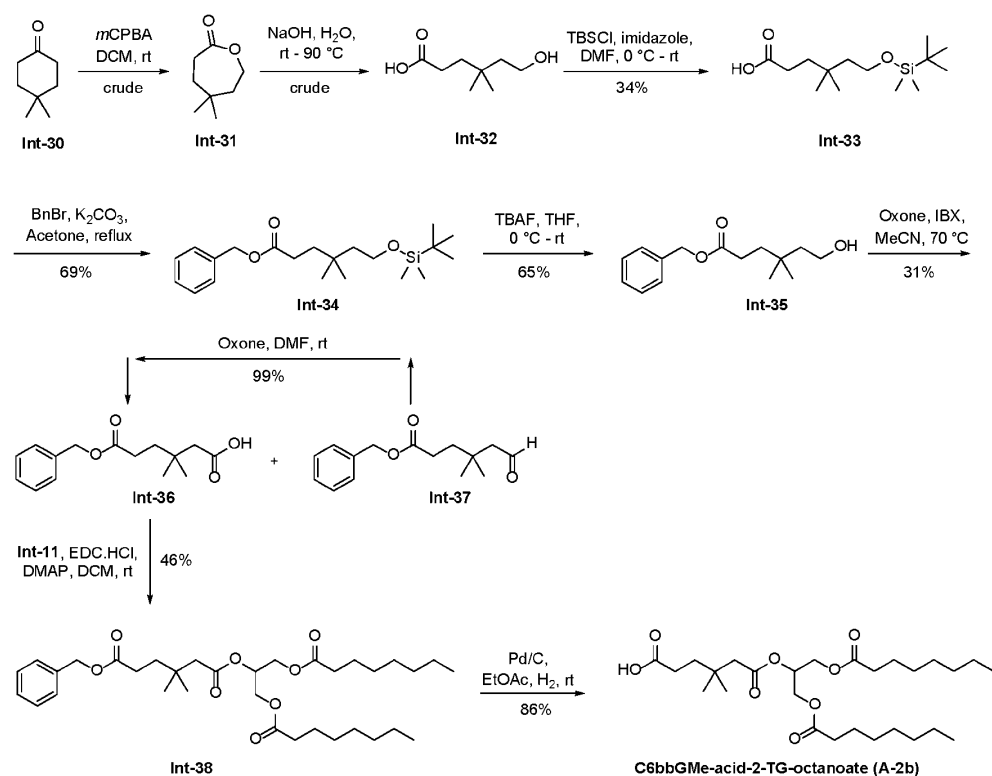
[0110] *Synthesis of Int-29 (C8b'bMe-Acid-2-TG-oleate)*. A solution of diacid **Int-28** (200 g, 0.988 mol, 1.0 eq) and **Int-6** (307 g, 0.4944 mol, 0.5 eq) in DCM (4000 mL, 20V) was prepared. DMAP (60.40 g, 0.4944 mol, 0.5 eq) was added followed by EDC-HCl (132.69 g, 0.6922 mol, 0.7 eq) drop wise at 0 °C. The reaction was stirred at RT for 8 hours. After reaction completion, the mixture was diluted with water (2000 mL, 10V) and stirred for 30 minutes. The aqueous layer was extracted with DCM (2 x 2000 mL) and the combined organic layer was dried over sodium sulfate and evaporated under reduced pressure to afford crude **Int-29** (420 g). Crude material was purified by column chromatography using silica gel (100-200 mesh). Desired product eluted at 5-20% ethyl acetate in hexane. Pure fractions were concentrated under vacuum to afford pure **Int-29** (240 g, 30.15% yield). ¹H NMR (400 MHz, CDCl₃): δ 5.36-5.29 (m, 5H), 4.33 (dd, J = 11.6, 5.6 Hz, 2H), 4.18 (dd, J = 11.9, 6.0 Hz, 2H), 2.40-2.21 (m, 6H), 2.21-2.12 (m, 2H), 2.03-1.95 (m, 10H), 1.62 (m, 4H), 1.31 (m, 44H), 1.00 (m, 6H), 0.88 (m, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 179.0, 173.3, 172.3, 130.0, 129.7, 68.9, 62.1, 41.7, 34.0, 33.9, 31.9, 30.3, 29.8, 29.7, 29.5, 29.4, 29.3, 29.2, 29.1, 27.22, 27.2, 26.9, 24.8, 24.7, 22.7, 19.5, 14.1. LC-MS (ESI, +ve) m/z: 824.37 (M+18) and (ESI, -ve) m/z: 803.85 (M-1).

[0111] *Synthesis of AGM-CASI-C8b'bMe-2-TG-oleate*. To a stirring solution of **Int-29** (145 mg, 180 μmol) in toluene (2 mL) was added Cs₂CO₃ (175 mg, 537 μmol). The mixture was stirred at room temperature for 15 minutes, and **Int-2** (60.0 mg, 179 μmol) and TBAI (33.0 mg, 89.3 μmol) were then added. The suspension was then heated at 50 °C for 3 hours. The reaction mixture was allowed to cool to room temperature. Water (50 mL) was added, and the organics were extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over sodium sulfate and reduced under vacuum to afford a crude residue. The material was purified by normal phase purification (Biotage Isolera, 12 g SiliCycle cartridge; eluent 0-30% over 16 CVs, ethyl acetate in heptane) to afford **AGM-CASI-C8b'bMe-2-TG-oleate** (102 mg, 52%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 7.75 (d, J = 9.4 Hz, 1H), 7.67 (dd, J = 4.5, 10.9 Hz, 2H), 7.33 (d, J = 6.5 Hz, 1H), 7.28-7.23 (m, 1H), 7.16 (dd, J = 2.0, 9.2 Hz, 1H), 5.81 (s, 2H), 5.40-5.22 (m, 5H), 4.29 (dd, J = 4.8, 12.2 Hz, 2H), 4.14 (dd, J = 5.8, 11.9 Hz, 2H), 4.06-4.00 (m, 5H), 3.26-3.19 (m, 2H), 2.57 (s, 3H), 2.46-2.34 (m, 1H), 2.30 (t, J = 7.6 Hz, 5H), 2.26-2.18 (m, 1H), 2.16-2.07 (m, 1H), 2.07-1.84 (m, 10H), 1.67-1.54 (m, 4H), 1.40-1.21 (m, 44H), 0.96-0.85 (m,

12H). ^{13}C NMR (100 MHz, CDCl_3): δ 173.3, 172.9, 172.16, 172.14, 171.69, 171.67, 158.2, 153.3, 133.5, 133.2, 130.2, 130.1, 129.8, 129.3, 127.8, 127.3, 123.3, 118.7, 102.6, 80.7, 69.0, 62.2, 55.7, 45.1, 41.7, 41.5, 41.4, 41.2, 34.1, 34.0, 33.8, 32.8, 32.0, 30.55, 30.43, 30.38, 30.3, 29.88, 29.82, 29.78, 29.74, 29.64, 29.59, 29.48, 29.44, 29.29, 29.23, 29.20, 27.34, 27.29, 27.0, 24.9, 22.8, 19.8, 19.7, 19.6, 19.5, 14.2. UPLC4-MS: (XB BEH 300 C4 20-95%): R_t = 7.42 minutes, 81.30% (UV), 94.0% (ELSD). MS (ESIpos): m/z = 1122.3 $[\text{M}+\text{NH}_4]^+$.

AGM-CASI-C6bbGMe-acid-2-TG-octanoate (II-7b)

Synthesis of C6bbGMe-acid-2-TG-octanoate (A-2b)



[0112] *Synthesis of 5,5-Dimethyloxepan-2-one (Int-31).* To a solution of 4,4-dimethylcyclohexanone (Int-30, 8.90 g, 70.5 mmol) in dichloromethane (250 mL) at ambient temperature, was added *meta*-chloroperoxybenzoic acid (18.3 g, 106 mmol) and the mixture stirred

for 16 hours. The reaction mixture was filtered under vacuum, washing with dichloromethane (3 x 50 mL). The filtrate was washed with a saturated aqueous solution of sodium hydrogen carbonate (3 x 100 mL), dried over magnesium sulfate, filtered, and concentrated at 40 °C to afford the desired product (**Int-31**, 9.59 g, crude) as a white solid. Material used without further purification. MF: C₈H₁₄O₂; MW: 142.20. ¹H NMR (400 MHz, CDCl₃): δ [ppm] = 4.23 - 4.17 (m, 2H), 2.64 - 2.56 (m, 2H), 1.69 - 1.62 (m, 2H), 1.61 - 1.52 (m, 2H), 1.02 (s, 6H). 14 protons expected, 14 observed. Material contaminated with 1.2% w/w mCPBA by ¹H NMR.

[0113] *Synthesis of 6-Hydroxy-4,4-dimethylhexanoic acid (Int-32).* To a solution of 5,5-dimethyloxepan-2-one (**Int-31**, 9.59 g, 64.7 mmol) in water (100 mL) at ambient temperature, was added sodium hydroxide (3.75 g, 93.9 mmol, 1.76 mL) and then stirred at 90 °C for 16 hours. The reaction mixture was cooled to room temperature and the pH was adjusted to pH 3 with 2N HCl (aq) and the product extracted into diethyl ether (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over magnesium sulfate, filtered, and concentrated at 40 °C to afford the desired product (**Int-32**, 8.71 g, crude) as a colorless gum. Material used without further purification. MF C₈H₁₆O₃; MW 160.21. ¹H NMR (400 MHz, CDCl₃): δ [ppm] = 3.72 (t, *J* = 7.5 Hz, 2H), 2.37 - 2.30 (m, 2H), 1.64 - 1.57 (m, 2H), 1.53 (t, *J* = 7.5 Hz, 2H), 0.92 (s, 6H). 16 protons expected, 14 observed. Exchangeable protons not observed.

[0114] *Synthesis of 6-((tert-Butyldimethylsilyl)oxy)-4,4-dimethylhexanoic acid (Int-33).* To a solution of 6-hydroxy-4,4-dimethyl-hexanoic acid (**Int-32**, 8.71 g, 53.3 mmol) in *N,N*-dimethylformamide (80 mL) under an atmosphere of argon at 0 °C, was added imidazole (8.70 g, 128 mmol) and the mixture stirred for 10 minutes. To the mixture was added *tert*-butyl dimethylsilyl chloride (10.4 g, 69.3 mmol), then the mixture was warmed to room temperature and stirred for 2 hours. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (100 mL) and then extracted into ethyl acetate (3 x 50 mL). The combined organic extracts were washed with brine (3 x 100 mL), dried over magnesium sulfate, filtered, and concentrated at 40 °C. Material purified by normal phase chromatography (Biotage Isolera, 40 g SiliaSep cartridge; eluent 0 - 100 % ethyl acetate in heptane over 15 CV) to afford the desired product (**Int-33**, 5.03 g, 34%) as a colorless oil. MF C₁₄H₃₀O₃Si; MW 274.47. ¹H NMR (400 MHz, CDCl₃): δ [ppm] = 3.67 (t, *J* = 7.3 Hz, 2H), 2.36 - 2.30 (m, 2H), 1.63 - 1.55 (m, 2H), 1.47 (t, *J* = 7.3 Hz, 2H), 0.93 - 0.86 (m, 15H), 0.05 (s, 6H). 30 Protons expected, 29 protons observed.

Exchangeable carboxylic acid proton not observed. Product contains residual *tert*-butyldimethylsilanol by ^1H NMR.

[0115] *Synthesis of benzyl 6-((tert-butyldimethylsilyl)oxy)-4,4-dimethylhexanoate (Int-34).* To a solution of 6-[*tert*-butyl(dimethyl)silyl]oxy-4,4-dimethyl-hexanoic acid (**Int-33**, 3.58 g, 12.4 mmol) in acetone (20 mL) at ambient temperature, was added potassium carbonate (2.06 g, 14.9 mmol), followed by benzyl bromide (2.54 g, 14.9 mmol, 1.77 mL) and stirred at 70 °C for 16 hours. The reaction mixture was cooled to room temperature, quenched with a saturated aqueous solution of ammonium chloride (100 mL) and extracted into ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over magnesium sulfate, filtered, and concentrated at 40 °C to afford a crude product. The crude material was purified by normal phase chromatography (Biotage Isolera, 40 g SiliaSep cartridge; eluent 0 - 40 % ethyl acetate in heptane), concentrating fractions at 40 °C to afford the product (**Int-34**, 3.20 g, 69% yield) as a colorless oil, which was contaminated with 4.4% w/w heptane by ^1H NMR. MF $\text{C}_{21}\text{H}_{36}\text{O}_3\text{Si}$, MW 364.59. ^1H NMR (400 MHz, CDCl_3): δ [ppm] = 7.46 - 7.30 (m, 5H), 5.11 (s, 2H), 3.66 (t, J = 7.3 Hz, 2H), 2.37 - 2.31 (m, 2H), 1.63 - 1.56 (m, 2H), 1.46 (t, J = 7.3 Hz, 2H), 0.90 - 0.86 (m, 15H), 0.04 (s, 6H). 36 protons expected, 36 protons observed. ^{13}C NMR (100 MHz, CDCl_3): δ [ppm] = 174.3, 136.2, 128.7, 128.37, 128.33, 66.4, 60.0, 44.0, 37.1, 32.0, 29.8, 27.3, 26.1, 18.4, -5.2. 15 carbon environments expected, 15 observed.

[0116] *Synthesis of benzyl 6-hydroxy-4,4-dimethylhexanoate (Int-35).* To a solution of benzyl 6-[*tert*-butyl(dimethyl)silyl]oxy-4,4-dimethyl-hexanoate (**Int-34**, 3.20 g, 8.60 mmol) in tetrahydrofuran (50 mL) under an atmosphere of argon at 0 °C, was added tetrabutylammonium fluoride solution (1M in THF, 10.3 mmol, 10.3 mL). The reaction mixture was allowed to warm to room temperature and stirred for 5 hours. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (100 mL) and extracted into ethyl acetate (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried over magnesium sulfate, filtered and concentrated at 40 °C to afford a crude oil. The crude material was purified by normal phase chromatography (Biotage Isolera, 40 g SiliaSep cartridge; eluent 0-100% ethyl acetate in heptane), concentrating fractions at 40 °C to afford the product (**Int-35**, 1.40 g, 65% yield) as a colorless oil, which was contaminated with 0.95% w/w heptane by ^1H NMR. MF $\text{C}_{15}\text{H}_{22}\text{O}_3$, MW 250.33. ^1H NMR (400 MHz, CDCl_3): δ [ppm] = 7.39 - 7.30 (m, 5H), 5.11 (s, 2H), 3.73 - 3.66 (m, 2H), 2.38 - 2.31 (m, 2H), 1.64 - 1.56 (m, 2H), 1.51 (t, J = 7.5 Hz, 2H), 0.90 (s, 6H). 22 protons

expected, 21 observed and x1 exchangeable alcohol proton not observed. ^{13}C NMR (100 MHz, CDCl_3): δ [ppm] = 174.2, 136.1, 128.7, 128.40, 128.37, 66.4, 59.7, 44.2, 37.0, 32.1, 29.7, 27.2. 12 carbon environments expected, 12 observed.

[0117] *Synthesis of 6-(benzyloxy)-3,3-dimethyl-6-oxohexanoic acid (Int-36) and benzyl 4,4-dimethyl-6-oxohexanoate (Int-37).* To a solution of benzyl 6-hydroxy-4,4-dimethyl-hexanoate (**Int-35**, 1.40 g, 5.59 mmol) in acetonitrile (50 mL) at ambient temperature, was added OxoneTM (4.47 g, 7.27 mmol) and IBX (1.04 g, 1.68 mmol, 45% purity) and then stirred at 70 °C for 4 hours. The reaction mixture was cooled to room temperature, quenched with 2N HCl (aq) solution (20 mL) and extracted into ethyl acetate (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over magnesium sulfate, filtered, and concentrated at 40 °C to afford a crude product. The crude material was purified by normal phase chromatography (Biotage Isolera, 25 g SiliaSep cartridge; eluent 0-100% ethyl acetate in heptane), concentrating fractions at 40 °C to afford the product (**Int-36**, 0.543 g, 31% yield) as a colorless oil. Benzyl 4,4-dimethyl-6-oxohexanoate (**Int 37**, 0.532 g, 2.14 mmol, 38% yield) was also obtained. MF $\text{C}_{15}\text{H}_{20}\text{O}_4$ MW 264.32. ^1H NMR (400 MHz, CDCl_3): δ [ppm] = 7.39 - 7.30 (m, 5H), 5.12 (s, 2H), 2.41 - 2.35 (m, 2H), 2.23 (s, 2H), 1.78 - 1.72 (m, 2H), 1.05 - 1.02 (m, 6H). 20 protons expected, 19 observed and x1 exchangeable carboxylic acid proton not observed.

[0118] *Synthesis of 6-(Benzyloxy)-3,3-dimethyl-6-oxohexanoic acid (Int-36).* To a solution of benzyl 4,4-dimethyl-6-oxo-hexanoate (**Int-37**, 543 mg, 2.14 mmol) in *N,N*-dimethylformamide (20 mL) at ambient temperature, was added OxoneTM (1.32 g, 2.14 mmol) and stirred for 72 hours. The reaction mixture was quenched with water (100 mL) and extracted into ethyl acetate (3 x 100 mL). The combined organic extracts were washed with brine (3 x 100 mL), dried over MgSO_4 , filtered and concentrated at 40 °C afford the product (**Int-36**, 635 mg, 99% yield) as a yellow oil, which was contaminated with 12% w/w *N,N*-dimethylformamide by ^1H NMR. MF $\text{C}_{15}\text{H}_{20}\text{O}_4$, MW 264.32. ^1H NMR (400 MHz, CDCl_3): δ [ppm] = 7.39 - 7.30 (m, 5H), 5.12 - 5.10 (m, 2H), 2.42 - 2.33 (m, 2H), 2.23 (s, 2H), 1.79 - 1.70 (m, 2H), 1.03 (s, 6H). 20 protons expected, 19 protons observed and x1 exchangeable carboxylic acid proton not observed.

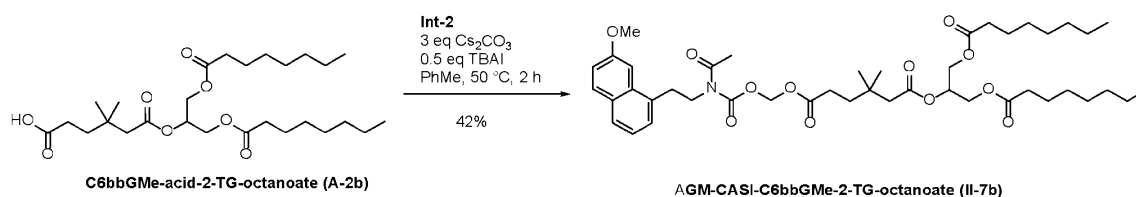
[0119] *Synthesis of 6-benzyl 1-(1,3-bis(octanoyloxy)propan-2-yl) 3,3-dimethylhexanedioate (Int-38).* To a solution of 6-benzyloxy-3,3-dimethyl-6-oxo-hexanoic acid (**Int-36**, 1.10 g, 3.75 mmol) and (2-hydroxy-3-octanoyloxy-propyl) octanoate (**Int-11**, 1.32 g, 3.75 mmol) in dichloromethane

(100 mL) at ambient temperature, was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.43 g, 7.49 mmol) and 4-dimethylaminopyridine (915 mg, 7.49 mmol) and stirred for 72 hours. The reaction mixture was diluted with a saturated aqueous solution of ammonium chloride (50 mL) and extracted into ethyl acetate (3 x 20 mL). The combined organic extracts were washed with brine (100 mL), dried over magnesium sulfate, filtered, and concentrated at 40 °C to afford a crude residue (2.2 g). The crude material was purified by normal phase chromatography (Biotage Isolera, 120 g SiliaSep cartridge; eluent 0-15% ethyl acetate in heptane) to afford the desired product (**Int-38**, 1.06 g, 46% yield) as a colorless oil. MF: C₃₄H₅₄O₈; MW: 590.79. ¹H NMR (400 MHz, CDCl₃): δ [ppm] = 7.40 - 7.30 (m, 5H), 5.27 (tt, *J* = 4.2, 6.0 Hz, 1H), 5.11 (s, 2H), 4.28 (dd, *J* = 11.9, 4.2 Hz, 2H), 4.12 (dd, *J* = 12.0, 6.1 Hz, 2H), 2.41 - 2.33 (m, 2H), 2.29 (t, *J* = 7.6 Hz, 4H), 2.22 (s, 2H), 1.75 - 1.67 (m, 2H), 1.65 - 1.57 (m, 4H), 1.34 - 1.21 (m, 16H), 1.00 (s, 6H), 0.92 - 0.83 (t, *J* = 6.7 Hz, 6H). 54 protons expected, 54 observed. ¹³C NMR (100 MHz, CDCl₃): δ [ppm] = 173.7, 173.4, 171.0, 136.1, 128.7, 128.42, 128.40, 69.1, 66.5, 62.3, 45.7, 36.8, 34.2, 33.1, 31.8, 29.7, 29.2, 29.1, 27.0, 25.0, 22.7, 14.2. 22 carbon environments expected, 22 observed. UPLC4-MS: (XB BEH300 C4 20-95%) R_t = 5.18 min, 97.6% (UV), 99.9% (ELSD), MS (ESIpos): *m/z* = 608.83 [M+NH₄]⁺

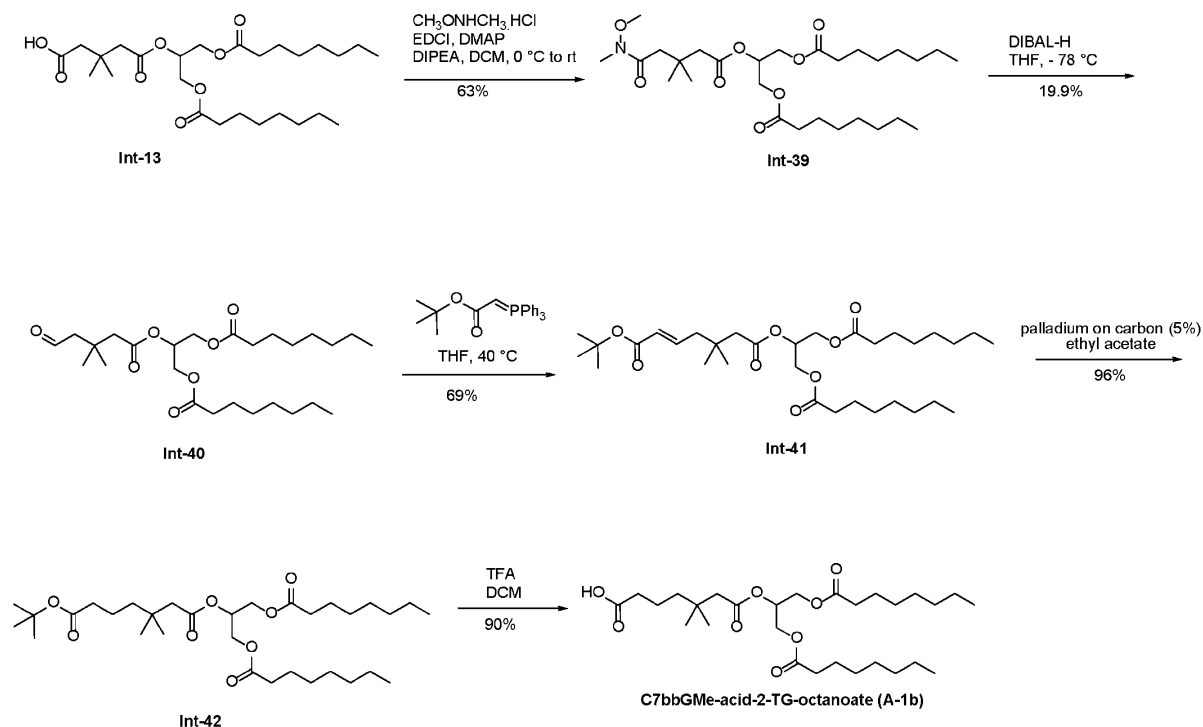
[0120] *Synthesis of 6-((1,3-bis(octanoyloxy)propan-2-yl)oxy)-4,4-dimethyl-6-oxohexanoic acid (A-2b).* To a solution of O6-benzyl O1-[2-octanoyloxy-1-(octanoyloxymethyl) ethyl] 3,3-dimethylhexanedioate (**Int-38**, 1.06 g, 1.70 mmol) in ethyl acetate (10 mL) under an atmosphere of argon, was added palladium on activated charcoal (363 mg, 171 μmol, 5% purity) portion wise and then stirred under a balloon of hydrogen for 20 hours. The reaction mixture was filtered through Celite, washing with ethyl acetate (100 mL). The filtrate was concentrated at 40 °C and then passed through a plug of silica gel, washing with ethyl acetate (100 mL) and the filtrate concentrated at 40 °C to afford the product (**A-2b**, 805 mg, 86% yield) as a colorless oil, which was contaminated with 8.7% w/w heptane by ¹H NMR. MF: C₂₇H₄₈O₈; MW: 500.66. ¹H NMR (400 MHz, CDCl₃): δ [ppm] = 5.30 - 5.25 (m, 1H), 4.30 (dd, *J* = 12.0, 4.2 Hz, 2H), 4.14 (dd, *J* = 12.0, 6.1 Hz, 2H), 2.39 - 2.34 (m, 2H), 2.30 (t, *J* = 7.5 Hz, 4H), 2.23 (s, 2H), 1.76 - 1.66 (m, 2H), 1.65 - 1.55 (m, 4H), 1.34 - 1.22 (m, 16H), 1.02 (s, 6H), 0.92 - 0.83 (t, *J* = 6.6 Hz, 6H). 48 protons expected. 47 protons observed and x1 exchangeable COOH proton not observed. ¹³C NMR (101 MHz, CDCl₃) δ = 178.6, 173.5, 170.9, 69.2, 62.3, 45.6, 36.5, 34.2, 33.1, 32.0, 29.24, 29.20, 29.17, 27.1, 25.0, 22.7, 14.3. 17 Carbon environments expected, 17 observed. UPLC4-MS: (XB BEH300

C4 20 to 95%) $R_t = 3.48$ min, 93.1% (UV), 100% (ELSD), MS (ESIpos): $m/z = 518.72$ $[M+NH_4]^+$.
 UPLC4: (XB C18 4.6 x 150mm x 3.5 μ m, 30 to 100%, 50 min TFA method) $R_t = 16.29$ min, 92.2%
 (total plot), 94.8% (220 nm).

Synthesis of AGM-CASI-C6bbGMe-2-TG-octanoate (II-7b)



[0121] To a solution of C6bbGMe-2-TG-octanoate (8.00 mg, 16.0 μmol) and **Int-2** (5.37 mg, 16.0 μmol) in toluene (1 mL), Cs_2CO_3 (15.6 mg, 47.9 μmol) and TBAI (2.95 mg, 7.99 μmol) were added. The reaction mixture was heated to 50 $^\circ\text{C}$ for 3 hours. The reaction mixture was cooled to room temperature. A saturated solution of NH_4Cl (aq) (20 mL) was added and the mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried over MgSO_4 and concentrated under vacuum to afford a crude product. Material was purified by normal phase chromatography (Biotage Isolera, 12 g SiliCycle cartridge; eluent 0 - 40% ethyl acetate in heptane over 15 CVs) to afford the product (**II-7b**, 5.48 mg, 42.9 % yield) as colorless oil. MF: $\text{C}_{44}\text{H}_{65}\text{O}_{12}\text{N}$ MW: 799.98. UPLC4-MS (XB BEH300 C4 20to95%): $R_t = 5.59$ min., 98.3% (UV), 95.4% (ELSD); MS(ESIpos): $m/z = 817.9$ $[\text{M}+\text{NH}_4]^+$. ^1H NMR (400 MHz, CDCl_3): δ [ppm] = 7.74 (d, $J = 8.9$ Hz, 1H), 7.67 (d, $J = 7.9$ Hz, 1H), 7.64 (d, $J = 2.3$ Hz, 1H), 7.33 - 7.30 (m, 1H), 7.28 - 7.25 (m, 1H), 7.16 (dd, $J = 2.4, 9.0$ Hz, 1H), 5.79 (s, 2H), 5.27 - 5.22 (m, 1H), 4.27 (dd, $J = 4.2, 11.9$ Hz, 2H), 4.12 (dd, $J = 6.1, 11.9$ Hz, 2H), 4.07 - 4.01 (m, 5H), 3.25 - 3.19 (m, 2H), 2.57 (s, 3H), 2.45 - 2.38 (m, 2H), 2.29 (t, $J = 7.6$ Hz, 4H), 2.22 (s, 2H), 1.75 - 1.63 (m, 2H), 1.63 - 1.54 (m, 4H), 1.32 - 1.23 (m, 16H), 1.00 (s, 6H), 0.87 (t, $J = 6.6$ Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ [ppm] = 173.4, 173.0, 172.5, 170.8, 158.3, 153.4, 133.5, 133.2, 130.2, 129.3, 127.8, 127.3, 123.3, 118.7, 102.6, 80.8, 69.2, 62.2, 55.7, 45.6, 45.1, 36.3, 34.2, 33.1, 32.8, 31.8, 31.1, 29.4, 29.2, 29.1, 27.1, 27.0, 25.0, 22.7, 14.2.

AGM-CASI-C7bbGMe-2-TG-octanoate (II-8b)**Synthesis of C7bbGMe-acid-2-TG-octanoate (A-1b)**

[0122] *Synthesis of 2-((5-(Methoxy(methyl)amino)-3,3-dimethyl-5-oxopentanoyl)oxy)propane-1,3-diyl dioctanoate (Int-39).* To a stirred solution of **Int-13** (200 mg, 411 μmol) in dichloromethane (2 mL) were added *N,O*-dimethylhydroxylamine hydrochloride (45.0 mg, 461 μmol), EDCI-HCl (105 mg, 548 μmol) and DMAP (50.0 mg, 409 μmol) at 0 °C and a solution of DIPEA (111 mg, 861 μmol , 0.150 mL) in dichloromethane (0.3 mL) was added dropwise over 5 min. The reaction mixture was then stirred at room temperature for 2 h. The reaction was concentrated under reduced pressure and the residue was dissolved in ethyl acetate (30 mL) and washed with water (30 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (20 mL) and the combined organic layers were washed with brine (2 x 30 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give a pale-yellow oil. Material was purified by normal phase chromatography (Biotage Isolera, 25 g SiliaSep cartridge; eluent 0-60% ethyl acetate in heptane over 10 CV) to give the product (**Int-39**, 139 mg, 62.6 % yield) as a colorless oil. MF: $\text{C}_{28}\text{H}_{51}\text{NO}_8$ MW: 529.70. ^1H NMR (400 MHz, CDCl_3): δ

[ppm] = 5.30 - 5.22 (m, 1H), 4.27 (dd, J = 4.6, 11.9 Hz, 2H), 4.14 (dd, J = 6.0, 11.9 Hz, 2H), 3.67 (s, 3H), 3.16 (s, 3H), 2.55 (s, 2H), 2.53 (s, 2H), 2.30 (t, J = 7.6 Hz, 4H), 1.66 - 1.54 (m, 4H), 1.37 - 1.21 (m, 16H), 1.14 (s, 6H), 0.88 (t, J = 6.9 Hz, 6H).

[0123] *Synthesis of 2-((3,3-Dimethyl-5-oxopentanoyl)oxy)propane-1,3-diyl dioctanoate (Int-40).*

To a stirred solution of 2-((5-(methoxy(methyl)amino)-3,3-dimethyl-5-oxopentanoyl)oxy)propane-1,3-diyl dioctanoate (**Int-39**, 4.22 g, 7.97 mmol) in dry tetrahydrofuran (50 mL) was added DIBAL-H (1M in toluene) (1 M, 9.79 mmol, 9.79 mL) dropwise over 5 min at -78 °C under an atmosphere of argon and the reaction mixture was stirred at -78 °C for 1.5 h. A further portion of DIBAL-H (1 M in toluene, 6.42 mmol, 6.42 mL) was added at -78 °C and the reaction mixture was stirred at -78 °C for 2 h. The reaction was quenched carefully with methanol (30 mL) and then with Rochelle's salt (100 mL) and stirred at room temperature for 1 h. The mixture was extracted with diethyl ether (3 x 50 mL) and the combined organic layers washed with brine (100 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure to give a crude colorless oil. Material was purified by normal phase chromatography (Biotage Isolera, 80 g SiliaSep cartridge; eluent 0-60% ethyl acetate in heptane over 10 CV) to afford the product (**Int-40**, 878 mg, 19.9 % yield, 85% purity) as a colorless oil. MF: C₂₆H₄₆O₇ MW: 470.64. UPLC4 (XB BEH 300 C4 20to95) R_t = 4.55 min, 89.8% (UV), 97.9% (ELSD). MS (ESIpos): m/z = 488.6 [M+NH₄]⁺. ¹H NMR (400 MHz, CDCl₃): δ [ppm] = 9.83 (t, J = 2.4 Hz, 1H), 5.27 (tt, J = 4.2, 6.0 Hz, 1H), 4.30 (dd, J = 4.2, 12.0 Hz, 2H), 4.14 (dd, J = 6.1, 12.0 Hz, 2H), 2.50 (d, J = 2.3 Hz, 2H), 2.43 (s, 2H), 2.30 (t, J = 7.6 Hz, 4H), 1.65 - 1.52 (m, 4H), 1.39 - 1.23 (m, 16H), 1.16 (s, 6H), 0.88 (t, J = 6.7 Hz, 6H). Product contained 10.1% residual heptane.

[0124] *Synthesis of 7-(1,3-Bis(octanoyloxy)propan-2-yl) 1-(tert-butyl) (E)-5,5-dimethylhept-2-enedioate (Int-41).*

A solution of 2-((3,3-dimethyl-5-oxopentanoyl)oxy)propane-1,3-diyl dioctanoate (**Int-40**, 878 mg, 1.68 mmol) and tert-butyl 2-(triphenylphosphanylidene)acetate (659 mg, 1.75 mmol) in tetrahydrofuran (10 mL) was stirred at 40 °C for 18 h. The reaction mixture was concentrated under reduced pressure to afford a crude residue. Material was purified by normal phase purification (Biotage Isolera, 40 g SiliCycle cartridge; eluent 0-50% ethyl acetate in heptane over 10 CVs) to afford the product (**Int-41**, 669 mg, 68.7 % yield, 98% purity) as a colorless oil. MF: C₃₂H₅₆O₈ MW: 568.78. ¹H NMR (400 MHz, CDCl₃): δ [ppm] = 6.90 - 6.82 (m, 1H), 5.78 (d, J = 15.4 Hz, 1H), 5.30 - 5.25 (m, 1H), 4.30 (dd, J = 4.2, 12.0 Hz, 2H), 4.14 (dd,

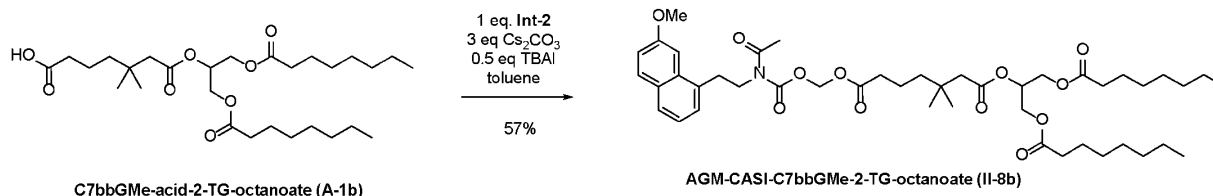
$J = 6.1, 11.9$ Hz, 2H), 2.31 (t, $J = 7.6$ Hz, 4H), 2.25 (s, 2H), 2.21 (dd, $J = 1.0, 7.9$ Hz, 2H), 1.65 - 1.54 (m, 4H), 1.48 (s, 9H), 1.33 - 1.25 (m, 16H), 1.04 (s, 6H), 0.88 (t, $J = 6.6$ Hz, 6H). Product contains 1.19% residual heptane by weight. ^{13}C NMR (100 MHz, CDCl_3): δ [ppm] = 173.4, 171.0, 165.9, 143.9, 126.3, 80.4, 69.1, 62.3, 45.8, 44.5, 34.2, 34.1, 31.8, 29.2, 29.1, 28.3, 27.3, 25.0, 22.8, 14.2.

[0125] *Synthesis of 1-(1,3-Bis(octanoyloxy)propan-2-yl) 7-(tert-butyl) 3,3-dimethylheptanedioate (Int-42).* To a solution of 7-(1,3-bis(octanoyloxy)propan-2-yl) 1-(tert-butyl) (E)-5,5-dimethylhept-2-enedioate (**Int-41**, 669 mg, 1.15 mmol) in ethyl acetate (10 mL) under an argon atmosphere, palladium on carbon 5% (246 mg, 115 μmol , 5% purity) was added. The argon atmosphere was evacuated under vacuum and a hydrogen atmosphere was introduced. The reaction mixture was stirred at room temperature for 16 hours. The mixture was filtered through Celite and was washed with ethyl acetate (3 x 50 mL). The filtrate was then concentrated under vacuum to afford the product (635 mg, 96% yield) as a colorless oil. MF: $\text{C}_{32}\text{H}_{58}\text{O}_8$ MW: 570.80; UPLC4 (XB BEH 300 C4 20to95) $R_t = 5.25$ min, 93.7% (UV), 99.9% (ELSD). MS (ESIpos): $m/z = 588.8$ $[\text{M}+\text{NH}_4]^+$. ^1H NMR (400 MHz, CDCl_3): δ [ppm] = 5.29 - 5.23 (m, 1H), 4.28 (dd, $J = 4.2, 11.9$ Hz, 2H), 4.14 (dd, $J = 6.1, 11.9$ Hz, 2H), 2.30 (t, $J = 7.5$ Hz, 4H), 2.23 (s, 2H), 2.18 (t, $J = 7.5$ Hz, 2H), 1.65 - 1.50 (m, 6H), 1.44 (s, 9H), 1.33 - 1.25 (m, 18H), 1.00 (s, 6H), 0.86 (t, $J = 6.7$ Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ [ppm] = 173.4, 173.1, 171.4, 80.2, 68.9, 62.3, 45.9, 41.9, 36.1, 34.2, 33.4, 31.8, 29.2, 29.0, 28.3, 27.2, 25.0, 22.7, 19.9, 14.2.

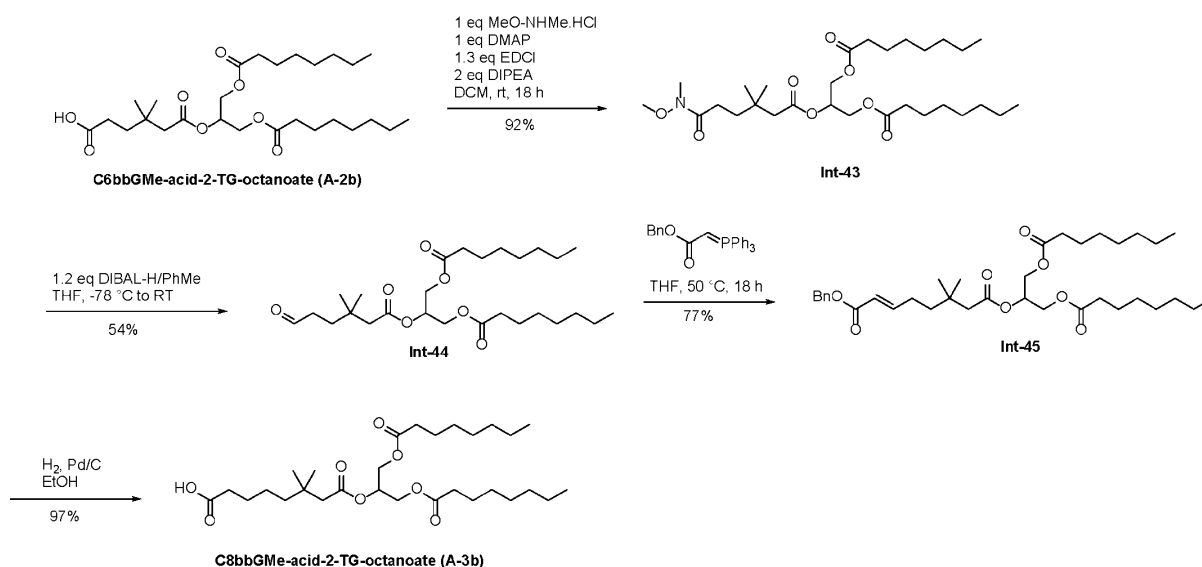
[0126] *Synthesis of C7bbGMe-acid-2-TG-octanoate (A-1b).* To a solution of 1-(1,3-bis(octanoyloxy)propan-2-yl) 7-(tert-butyl) 3,3-dimethylheptanedioate (**Int-42**, 635 mg, 1.11 mmol) in dichloromethane (10 mL) under argon, TFA (2.54 g, 22.3 mmol, 1.69 mL) was added. The reaction mixture was allowed to stir at room temperature for 16 hours. A saturated solution of NaHCO_3 (aq) (50 mL) was carefully added and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over MgSO_4 and concentrated under vacuum to afford the product (526 mg, 98% yield) as a yellow oil. MF: $\text{C}_{28}\text{H}_{50}\text{O}_8$ MW: 514.69. UPLC4 (XB BEH 300 C4 20to95) $R_t = 3.64$ min, 100.0% (UV), 99.7% (ELSD). MS (ESIpos): $m/z = 532.7$ $[\text{M}+\text{NH}_4]^+$. ^1H NMR (400 MHz, CDCl_3): δ [ppm] = 5.31 - 5.23 (m, 1H), 4.28 (dd, $J = 4.3, 11.9$ Hz, 2H), 4.15 (dd, $J = 6.0, 11.9$ Hz, 2H), 2.37 - 2.28 (m, 6H), 2.24 (s, 2H), 1.68 - 1.56 (m, 6H), 1.38 - 1.22 (m, 18H), 1.01 (s, 6H), 0.88 (t, $J = 6.7$ Hz, 6H). Exchangeable CO_2H proton not observed. Product contains residual ethyl acetate 1.02% by weight.

^{13}C NMR (100 MHz, CDCl_3): δ [ppm] = 178.3, 173.6, 171.4, 69.0, 62.3, 45.8, 41.5, 34.4, 34.2, 33.4, 31.8, 29.2, 29.0, 27.3, 25.0, 22.7, 19.6, 14.2.

Synthesis of AGM-CASI-C7bbGMe-2-TG-octanoate (**II-8b**)



[0127] *Synthesis of AGM-CASI-C7bbGMe-2-TG-octanoate (II-8b).* To a solution of C7bbGMe-acid-2-TG-octanoate (**A-1b**) (400 mg, 762 μmol) and **Int-2** (256 mg, 762 μmol) in toluene (10 mL) under argon, Cs_2CO_3 (744 mg, 2.28 mmol) and TBAI (141 mg, 381 μmol) were added. The reaction mixture was heated to 50 $^\circ\text{C}$ for 2 hours. The reaction mixture was cooled to room temperature and a saturated solution of NH_4Cl (aq) 50 mL was added. The aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over MgSO_4 and concentrated under vacuum to afford a crude product. Material was purified by normal phase chromatography (Biotage Isolera, 40 g SiliCycle cartridge; eluent 0 - 80% ethyl acetate in heptane over 15 CVs) to afford the product (**II-8b**, 356 mg, 57.1 % yield) as a colorless oil. MF: $\text{C}_{45}\text{H}_{67}\text{NO}_{12}$ MW: 814.01. UPLC4 (XB BEH 300 C4 20to95) R_t = 5.53 min, 87.1% (UV), 92.8% (ELSD). MS (ESIpos): m/z = 832.1 $[\text{M}+\text{NH}_4]^+$. ^1H NMR (400 MHz, CDCl_3): δ [ppm] = 7.74 (d, J = 8.9 Hz, 1H), 7.67 (d, J = 7.9 Hz, 1H), 7.64 (d, J = 2.3 Hz, 1H), 7.35 - 7.30 (m, 1H), 7.29 - 7.23 (m, 1H), 7.16 (dd, J = 2.3, 8.9 Hz, 1H), 5.80 (s, 2H), 5.27 - 5.20 (m, 1H), 4.27 (dd, J = 4.3, 11.9 Hz, 2H), 4.12 (dd, J = 6.0, 12.0 Hz, 2H), 4.08 - 4.01 (m, 5H), 3.26 - 3.19 (m, 2H), 2.57 (s, 3H), 2.38 (t, J = 7.4 Hz, 2H), 2.29 (t, J = 7.6 Hz, 4H), 2.21 (s, 2H), 1.69 - 1.53 (m, 6H), 1.37 - 1.22 (m, 18H), 0.98 (s, 6H), 0.87 (t, J = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ [ppm] = 173.4, 173.0, 172.2, 171.2, 158.3, 153.4, 133.5, 133.2, 130.2, 129.3, 127.8, 127.3, 123.3, 118.7, 102.6, 80.7, 69.0, 62.3, 55.7, 45.7, 45.1, 41.6, 34.4, 34.2, 33.4, 32.9, 31.8, 29.2, 29.0, 27.2, 27.1, 25.0, 22.7, 19.5, 14.2.

AGM-CASl-C8bbGMe-2-TG-octanoate (II-9b)**Synthesis of C8bbGMe-acid-2-TG-octanoate (A-3b)**

[0128] *Synthesis of 2-((6-(Methoxy(methyl)amino)-3,3-dimethyl-6-oxohexanoyl)oxy)propane-1,3-diyl dioctanoate (Int-43).* To a flask charged with *N,O*-dimethylhydroxylamine hydrochloride (351 mg, 3.60 mmol), EDCI-HCl (747 mg, 3.89 mmol) and DMAP (366 mg, 3.00 mmol) was added a solution of **A-2b** (1.50 g, 3.00 mmol) in dichloromethane (15 mL) under argon at 0 °C. DIPEA (1.04 mL, 5.99 mmol) was added dropwise, and the mixture was allowed to warm to rt and stirred for 18 hours. The reaction was then concentrated under reduced pressure and the residue dissolved in ethyl acetate (100 mL). The mixture was then washed with water (200 mL). The layers were separated, and the aqueous layer was extracted further with ethyl acetate (2 x 100 mL) and the combined organic layers were washed with brine (2 x 100 mL). The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo. The crude product was purified by normal phase chromatography (Biotage Isolera, 120 g SiliaSep cartridge; eluent 0-50% ethyl acetate in heptane over 10 CVs) to afford the desired product (**Int-43**, 1.50 g, 92.1 % yield) as a colorless oil. MF: C₂₉H₅₃NO₈ MW: 543.38. ¹H NMR (400 MHz, CDCl₃): δ [ppm] = 5.29-5.24 (m, 1H), 4.29 (dd, *J* = 12.0, 4.2 Hz, 2H), 4.14 (dd, *J* = 12.0, 6.1 Hz, 2H), 3.70 (s, 3H), 3.17 (s, 3H), 2.42 (t,

$J = 8.2$ Hz, 2H), 2.30 (t, $J = 7.6$ Hz, 4H), 2.25 (s, 2H), 1.69-1.64 (m, 2H), 1.62-1.56 (m, 4H), 1.29 (d, $J = 14.2$ Hz, 16H), 1.03 (s, 6H), 0.87 (t, $J = 6.8$ Hz, 6H).

[0129] *Synthesis of 2-((3,3-Dimethyl-6-oxohexanoyl)oxy)propane-1,3-diyl dioctanoate (Int-44).*

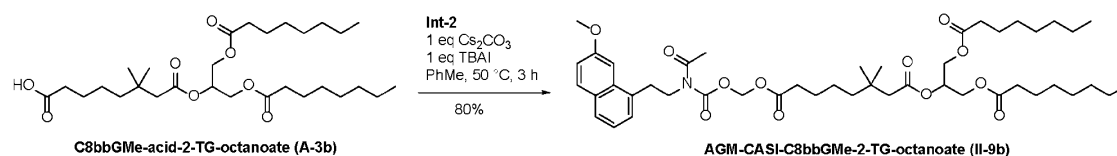
To a stirred solution of 2-((6-(methoxy(methyl)amino)-3,3-dimethyl-6-oxohexanoyl)oxy)propane-1,3-diyl dioctanoate (**Int-43**, 1.00 g, 1.84 mmol) in dry tetrahydrofuran (16 mL) was added diisobutylaluminium hydride (1M in heptane, 2.21 mL, 2.21 mmol) dropwise over 5 min at -78 °C under an atmosphere of argon. The reaction mixture was then stirred at -78 °C for 1.5 hours. A further portion of diisobutylaluminium hydride (1M in heptane, 1.10 mL, 1.10 mmol) was added at -78 °C and the reaction mixture was stirred at -78 °C for a further 2 hours. The reaction was then quenched carefully with methanol (30 mL) and then with Rochelle's salt (100 mL), allowed to warm, and stirred at room temperature for 1 h. The mixture was extracted with diethyl ether (3 x 50 mL) and the combined organic layers washed with brine (100 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure to give a crude colorless oil. The material was purified by normal phase chromatography (Biotage Isolera, 80 g SiliaSep cartridge; eluent 0-60% ethyl acetate in heptane over 10 CVs) gave the desired product (**Int-44**, 480 mg, 53.9 % yield) as a colorless oil. MF: $C_{27}H_{48}O_7$ MW: 484.34. 1H NMR (400 MHz, $CDCl_3$): δ [ppm] = 9.78 (t, $J = 1.6$ Hz, 1H), 5.29-5.24 (m, 1H), 4.29 (dd, $J = 12.0, 4.2$ Hz, 2H), 4.13 (dd, $J = 12.0, 5.9$ Hz, 2H), 2.45 (dt, $J = 1.5, 8.1$ Hz, 2H), 2.30 (t, $J = 7.5$ Hz, 4H), 2.23 (s, 2H), 1.69-1.65 (m, 2H), 1.64-1.56 (m, 4H), 1.31-1.21 (m, 16H), 1.01 (s, 6H), 0.87 (t, $J = 6.8$ Hz, 6H).

[0130] *Synthesis of 1-Benzyl 8-(1,3-bis(octanoyloxy)propan-2-yl) (E)-6,6-dimethyloct-2-enedioate (Int-45).*

A suspension of 2-((3,3-dimethyl-6-oxohexanoyl)oxy)propane-1,3-diyl dioctanoate (**Int-44**, 480 mg, 990 μ mol) and benzyl 2-(triphenylphosphoranylidene)acetate (406 mg, 990 μ mol) in tetrahydrofuran (12 mL) was heated to 50 °C and stirred for 16 hours. The reaction mixture was then concentrated to dryness. The material was then purified by normal phase purification (Biotage Isolera, 40 g SiliaSep cartridge; eluent 0-20% ethyl acetate in heptane over 16 CVs) to afford the desired product (**Int-45**, 470 mg, 762 μ mol, 76.9 % yield) as a colorless oil. MF: $C_{36}H_{56}O_8$ MW: 616.40. 1H NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.37-7.29 (m, 5H), 7.01 (dt, $J = 15.6, 6.8$ Hz, 1H), 5.88 (d, $J = 15.6$ Hz, 1H), 5.30-5.24 (m, 1H), 5.17 (s, 2H), 4.29 (dd, $J = 12.0, 4.2$ Hz, 2H), 4.13 (dd, $J = 12.0, 6.1$ Hz, 2H), 2.29 (t, $J = 7.6$ Hz, 4H), 2.23-2.18 (m, 4H), 1.66-1.56 (m, 4H), 1.49-1.45 (m, 2H), 1.34-1.21 (m, 16H), 1.01 (s, 6H), 0.87 (t, $J = 6.8$ Hz, 6H).

[0131] *Synthesis of C8bbGMe-acid-2-TG-octanoate (A-3b).* To a solution of 1-benzyl 8-(1,3-bis(octanoyloxy)propan-2-yl) (E)-6,6-dimethyloct-2-enedioate (**Int-45**, 470 mg, 762 μmol) in ethanol (30 mL) was added palladium on activated charcoal (81.1 mg, 76.2 μmol , 10% loading). The mixture was subjected to a vacuum after which a hydrogen atmosphere was introduced. The mixture was stirred for 2 hours, then passed through a short plug of Celite and concentrated to dryness. The material was then purified by normal phase chromatography (Biotage Isolera, 40 g SiliaSep cartridge; eluent 0-60% ethyl acetate in heptane over 10 CV) to give the desired (**A-3b**, 400 mg, 97.3 % yield) as a colorless oil. MF: $\text{C}_{29}\text{H}_{52}\text{O}_8$; MW: 528.73; ^1H NMR (400 MHz, CDCl_3): δ [ppm] = 5.29-5.24 (m, 1H), 4.28 (dd, J = 11.7, 4.4 Hz, 2H), 4.15 (dd, J = 11.9, 6.0 Hz, 2H), 2.36 (t, J = 7.3 Hz, 2H), 2.31 (t, J = 7.6 Hz, 4H), 2.21 (s, 2H), 1.65-1.57 (m, 6H), 1.31 (dd, J = 17.7, 14.3 Hz, 20H), 0.98 (s, 6H), 0.87 (t, J = 6.7 Hz, 6H); Exchangeable CO_2H signal not observed.

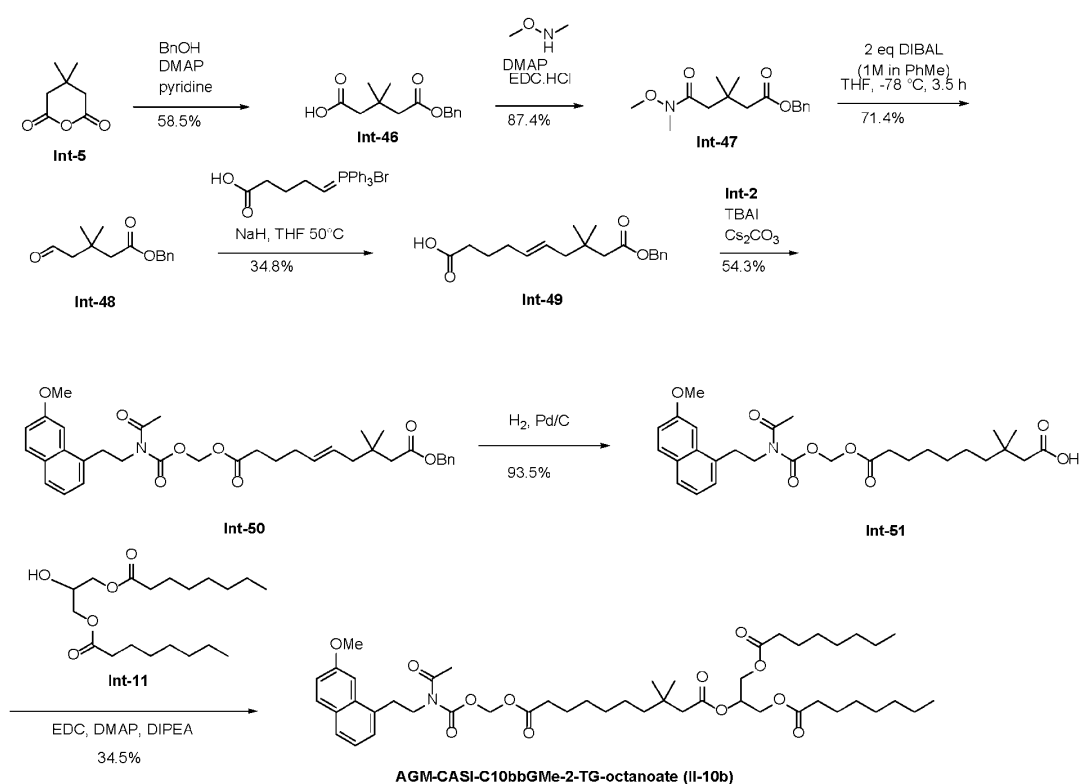
Synthesis of AGM-CASI-C8bbGMe-2-TG-octanoate (II-9b)



[0132] *Synthesis of AGM-CASI-C8bbGMe-2-TG-octanoate (II-9b).* **A-3b** (400 mg, 757 μmol), **Int-2** (254 mg, 757 μmol) and TBAI (26.9 mg, 72.7 μmol) were suspended in anhydrous *N,N*-dimethylformamide (12 mL). Cs_2CO_3 (244 mg, 749 μmol) was added, and the mixture heated to 50 °C in a sealed vial and stirred for 3 hours. The reaction was then cooled to room temp. and diluted with water (3 mL). The aqueous phase was extracted with ethyl acetate (4 mL). The organic phase was washed with water (5 x 1 mL), dried with sodium sulfate, filtered and the filtrate concentrated. The crude material was purified by reverse phase chromatography (Siliasep C18 12 g, 10-100% MeCN in water with 0.1% formic acid in both solvents) to afford the desired product (**II-9b**, 500 mg, 604 μmol , 79.8 % yield) as a colorless oil. MF: $\text{C}_{46}\text{H}_{69}\text{NO}_{12}$ MW: 827.48; UPLC4-MS: (XB BEH300 C4 20 to 95%): R_t = 5.52 min., 87.5% (UV), 99.7% (ELSD); MS(ESIpos): m/z = 846.3 $[\text{M}+\text{NH}_4]^+$. ^1H NMR (400 MHz, CDCl_3): δ [ppm] = 7.74 (d, J = 9.0 Hz, 1H), 7.67 (d, J = 8.1 Hz, 1H), 7.64 (d, J = 2.2 Hz, 1H), 7.32 (d, J = 6.4 Hz, 1H), 7.26 (t, J = 7.5 Hz, 5H), 7.16 (dd, J = 8.8, 2.4 Hz, 1H), 5.81 (s, 2H), 5.27-5.22 (m, 1H), 4.27 (dd, J = 12.0, 4.2

Hz, 2H), 4.13 (dd, $J = 11.9, 6.0$ Hz, 2H), 4.05-4.01 (m, 5H), 3.24-3.19 (m, 2H), 2.57 (s, 3H), 2.41 (t, $J = 7.5$ Hz, 2H), 2.29 (t, $J = 7.5$ Hz, 4H), 2.18 (s, 2H), 1.67-1.59 (m, 6H), 1.34-1.22 (m, 20H), 0.95 (s, 6H), 0.87 (t, $J = 6.7$ Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ [ppm] = 173.4, 173.0, 172.3, 171.3, 158.2, 153.4, 133.4, 133.2, 130.2, 129.3, 127.8, 127.3, 123.4, 118.7, 102.6, 80.7, 68.9, 62.3, 55.7, 45.9, 45.1, 42.0, 34.2, 34.0, 33.4, 32.8, 31.8, 29.2, 29.1, 27.2, 27.1, 25.3, 25.0, 23.7, 22.7, 14.2.

AGM-CASI-C10bbGMe-2-TG-octanoate (II-10b)



[0133] Synthesis of 5-(benzyloxy)-3,3-dimethyl-5-oxopentanoic acid (Int-46). To a solution of 3,3-dimethylglutaric anhydride (**Int-5**, 10.0 g, 70.4 mmol) and benzyl alcohol (7.28 mL, 70.4 mmol) in dichloromethane (100 mL) and pyridine (57.0 mL, 708 mmol) was added DMAP (862 mg, 7.06 mmol). The mixture was then allowed to stir at 50 °C for 44 hours. The mixture was diluted with dichloromethane (150 mL) and washed with 2M hydrochloric acid (2 x 300 mL) and

brine (300 mL). The dichloromethane layer was dried over sodium sulfate, filtered, and the filtrate concentrated to give the crude product as a yellow oil. The crude product was purified by normal phase purification (Biotage Isolera, 330 g SilliCycle cartridge; eluent 0-30% ethyl acetate in heptane over 12 CVs) to afford the desired product (**Int-46**, 10.3 g, 58.5 % yield) as a colorless oil. MF: C₁₄H₁₈O₄ MW: 250.12; ¹H NMR (400 MHz, CDCl₃): δ [ppm] = 7.40 - 7.27 (m, 5H), 5.12 (s, 2H), 2.50 (s, 2H), 2.47 (s, 2H), 1.13 (s, 6H); Exchangeable CO₂H proton not observed. ¹³C NMR (100 MHz, CDCl₃): δ [ppm] = 177.91, 177.87, 172.1, 136.0, 128.7, 128.42, 128.37, 66.3, 45.1, 32.8, 27.9;

[0134] *Synthesis of benzyl 5-(methoxy(methyl)amino)-3,3-dimethyl-5-oxopentanoate (Int-47)*. To a flask charged with *N,O*-dimethylhydroxylamine hydrochloride (4.80 g, 49.2 mmol), EDCI-HCl (10.2 g, 53.2 mmol) and DMAP (5.00 g, 41.0 mmol) under argon was added a solution of 5-benzyloxy-3,3-dimethyl-5-oxo-pentanoic acid (**Int-46**, 10.3 g, 41.0 mmol) in dichloromethane (100 mL) at 0 °C. DIPEA (14.3 mL, 81.9 mmol) was added dropwise, and the mixture was then allowed to warm to RT and stirred overnight for 18 hours. The reaction was concentrated under reduced pressure and the residue then dissolved in ethyl acetate (100 mL) and washed with water (200 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine (2 x 100 mL). The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to give a crude product, which was purified by normal phase chromatography (Biotage Isolera, 330 g SiliCycle SiliaSep cartridge; eluent 0-50% ethyl acetate in heptane over 10 CVs) to afford the desired product (10.5 g, 87.4 % yield) as a colorless oil. MF: C₁₆H₂₃NO₄ MW: 250.12; ¹H NMR (400 MHz, CDCl₃): δ [ppm] = 7.37 - 7.29 (m, 5H), 5.09 (s, 2H), 3.61 (s, 3H), 3.14 (s, 3H), 2.57 (s, 2H), 2.53 (s, 2H), 1.13 (s, 6H); ¹³C NMR (400 MHz, CDCl₃): δ [ppm] = 173.0, 172.3, 136.2, 128.6, 128.3, 128.2, 66.0, 61.1, 45.2, 41.1, 33.1, 31.9, 28.2.

[0135] *Synthesis of benzyl 3,3-dimethyl-5-oxopentanoate (Int-48)*. To a stirred solution of benzyl 5-(methoxy(methyl)amino)-3,3-dimethyl-5-oxopentanoate (2.00 g, 6.82 mmol) in dry tetrahydrofuran (21 mL) was added diisobutylaluminium hydride (1M in toluene, 8.18 mL, 8.18 mmol), dropwise over 5 min at -78 °C under an atmosphere of argon. The mixture was then stirred at -78 °C for 90 minutes. A further portion of diisobutylaluminium hydride (1 M, 5.45 mL, 0.8 eq.) was added at -78 °C and the mixture stirred at that temperature for a further 2 hours. The reaction was quenched carefully with methanol (30 mL) and then with Rochelle's salt (100 mL)

and then allowed to warm and stir at room temperature for 1 hour. The mixture was then extracted with diethyl ether (3 x 50 mL) and the combined organic layers washed with brine (100 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure to give a crude colorless oil. The crude product was purified by normal phase chromatography (Biotage Isolera, 80 g SiliaSep cartridge; eluent 0-60% ethyl acetate in heptane over 10 CV, loaded with heptane) gave the desired product (1.20 g, 71.4 % yield) as a colorless oil. MF: C₁₄H₁₈O₃ MW: 234.13; ¹H NMR: (400 MHz, CDCl₃) δ [ppm] = 9.81 (t, *J* = 2.3 Hz, 1H), 7.41-7.30 (m, 5H), 5.11 (s, 2H), 2.48 (d, *J* = 2.4 Hz, 2H), 2.44 (s, 2H), 1.14 (s, 6H).

[0136] *Synthesis of (E)-10-(benzyloxy)-8,8-dimethyl-10-oxodec-5-enoic acid (Int-49).* To a stirred suspension of (4-carboxybutyl)triphenylphosphonium bromide (3.40 g, 7.68 mmol) in dry tetrahydrofuran (12 mL) was added sodium hydride (384 mg, 9.60 mmol, 60% dispersion in mineral oil) at 0 °C. The reaction mixture was stirred at 50 °C for 1 hour under an atmosphere of argon. A solution of benzyl 3,3-dimethyl-5-oxopentanoate (**Int-48**, 900 mg, 3.84 mmol) in dry tetrahydrofuran (5 mL) was added dropwise, and the reaction mixture was stirred at 50 °C for 1 hour. Heating was then removed, and the mixture was allowed to cool and stir at room temperature overnight. The reaction was quenched with a saturated aqueous solution of ammonium chloride (20 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over magnesium sulfate, filtered and concentrated in vacuo to give a pale yellow oil. The crude product was then purified by normal phase chromatography (Biotage Isolera, 25 g SiliaSep cartridge; eluent 0-60% ethyl acetate in heptane over 10 CVs) to give the desired product (**Int-49**, 500 mg, 34.8 % yield) as a colorless oil. Materials used without further purification. MF: C₁₉H₂₆O₄ MW: 318.18; ¹H NMR (400 MHz, CDCl₃) δ [ppm] = 7.41 - 7.31 (m, 5H), 5.52 - 5.41 (m, 2H), 5.10 (s, 2H), 2.33 (t, *J* = 7.6 Hz, 2H), 2.26 (s, 2H), 2.09-2.04 (m, 3H), 1.73 - 1.63 (m, 2H), 0.95 - 1.04 (m, 6H); Exchangeable CO₂H proton not observed.

[0137] *Synthesis of 10-(((Acetyl(2-(7-methoxynaphthalen-1-yl)ethyl)carbamoyl)oxy)methyl) 1-benzyl (E)-3,3-dimethyldec-5-enedioate (Int-50).* (E)-10-Benzyloxy-8,8-dimethyl-10-oxodec-5-enoic acid (**Int-49**, 500 mg, 1.49 mmol), **Int-2** (501 mg, 1.49 mmol) and TBAI (53.0 mg, 143 μmol) were suspended in anhydrous *N,N*-dimethylformamide (7.5 mL). Cesium carbonate (481 mg, 1.48 mmol) was added, and the mixture heated to 50 °C in sealed vial. The mixture was stirred at this temperature for 3 hours. The reaction was cooled to room temperature and diluted with water (3 mL). The aqueous phase was extracted into ethyl acetate (4 mL). The organic phase was

then washed with water (5 x 1 mL), dried with sodium sulfate and filtered. The filtrate was concentrated in vacuo give a crude yellow liquid. The crude material was purified by reverse phase chromatography (SiliaSep 40 g C18, 10-100% acetonitrile in water with 0.1% formic acid in both solvents) to afford the desired product (**Int-50**, 500 mg, 809 μ mol, 54.3 % yield) as a colourless oil. MF: C₃₆H₄₃NO₈ MW: 617.3; ¹H NMR (400 MHz, CDCl₃) δ [ppm] = 7.74 (d, *J* = 9.0 Hz, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.63 (d, *J* = 2.2 Hz, 1H), 7.37-7.24 (m, 7H), 7.16 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.79 (s, 2H), 5.49-5.37 (m, 2H), 5.08 (s, 2H), 4.06-3.99 (m, 5H), 3.24-3.20 (m, 2H), 2.57 (s, 3H), 2.38 (t, *J* = 7.7 Hz, 2H), 2.23 (s, 2H), 2.08-2.01 (m, 4H), 1.74-1.66 (m, 2H), 0.97 (s, 6H). 43H expected, 43H observed.

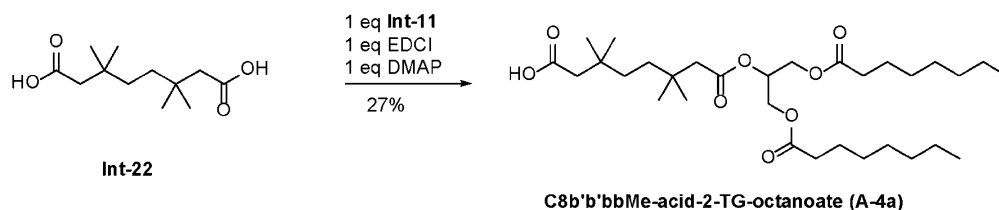
[0138] *Synthesis of 10-(((acetyl(2-(7-methoxynaphthalen-1-yl)ethyl)carbamoyl)oxy)methoxy)-3,3-dimethyl-10-oxodecanoic acid (Int-51).* To a solution of 10-(((acetyl(2-(7-methoxynaphthalen-1-yl)ethyl)carbamoyl)oxy)methyl) 1-benzyl (*E*)-3,3-dimethyldec-5-enedioate (**Int-50**, 500 mg, 809 μ mol) in ethanol (100 mL) was added palladium on activated charcoal (258 mg, 243 μ mol, 10% catalyst loading). The mixture was placed under vacuum, after which a hydrogen atmosphere was introduced (1 atm, balloon pressure). The mixture was stirred for 30 minutes, then passed through a short plug of Celite and concentrated to dryness. The crude product was purified by normal phase chromatography (Biotage Isolera, 25 g SiliaSep cartridge; eluent 0-60% ethyl acetate in heptane over 10 CV) to give the desired product (**Int-51**, 421 mg, 93.5 % yield) as a colourless gum. MF: C₂₉H₃₉NO₈ MW: 529.27; ¹H NMR (400 MHz, CDCl₃): δ [ppm] = 7.76 (d, *J* = 9.0 Hz, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.63 (d, *J* = 2.2 Hz, 1H), 7.32 (d, *J* = 6.4 Hz, 1H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.16 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.81 (s, 2H), 4.06-4.01 (m, 5H), 3.24-3.20 (m, 2H), 2.57 (s, 3H), 2.40 (t, *J* = 7.5 Hz, 2H), 2.18 (s, 2H), 1.69-1.61 (m, 2H), 1.35-1.25 (m, 8H), 0.97 (s, 6H). Exchangable CO₂H not observed; UPLC2-MS: (BEH-C18 Long Acid 2 to 95%) R_t = 3.21 min (71.8%), MS (ESIpos): *m/z* = [M+Na]⁺ 552.4.

[0139] *Synthesis of AGM-CASI-C10bbGMe-2-TG-octanoate (II-10b).* To a solution of 10-(((acetyl(2-(7-methoxynaphthalen-1-yl)ethyl)carbamoyl)oxy)methoxy)-3,3-dimethyl-10-oxodecanoic acid (**Int-51**, 450 mg, 850 μ mol) and **Int-11** (293 mg, 850 μ mol) in dichloromethane (10 mL), EDCI-HCl (264 mg, 1.70 mmol) and DMAP (208 mg, 1.70 mmol) were added. The reaction was stirred at room temperature for 18 hours. A solution of saturated aqueous ammonium chloride (5 mL) was added, and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine (5 mL), dried

over sodium sulfate and concentrated under vacuum to afford a crude residue. Material was purified by normal phase chromatography (Biotage Isolera, 40 g SiliCycle cartridge; eluent 0 - 40% ethyl acetate in heptane over 15 CVs) to afford the desired product (**II-10b**, 60 mg, 293 μ mol, 34.5 % yield, 96.61% purity) as colourless oil. MF: C₄₈H₇₃NO₁₂ MW: 855.51; UPLC4: (XB BEH300 C4 20 to 95%) Rt = 5.78 min., 96.6% (UV); 99.8% (ELSD); MS(ESIpos): m/z = 874.1 [M+NH₄]⁺; ¹H NMR (400 MHz, CDCl₃): δ [ppm] = 7.74 (d, *J* = 9.0 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 2.4 Hz, 1H), 7.32 (d, *J* = 6.1 Hz, 1H), 7.28-7.24 (m, 1H), 7.16 (dd, *J* = 9.0, 2.4 Hz, 1H), 5.81 (s, 2H), 5.28-5.23 (m, 1H), 4.27 (dd, *J* = 11.9, 4.3 Hz, 2H), 4.13 (dd, *J* = 11.9, 6.0 Hz, 2H), 4.06-4.02 (m, 5H), 3.24-3.20 (m, 2H), 2.57 (s, 3H), 2.40 (t, *J* = 7.6 Hz, 2H), 2.30 (t, *J* = 7.6 Hz, 4H), 2.18 (s, 2H), 1.69-1.58 (m, 6H), 1.37-1.21 (m, 24H), 0.94 (s, 6H), 0.87 (t, *J* = 6.7 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃): δ [ppm] = 173.4, 173.0, 172.4, 171.5, 158.3, 153.4, 133.5, 133.2, 130.2, 129.3, 127.8, 127.3, 123.4, 118.7, 102.6, 80.7, 68.8, 65.2, 62.3, 55.7, 46.0, 45.1, 42.5, 34.19, 34.0, 33.4, 32.9, 31.8, 30.1, 29.2, 29.1, 27.3, 27.1, 25.0, 24.7, 24.0, 22.7, 14.2.

Synthesis of AGM-CASI-C8b'b'bbMe-2-TG-octanoate (III-1b)

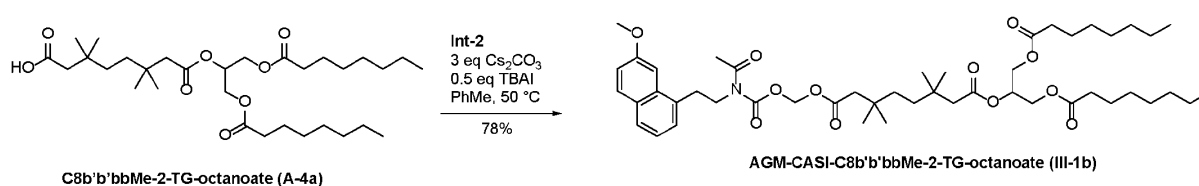
Synthesis of C8b'b'bbMe-2-TG-octanoate (A-4a)



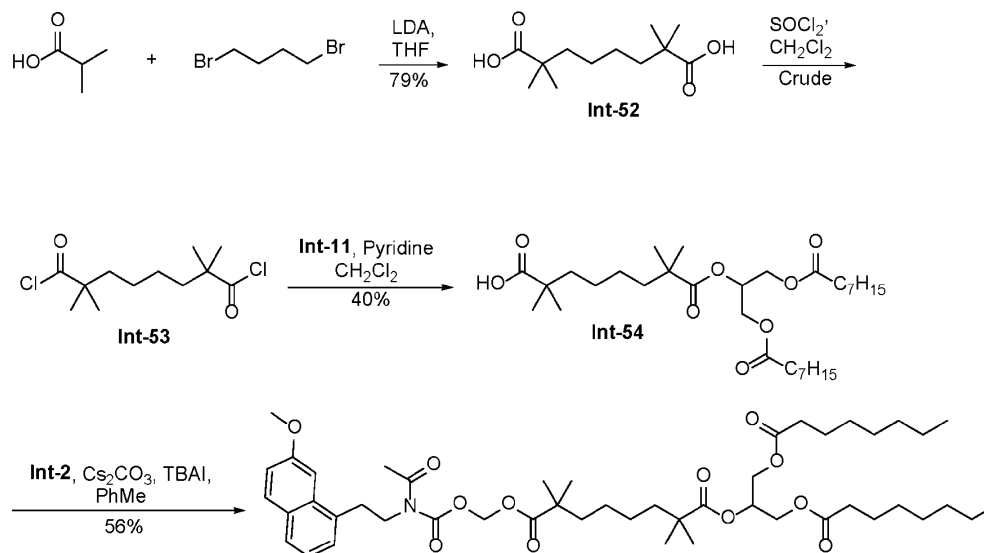
[0140] *Synthesis of C8b'b'bbMe-2-TG-octanoate (A-4a).* To a stirring solution of 3,3,6,6-tetramethyloctanedioic acid (**Int-22**, 394 mg, 1.71 mmol) and **Int-11** (589 mg, 1.71 mmol) in dichloromethane (60 mL) was added EDCI (328 mg, 1.71 mmol) and DMAP (209 mg, 1.71 mmol). The mixture was stirred at room temperature for 24 hrs. The reaction mixture was concentrated and purified by normal phase chromatography (Biotage Isolera, 40 g SiliCycle cartridge; eluent 0 - 20% acetone in heptane). Material re-purified by normal phase chromatography (Biotage Isolera, 40 g SiliCycle cartridge; eluent 0 - 20% acetone in heptane) to afford the desired product (**A-4a**, 260 mg, 27.2 % yield) as a colourless oil.

[0141] MF: C₃₁H₅₆O₈ MW: 556.77; UPLC4-MS: (XB BEH300 C4 20to95): R_t = 4.29 min., 94.69% (UV), 99.65% (ELSD). MS (ESIpos) m/z = 574.88 [M+NH₄]⁺. MS (ESI_{neg}) m/z = 555.73 [M-H]⁻; ¹H NMR (400 MHz, CDCl₃) δ = 5.29 - 5.23 (m, 1H), 4.28 (dd, *J* = 4.3, 11.9 Hz, 2H), 4.15 (dd, *J* = 6.0, 11.9 Hz, 2H), 2.31 (t, *J* = 7.5 Hz, 4H), 2.22 (d, *J* = 2.6 Hz, 4H), 1.65 - 1.56 (m, 4H), 1.34 - 1.23 (m, 20H), 1.02 (s, 6H), 0.98 (s, 6H), 0.88 (t, *J* = 6.7 Hz, 6H); Exchangeable carboxylic acid proton not observed; ¹³C NMR (101 MHz, CDCl₃) δ = 177.3, 173.5, 171.4, 68.9, 62.3, 45.7, 45.5, 36.1, 36.0, 34.2, 33.2, 33.0, 31.8, 29.2, 29.0, 27.4, 27.3, 25.0, 22.7, 14.2.

Synthesis of AGM-CASI-C8b'b'bbMe-2-TG-octanoate (III-1b)



[0142] *Synthesis of AGM-CASI-C8b'b'bbMe-2-TG-octanoate (III-1b).* A solution of **Int-2** (130 mg, 387 μmol), **A-4a** (210 mg, 376 μmol), caesium carbonate (369 mg, 1.13 mmol) and TBAI (70.0 mg, 190 μmol) in toluene (5 mL) under argon was heated to 50 °C and stirred for 4 hours. The mixture was cooled and diluted with ethyl acetate (50 mL), washed with water (50 mL), and brine (50 mL). The organic layer was dried over MgSO₄, filtered and concentrated to afford an orange oil. Material purified by normal phase chromatography (Biotage Isolera, 25 g Siliasep cartridge; eluent 0-35% ethyl acetate in heptane over 20CV) to give the desired product (259 mg, 78.2 % yield) as a colourless oil. MF: C₄₈H₇₃O₁₂N MW: 856.09; UPLC4-MS: (XB BEH300 C4 20to95): R_t = 5.79 min., 97.2% (UV), 99.9% (ELSD). MS (ESIpos) m/z = 874.2 [M+NH₄]⁺; ¹H NMR (400 MHz, CDCl₃) δ [ppm] = 7.74 (d, *J* = 8.9 Hz, 1H), 7.69 - 7.64 (m, 2H), 7.36 - 7.31 (d, *J* = 9.0 Hz, 1H), 7.29 - 7.23 (m, 1H), 7.16 (dd, *J* = 2.3, 8.9 Hz, 1H), 5.80 (s, 2H), 5.28 - 5.22 (m, 1H), 4.27 (dd, *J* = 4.3, 11.9 Hz, 2H), 4.13 (dd, *J* = 5.9, 11.9 Hz, 2H), 4.07 - 4.00 (m, 5H), 3.26 - 3.19 (m, 2H), 2.57 (s, 3H), 2.32 - 2.26 (m, 6H), 2.20 (s, 2H), 1.65 - 1.55 (m, 4H), 1.34 - 1.22 (m, 20H), 1.00 (s, 6H), 0.96 (s, 6H), 0.87 (t, *J* = 6.7 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃) δ [ppm] = 173.4, 173.0, 171.3, 170.8, 158.3, 153.4, 133.5, 133.2, 130.2, 129.3, 127.8, 127.3, 123.3, 118.7, 102.6, 80.6, 68.9, 62.3, 55.7, 45.7, 45.3, 45.1, 36.2, 34.2, 33.3, 33.2, 32.8, 31.8, 29.2, 29.0, 27.2, 27.1, 25.0, 22.7, 14.2.

AGM-CASI-C8a'a'aaMe-2-TG-octanoate (IV-1b)**AGM-CASI-C8a'a'aaMe-2-TG-octanoate (IV-1b)**

[0143] Synthesis of 2,2,7,7-tetramethyloctanedioic acid (Int-52). To an ice-cooled solution of diisopropylamine (13.2 mL, 93.9 mmol) in dry tetrahydrofuran (50 mL) was added *n*-butyllithium (1.6 M, hexanes, 60 mL, 96.0 mmol) dropwise. The reaction was stirred for 30 minutes at 0 °C then 2-methylpropanoic acid (4.40 mL, 47.3 mmol) was added dropwise. The mixture was stirred for 60 minutes then warmed to room temperature over 30 minutes. The reaction mixture was then cooled to 0 °C and 1,4-dibromobutane (2.80 mL, 23.6 mmol) in tetrahydrofuran (10 mL) was added dropwise. The resulting white suspension was stirred at 0 °C for 1 hour then at room temperature for 16 hours. The reaction mixture was poured into ice-cold hydrochloric acid (1 M, aqueous, 200 mL) then extracted with ethyl acetate (200 mL). The organics were washed with brine (100 mL) then dried over sodium sulfate, filtered, and concentrated. The crude residue was triturated with heptane (20 mL) then filtered to afford the desired product (**Int-52**, 4.50 g, 79% yield) as a colourless solid. MF: C₁₂H₂₂O₄ MW: 230.30; ¹H NMR (400 MHz, CDCl₃): δ [ppm] = 1.57 – 1.50 (m, 4H), 1.29 – 1.25 (m, 4H), 1.17 (s, 12H); 2 x exchangeable CO₂H protons not observed.

[0144] Synthesis of 2,2,7,7-tetramethyloctanedioyl dichloride (Int-53). A mixture of 2,2,7,7-tetramethyloctanedioic acid (**Int-52**, 2.00 g, 8.25 mmol) and *N,N*-dimethylformamide (100 μL,

1.29 mmol) in thionyl chloride (10 mL) was heated to reflux for 2 hours. The reaction was cooled to room temperature then diluted with toluene (5 mL) and concentrated under reduced pressure to afford the desired product (2.20 g, crude) as a colourless oil. MF: C₁₂H₂₀Cl₂O₂ MW: 267.19; ¹H NMR (400 MHz, CDCl₃): δ [ppm] = 1.71 – 1.64 (m, 4H), 1.37 – 1.26 (m, 16H).

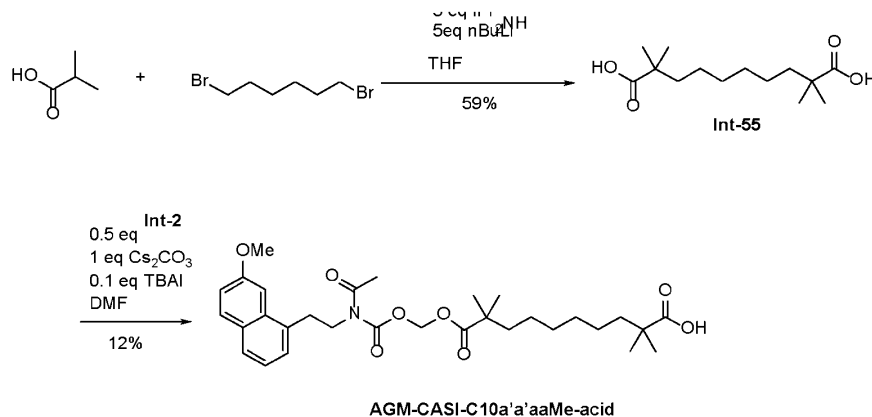
[0145] *Synthesis of 8-((1,3-Bis(octanoyloxy)propan-2-yl)oxy)-2,2,7,7-tetramethyl-8-oxooctanoic acid (Int-54).* A solution of (2-hydroxy-3-octanoyloxy-propyl) octanoate (**Int-11**, 1.37 g, 3.90 mmol) and pyridine (4.00 mL, 49.6 mmol) in dichloromethane (20 mL) was added to a solution of 2,2,7,7-tetramethyloctanedioyl dichloride (**Int-53**, 2.19 g, 7.80 mmol) in dichloromethane (10 mL) and the mixture heated to reflux for 16 hours. The reaction was cooled to room temperature then diluted with ethyl acetate (50 mL) and washed with hydrochloric acid (1 M, aqueous, 2 x 10 mL) then brine (10 mL) then dried over sodium sulfate, filtered, and concentrated. Material purified by normal phase chromatography (Biotage Isolera, 80 g SiliCycle cartridge; eluent 0 - 40% ethyl acetate in heptane over 15 CV) to afford the desired product (860 mg, 40% yield) as a colourless oil. MF: C₃₁H₅₆O₈ MW: 556.77; UPLC4-MS: (XB BEH 300 C4 20-95%): R_t = 4.48 min., 57.7% (UV), 98.2% (ELSD). MS (ESIneg): m/z = 555.71 [M-H]⁻; ¹H NMR (400 MHz, CDCl₃): δ [ppm] = 5.30 – 5.23 (m, 1H), 4.32 (dd, J = 11.9, 4.4 Hz, 2H), 4.16 (dd, J = 11.9, 6.0 Hz, 2H), 2.33 (t, J = 7.6 Hz, 4H), 1.67 – 1.60 (m, J = 7.3 Hz, 4H), 1.58 – 1.51 (m, 4H), 1.37 – 1.22 (m, 20H), 1.21 (s, 6H), 1.17 (s, 6H), 0.90 (t, J = 6.5 Hz, 6H); 1 x exchangeable OH proton not observed. ¹³C NMR (101 MHz, CDCl₃): δ [ppm] = 176.9, 173.4, 68.8, 62.1, 42.4, 42.0, 40.40, 40.35, 34.1, 31.6, 29.1, 28.9, 25.5, 25.4, 25.1, 25.0, 24.9, 22.6, 14.1.

[0146] *Synthesis of AGM-CASI-C8a'a'aaMe-2-TG-octanoate (IV-1b).* To a solution of chloromethyl acetyl(3-(7-methoxynaphthalen-1-yl)propyl)carbamate (**Int-2**, 327 mg, 956 μmol) and 8-((1,3-Bis(octanoyloxy)propan-2-yl)oxy)-2,2,7,7-tetramethyl-8-oxooctanoic acid (**Int-54**, 560 mg, 957 μmol) in toluene (30 mL) was added caesium carbonate (934 mg, 2.87 mmol) and tetrabutylammonium iodide (177 mg, 479 μmol). The reaction was heated to 50 °C and stirred for 3 hours then cooled to room temperature and saturated ammonium chloride (aqueous, 100 mL) was added. The aqueous layer was extracted with ethyl acetate (3 x 100 mL) and the combined organic layers washed with brine then dried over sodium sulfate, filtered, and concentrated. Material was purified by normal phase chromatography (Biotage Isolera, 80 g SiliCycle cartridge; eluent 0-25% ethyl acetate in heptanes) to afford the desired product (**IV-1b**, 460 mg, 56% yield) as a colourless oil. MF: C₄₈H₇₃O₁₂N MW: 856.09; UPLC4-MS: (XB BEH300 C4 20to95%): R_t =

5.88 min., 99.0% (UV), 100% (ELSD); MS (ESIpos): m/z = 874.18 $[M+NH_4]^+$; 1H -NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.74 (d, J = 8.8 Hz, 1H), 7.68-7.65 (m, 2H), 7.33 (d, J = 6.4 Hz, 1H), 7.29-7.24 (m, 1H), 7.15 (dd, J = 8.9, 2.3 Hz, 1H), 5.83 (s, 2H), 5.24-5.19 (m, 1H), 4.27 (dd, J = 11.7, 4.4 Hz, 2H), 4.11 (dd, J = 11.9, 6.0 Hz, 2H), 4.05-4.00 (m, 5H), 3.23-3.19 (m, 2H), 2.57 (s, 3H), 2.29 (t, J = 7.6 Hz, 4H), 1.61-1.52 (m, 6H), 1.44-1.40 (m, 2H), 1.35-1.23 (m, 16H), 1.21-1.12 (m, 10H), 1.09 (s, 6H), 0.87 (t, J = 6.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ [ppm] = 176.8, 176.5, 173.2, 172.8, 158.1, 153.1, 133.3, 133.1, 130.1, 129.2, 127.7, 127.2, 123., 118.6, 102.4, 80.9, 68.8, 62.1, 55.6, 45.0, 42.4, 42.3, 40.2, 40.1, 34.0, 32.7, 31.6, 29.1, 28.9, 26.9, 25.4, 25.2, 25.0, 24.9, 24.85, 22.6, 14.1.

AGM-CASI-C10a'a'aaMe-acid-octanoate (IV-2b)

Synthesis of AGM-CASI-C10a'a'aaMe-Acid

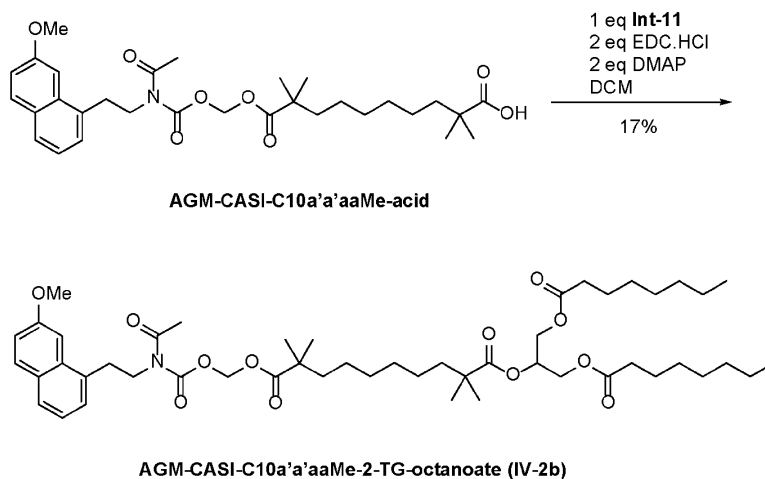


[0147] *Synthesis of 2,2,9,9-tetramethyldecanedioic acid (Int-55).* Diisopropylamine distilled and stored over KOH under argon before running the experiment. To an ice-cooled solution of diisopropylamine, 99+% (8.30 g, 82.0 mmol, 11.6 mL, 5 eq.) in dry tetrahydrofuran (40 mL) was added n -BuLi in hexanes (2.5 M, 32.8 mL, 5 eq.) drop-wise. The reaction mixture was stirred for 30 mins at 0 °C, then 2-methylpropanoic acid (2.90 g, 32.9 mmol, 3.06 mL, 2.01 eq.) was added dropwise. The mixture was stirred for 60 mins at this temperature, then allowed to warm to room temperature over 30 mins. The mixture was then cool down to 0 °C and 1,6-dibromohexane (4.00 g, 16.4 mmol, 2.48 mL, 1 eq.) was added dropwise. The white suspension was stirred at 0°C for 1 hour, then room temperature for 16 hours. The reaction mixture was poured into ice-cold 1N HCl (200 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organics were washed with

saturated brine (100 mL), dried over anhydrous sodium sulfate and concentrated to give crude product. The crude was purified through recrystallizing with a minimum amount of hot heptane (20 mL) to afford the product (**Int-55**, 2.51 g, 59.3 % yield) as an off white solid. MF: C₁₄H₂₆O₄ MW: 258.35; ¹H NMR (400 MHz, DMSO-d₆): δ [ppm] = 11.98 (s, 2H), 1.43-1.39 (m, 4H), 1.26-1.11 (m, 8H), 1.06 (s, 12H); ¹³C NMR (100 MHz, DMSO-d₆): δ [ppm] = 178.8, 41.2, 40.2, 29.5, 25.0, 24.5.

[0148] *Synthesis of AGM-CASI-C10a'a'aaMe-Acid.* To a solution of 2,2,9,9-tetramethyldecanedioic acid (**Int-55**, 250 mg, 968 μmol, 1 eq.) and **Int-2** (166 mg, 484 μmol, 0.5 eq.) in *N,N*-dimethylformamide (2 mL) under argon, Cs₂CO₃ (315 mg, 968 μmol, 1 eq.) and TBAI (35.7 mg, 96.8 μmol, 0.1 eq.) were added. The reaction mixture was heated to 50 °C for 2 hours. The reaction mixture was cooled to room temperature and a saturated solution of NH₄Cl (aq) 50 mL was added. The aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over MgSO₄ and concentrated under vacuum to afford a crude product. Material was purified by reverse phase chromatography (Biotage Isolera, 40 g SiliCycle C18 cartridge; gradient 90 - 100% (acetonitrile + 0.1% formic acid) in (water + 0.1% formic acid) over 10 CVs) to afford the product (AGM-CASI-C10a'a'aaMe-Acid, 66.0 mg, 12.2 % yield) as a white solid. MF: C₃₁H₄₃O₈N MW: 557.67; UPLC6-MS: (BEH-C8 Long Base 2 to 95%): R_t = 1.66 min (95.7%); MS(ESIpos): m/z = 580.2 [M+Na]⁺; ¹H NMR (400 MHz, CDCl₃): δ [ppm] = 7.74 (d, *J* = 8.8 Hz, 1H), 7.68-7.65 (m, 2H), 7.33 (d, *J* = 6.8 Hz, 1H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.16 (dd, *J* = 8.9, 2.3 Hz, 1H), 5.84 (s, 2H), 4.05-3.97 (m, 5H), 3.24-3.15 (m, 2H), 2.57 (s, 3H), 1.54 (d, *J* = 10.3 Hz, 2H), 1.43 (d, *J* = 7.1 Hz, 2H), 1.24-1.15 (m, 20H); Exchangeable acidic proton not observed; ¹³C NMR (100 MHz, CDCl₃): δ [ppm] = 184.2, 176.8, 173.0, 158.3, 153.3, 133.5, 133.2, 130.2, 129.3, 127.8, 127.3, 123.4, 118.7, 102.6, 81.0, 55.7, 45.1, 42.6, 42.2, 40.5, 40.4, 32.9, 29.99, 29.95, 29.8, 27.0, 25.0, 24.9, 24.7.

Synthesis of AGM-CASI-C10a'a'aaMe-acid-octanoate (IV-2b)

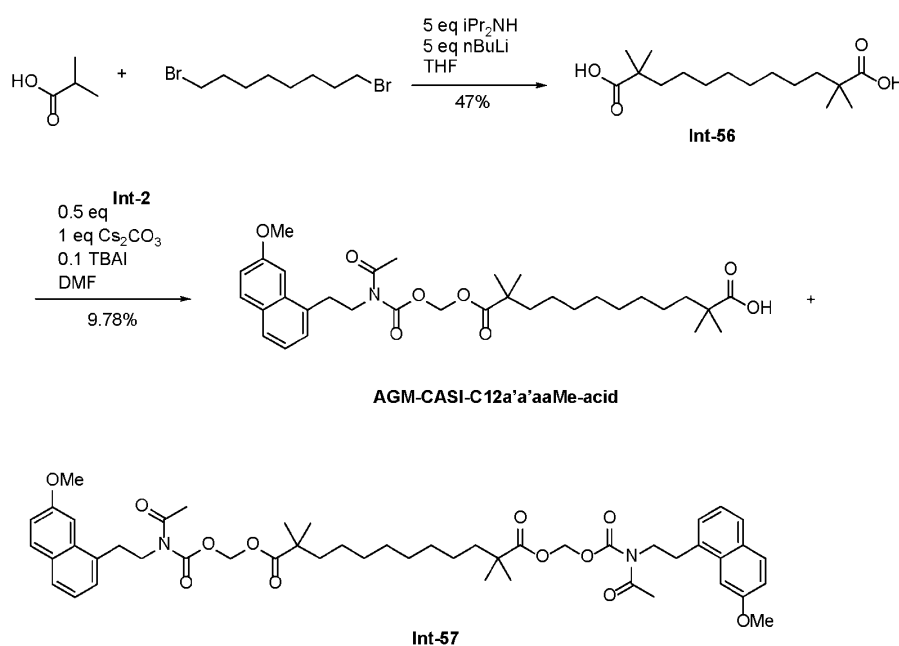


[0149] *Synthesis of AGM-CASI-C10a'a'aaMe-octanoate (IV-2b).* To a solution of **AGM-CASI-C10a'a'aaMe-acid** (372 mg, 647 μ mol) and **Int-11** (223 mg, 647 μ mol) in dichloromethane (10 mL), EDC.HCl (201 mg, 1.29 mmol) and DMAP (158 mg, 1.29 mmol) were added. The reaction was stirred at room temperature for 72 hours. A saturated solution of NH_4Cl (aq) (50 mL) was added and the aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated under vacuum to afford a crude residue. The crude product was purified by normal phase chromatography (Biotage Isolera, 40 g SiliCycle cartridge; eluent 0 - 40% ethyl acetate in heptane over 15 CVs) to afford the product (**AGM-CASI-C10a'a'aaMe-octanoate (IV-2b)**, 97.0 mg, 17.0 % yield) as colourless oil. MF: $\text{C}_{50}\text{H}_{77}\text{O}_{12}\text{N}$ MW: 884.14; UPLC4 (XB BEH 300 C4 20to95) R_t = 5.96 min, 89.2% (UV), 97.2% (ELSD). MS (ESIpos): m/z = 902.4 $[\text{M}+\text{NH}_4]^+$; UPLC4 (XB BEH 300 C18 30 to 100 Ext TFA) R_t = 41.40 min, 95.9% (UV); ^1H NMR (400 MHz, CDCl_3): δ [ppm] = 7.74 (d, J = 8.9 Hz, 1H), 7.68-7.65 (m, 2H), 7.33 (d, J = 6.1 Hz, 1H), 7.28-7.24 (m, 1H), 7.15 (dd, J = 8.9, 2.4 Hz, 1H), 5.84 (s, 2H), 5.28-5.20 (m, 1H), 4.27 (dd, J = 11.9, 4.4 Hz, 2H), 4.12 (dd, J = 11.9, 4.4 Hz, 2H), 4.05-4.00 (m, 5H), 3.23-3.19 (m, 2H), 2.56 (s, 3H), 2.32-2.27 (m, 4H), 1.61-1.51 (m, 6H), 1.43-1.39 (m, 2H), 1.35-1.27 (m, 16H), 1.19-1.14 (m, 14H), 1.11 (s, 6H), 0.87 (t, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ [ppm] = 177.5, 177.1, 176.7, 173.4, 172.9, 158.2, 153.3, 133.4, 133.2,

130.2, 129.3, 127.8, 127.3, 123.3, 118.7, 102.5, 80.9, 69.0, 68.9, 62.2, 55.7, 45.1, 42.5, 42.4, 40.6, 40.5, 40.4, 34.3, 34.2, 32.9, 31.8, 30.2, 30.1, 29.2, 29.1, 27.1, 25.1, 25.0, 25.0, 22.7, 14.2.

AGM-CASI-C12a'a'aaMe-2-TG-octanoate (IV-3b)

Synthesis of AGM-CASI-C12a'a'aaMe-acid

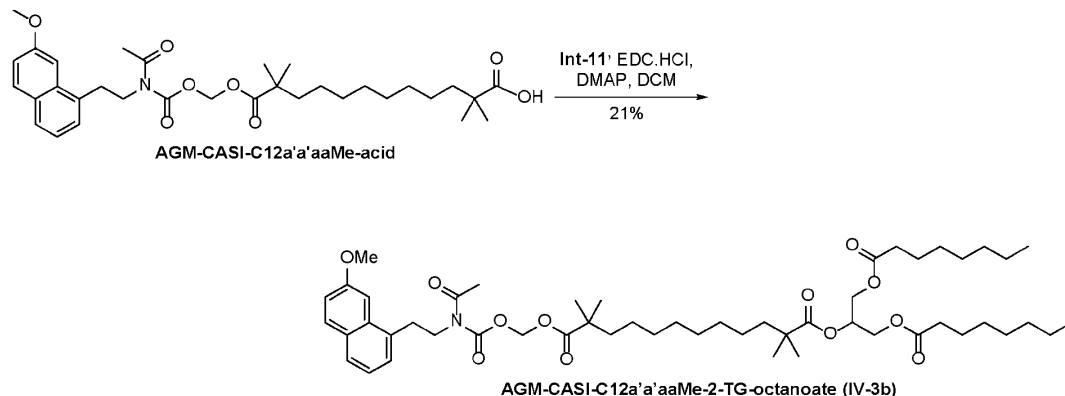


[0150] *Synthesis of 2,2,11,11-tetramethyldodecanedioic acid (Int-56).* 100 mL of diisopropylamine was distilled from a bed of KOH by fractional distillation and was kept in a 100 mL flask over KOH under argon. To an ice-cooled solution of diisopropylamine, 99+% (7.44 g, 73.5 mmol, 10.4 mL, 5 eq.) in tetrahydrofuran (40 mL) at 0°C under argon, n-BuLi in hexanes (2.5 M, 29.4 mL, 5 eq.) was added dropwise. The reaction mixture was left to stir whilst maintaining for 1 hour. 2-methylpropanoic acid (2.60 g, 29.5 mmol, 2.74 mL, 2.01 eq.) was then added dropwise. The mixture was stirred at 0°C for 30 mins and was allowed to warm up to room temperature and stirred for further 30 mins. The reaction mixture was cooled to 0°C and 1,8-dibromooctane (4.00 g, 14.7 mmol, 2.71 mL, 1 eq.) was added dropwise. The mixture was allowed to warm to room temperature and left to stir for 16 hours. The reaction mixture was poured into ice-cold 1N HCl (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organics were washed with

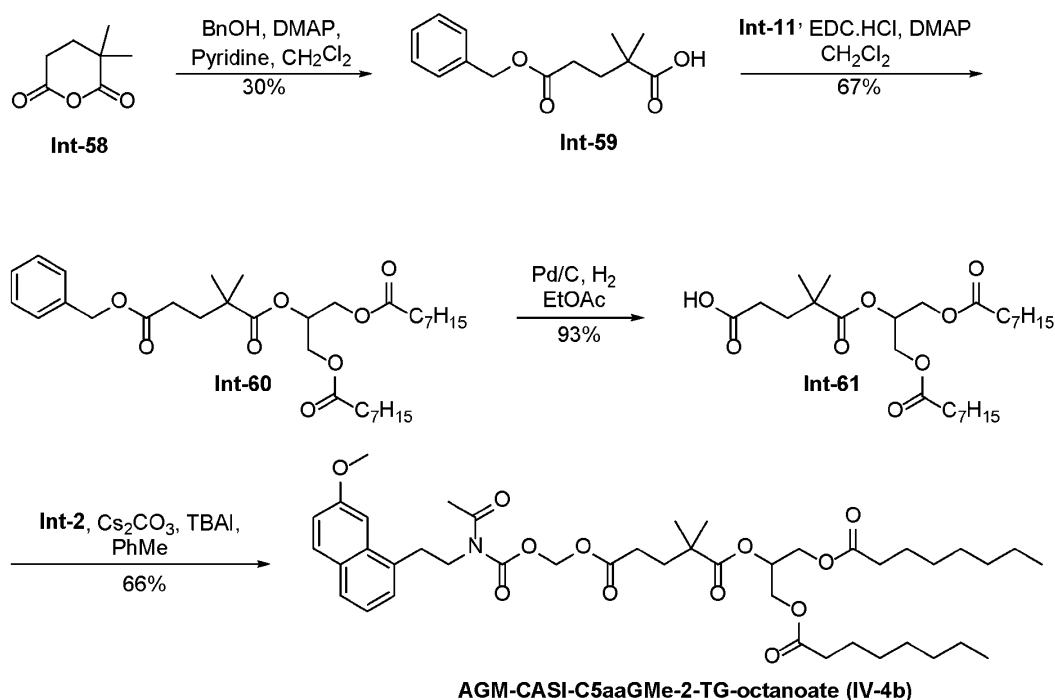
saturated brine (100 mL), dried over anhydrous sodium sulfate and concentrated to give crude as a colorless solid. The crude was recrystallized with a minimum amount of hot heptane (20 mL) and filtered to give the product (**Int-56**, 2.02 g, 48.0 % yield) as an off white solid. MF: C₁₆H₃₀O₄ MW: 286.41; ¹H NMR (400 MHz, DMSO-d₆): δ [ppm] = 11.97 (s, 2H), 1.43-1.39 (m, 4H), 1.28-1.22 (m, 12H), 1.05 (s, 12H); ¹³C NMR (100 MHz, DMSO-d₆): δ [ppm] = 178.8, 41.3, 40.3, 40.2, 38.9, 29.6, 29.0, 25.1, 24.6.

[0151] *Synthesis of AGM-CASI-C12a'a'aaMe-Acid.* To a solution of 2,2,11,11-tetramethyldodecanedioic acid (250 mg, 873 μmol, 1 eq.) and **Int-2** (150 mg, 436 μmol, 0.5 eq.) in *N,N*-dimethylformamide (2 mL) under argon, Cs₂CO₃ (284 mg, 873 μmol, 1 eq.) and TBAI (32.2 mg, 87.3 μmol, 0.1 eq.) were added. The reaction mixture was heated to 50 °C for 2 hours. The reaction mixture was cooled to room temperature and a saturated solution of NH₄Cl (aq) 50 mL was added. The organics were extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over MgSO₄ and concentrated under vacuum to afford a crude product. Material was purified by reverse phase chromatography (Biotage Isolera, 25 g SiliCyle C18 cartridge; gradient 90 - 100% (acetonitrile + 0.1% formic acid) in (water + 0.1% formic acid) over 10 CVs) to afford the product (AGM-CASI-C12a'a'aaMe-Acid, 50.0 mg, 9.78 % yield) as a white gum. MF: C₃₃H₄₇O₈N MW: 585.73; C₁₈UPLC6-MS: (BEH-C8 Long Base 2 to 95%) R_t = 1.80 min (92.0%), MS (ESIpos): m/z = [M+Na]⁺ 608.2. ¹H NMR (400 MHz, CDCl₃): δ [ppm] = 7.74 (d, J = 9.0 Hz, 1H), 7.68-7.65 (m, 2H), 7.33 (d, J = 6.4 Hz, 1H), 7.28-7.23 (m, 1H), 7.16 (dd, J = 9.0, 2.4 Hz, 1H), 5.84 (s, 2H), 4.05-3.97 (m, 5H), 3.24-3.20 (m, 2H), 2.59-2.54 (m, 3H), 1.55-1.42 (m, 4H), 1.26-1.12 (m, 24H); Exchangeable carboxylic acid proton not observed. ¹³C NMR (100 MHz, CDCl₃): δ [ppm] = 184.3, 176.8, 173.0, 158.2, 153.3, 133.4, 133.2, 130.2, 129.3, 127.8, 127.3, 123.3, 118.7, 102.5, 81.0, 55.7, 45.1, 42.6, 42.2, 40.6, 40.5, 32.8, 30.2, 29.60, 29.55, 27.0, 26.5, 25.1, 25.0, 24.9. The **Int-57** was also obtained during the reaction (72.0 mg, 9.32 % yield) as a white solid.

Synthesis of AGM-CASI-C12a'a'aaMe-2-TG-octanoate (IV-3b)



[0152] *Synthesis of AGM-CASI-C12a'a'aaMe-2-TG-octanoate (IV-3b).* To a solution of **AGM-CASI-C12a'a'aaMe-acid** (205 mg, 297 μmol) and **Int-11** (103 mg, 299 μmol) in dichloromethane (6 mL) at ambient temperature, was added EDCI.HCl (114 mg, 595 μmol), followed by DMAP (73.0 mg, 598 μmol) and stirred for 63 hours. The reaction mixture was concentrated under vacuum and the crude material was purified by normal phase chromatography (Biotage Isolera, 40 g SiliCycle cartridge; eluent 0 - 20% ethyl acetate in heptane) to afford the desired product (57 mg, 21% yield) as colourless oil. MF $\text{C}_{52}\text{H}_{81}\text{NO}_{12}$, MW 912.20; UPLC4 (XB BEH 300 C4 20to95) R_t = 6.19 min, 94.9% (UV), 100.0% (ELSD). MS (ESIpos): m/z = 930.5 $[\text{M}+\text{NH}_4]^+$; ^1H NMR (400 MHz, CDCl_3): δ [ppm] = 7.75 (d, J = 10.8 Hz, 1H), 7.68-7.65 (m, 2H), 7.33 (d, J = 6.6 Hz, 1H), 7.27-7.24 (m, 1H), 7.15 (dd, J = 8.9, 2.3 Hz, 1H), 5.84 (s, 2H), 5.30-5.21 (m, 1H), 4.29 (dd, J = 11.9 Hz, 2H), 4.12 (dd, J = 11.7 Hz, 2H), 4.05-3.99 (m, 5H), 3.23-3.19 (m, 2H), 2.56 (s, 3H), 2.25-2.32 (m, 4H), 1.62-1.42 (m, 8H), 1.32-1.13 (m, 40H), 0.87 (t, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ [ppm] = 177.6, 177.2, 176.8, 173.4, 172.9, 158.2, 153.3, 133.4, 133.2, 130.2, 129.3, 127.8, 127.3, 123.3, 118.7, 102.5, 80.9, 69.0, 68.9, 62.3, 55.7, 45.1, 42.6, 42.5, 40.7, 40.6, 40.5, 34.3, 34.2, 32.9, 31.8, 30.3, 30.2, 29.7, 29.2, 29.1, 27.1, 25.2, 25.1, 25.02, 25.00, 22.7, 14.2; UPLC4: (XB C18 4.6 x 150mm x 3.5 μm , 30to100%, 50 min TFA method) R_t = 45.3 min, 97.9% (total plot).

AGM-CASI-C5aaGMe-2-TG-octanoate (IV-4b)

[0153] *Synthesis of 5-(Benzyloxy)-2,2-dimethyl-5-oxopentanoic acid (Int-59).* To a stirred solution of 3,3-dimethyltetrahydropyran-2,6-dione (**Int-58**, 1.00 g, 7.03 mmol) and benzyl alcohol (0.80 mL, 7.73 mL) in dichloromethane (25 mL) was added pyridine (5.60 mL, 69.5 mL) and 4-dimethylaminopyridine (86.0 mg, 704 μmol). The mixture was then stirred at 50 °C for 16 hours. The reaction mixture was diluted with dichloromethane (100 mL) and washed with hydrochloric acid (1 M, aqueous, 2 x 100 mL) then brine (100 mL). The organics were dried over sodium sulfate, filtered, and concentrated. Material purified by normal phase chromatography (Biotage Isolera, 80 g SilliCycle cartridge; eluent 5-40% ethyl acetate in heptane over 10 CV). Product fractions were combined and concentrated then repurified by normal phase chromatography (Biotage Isolera, 40 g SilliCycle cartridge; eluent 0-30% ethyl acetate in dichloromethane over 15 CV) to afford the desired product (**Int-59**, 560 mg, 30% yield) as a colourless oil. MF: $\text{C}_{14}\text{H}_{18}\text{O}_4$ MW: 250.29; ^1H

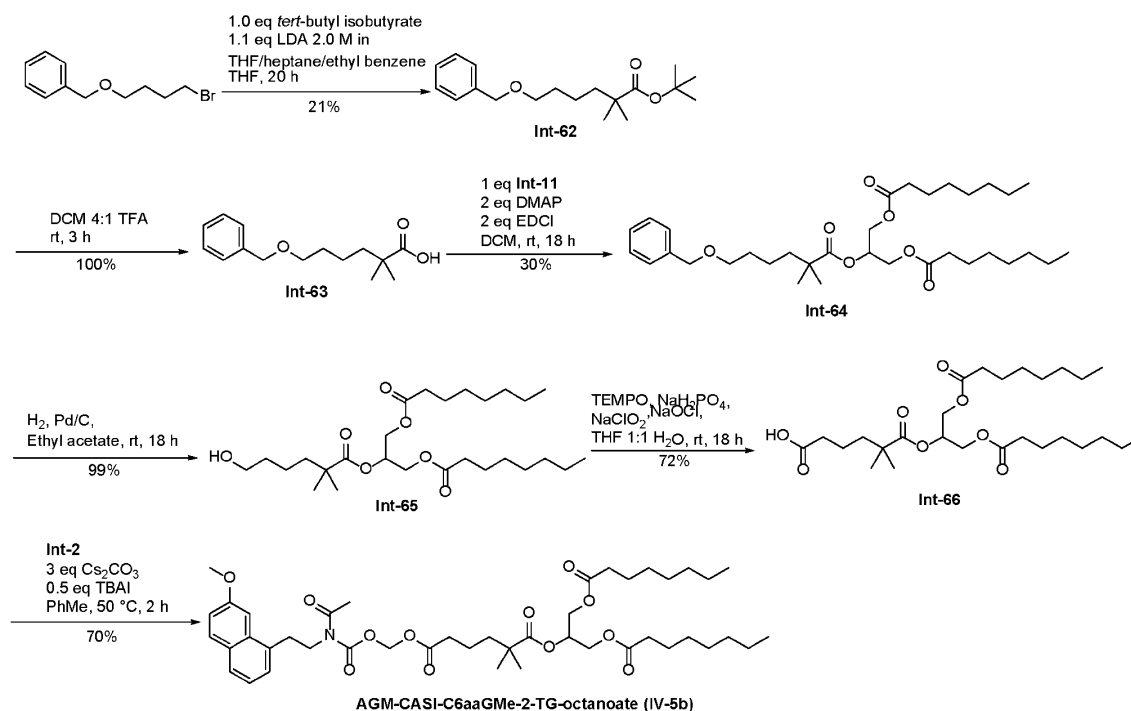
NMR (400 MHz, CDCl₃): δ [ppm] = 7.39-7.30 (m, 5H), 5.11 (s, 2H), 2.42-2.38 (m, 2H), 1.95-1.91 (m, 2H), 1.21 (s, 6H). Exchangeable carboxylic acid proton not observed.

[0154] *Synthesis of 5-Benzyl 1-(1,3-bis(octanoyloxy)propan-2-yl) 2,2-dimethylpentanedioate (Int-60).* To a stirred solution of 5-benzyloxy-2,2-dimethyl-5-oxo-pentanoic acid (**Int-59**, 560 mg, 2.13 mmol) and (2-hydroxy-3-octanoyloxy-propyl) octanoate (**Int-11**, 746 mg, 2.12 mmol) in dichloromethane (25 mL) was added *N*-Ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide hydrochloride (658 mg, 4.24 mmol) and 4-dimethylaminopyridine (502 mg, 4.26 mmol) and the reaction stirred at room temperature for 40 hours. The reaction was quenched by addition of saturated ammonium chloride (aqueous, 50 mL) and the organics extracted into ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (50 mL) then dried over sodium sulfate, filtered, and concentrated. Material purified by normal phase chromatography (Biotage Isolera, 80 g SiliCycle cartridge; eluent 0 - 40% ethyl acetate in heptane over 15 CV) to afford the desired product (860 mg, 67% yield) as a colourless oil. MF: C₃₃H₅₂O₈, MW: 576.76; UPLC4-MS: (XB BEH 300 C4 20-95%): R_t = 5.07 min., 99.7% (UV), 100% (ELSD). MS (ESIpos): m/z = 594.8 [M+NH₄]⁺; ¹H NMR (400 MHz, CDCl₃): δ [ppm] = 7.38-7.30 (m, 5H), 5.29-5.22 (m, 1H), 5.10 (s, 2H), 4.31 (dd, *J* = 12.0, 4.2 Hz, 2H), 4.12 (dd, *J* = 12.0, 6.4 Hz, 2H), 2.37-2.33 (m, 2H), 2.28 (t, *J* = 7.6 Hz, 4H), 1.93-1.89 (m, 2H), 1.61-1.55 (m, 4H), 1.34-1.27 (m, 16H), 1.18 (s, 6H), 0.87 (t, *J* = 6.8 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃): δ [ppm] = 176.3, 173.4, 173.2, 136.0, 128.7, 128.29, 128.36, 69.4, 66.5, 62.2, 42.0, 35.0, 34.1, 31.8, 30.2, 29.2, 29.1, 25.04, 24.97, 22.7, 14.2.

[0155] *Synthesis of 5-((1,3-Bis(octanoyloxy)propan-2-yl)oxy)-4,4-dimethyl-5-oxopentanoic acid (Int-61).* A solution of 5-benzyl 1-(1,3-bis(octanoyloxy)propan-2-yl) 2,2-dimethylpentanedioate (**Int-60**, 860 mg, 1.49 mmol) in ethyl acetate (30 mL) was placed under an argon atmosphere. Palladium on carbon (317 mg, 149 μ mol, 5% w/w) was added and the mixture evacuated and backfilled with hydrogen (x 3) then stirred at room temperature for 4 hours. The mixture was filtered through a pad of Celite® and the filter cake washed with ethyl acetate (2 x 20 mL). The combined filtrates were concentrated to afford the desired product (**Int-61**, 710 mg, 93% yield) as a colourless oil. MF: C₂₆H₄₆O₈ MW: 486.64; UPLC4-MS: (XB BEH 300 C4 20-95%): R_t = 3.32 min., 100% (UV), 100% (ELSD). MS (ESIpos): m/z = 504.7 [M+NH₄]⁺. MS (ESIneg): m/z = 485.6 [M-H]⁻; ¹H NMR (400 MHz, CDCl₃): δ [ppm] = 5.27-5.24 (m, 1H), 4.34 (dd, *J* = 12.0, 4.2 Hz, 2H), 4.13 (dd, *J* = 11.9, 6.2 Hz, 2H), 2.38-2.29 (m, 6H), 1.91-1.87 (m, 2H), 1.64-1.57 (m, 4H),

1.31-1.28 (m, 16H), 1.20 (s, 6H), 0.88 (t, $J = 6.8$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ [ppm] = 177.4, 176.2, 173.5, 69.5, 62.2, 42.0, 34.8, 34.2, 31.8, 29.7, 29.2, 29.0, 25.1, 25.0, 22.7, 14.2.

[0156] *Synthesis of AGM-CASI-5aaGMe-2-TG-octanoate (IV-4b)*. To a stirred solution of 5-((1,3-bis(octanoyloxy)propan-2-yl)oxy)-4,4-dimethyl-5-oxopentanoic acid (**Int-61**, 500 mg, 977 μmol) and **Int-2** (334 mg, 977 μmol) in toluene (25 mL) was added cesium carbonate (955 mg, 2.93 mmol) and tetrabutylammonium iodide (180 mg, 487 μmol). The reaction mixture was heated to 50 °C and stirred for 3 hours then cooled to room temperature and quenched with saturated ammonium chloride (aqueous, 50 mL). The mixture was diluted with ethyl acetate (100 mL) and the organics washed with brine (50 mL) then dried over sodium sulfate, filtered, and concentrated. Material purified by normal phase chromatography (Biotage Isolera, 80 g SiliCycle cartridge; eluent 0-25% ethyl acetate in heptane over 12 CV) to afford the desired product (510 mg, 66% yield) as a colorless oil. MF: $\text{C}_{43}\text{H}_{63}\text{O}_{12}\text{N}$ MW: 785.96; UPLC4-MS: (XB BEH300 C4 20to95%) $R_t = 5.41$ min., 99.6% (UV), 100% (ELSD); MS (ESIpos): $m/z = 804.0$ $[\text{M}+\text{NH}_4]^+$; ^1H NMR (400 MHz, CDCl_3): δ [ppm] = 7.74 (d, $J = 8.9$ Hz, 1H), 7.67 (d, $J = 8.1$ Hz, 1H), 7.64 (d, $J = 2.2$ Hz, 1H), 7.32 (d, $J = 6.0$ Hz, 1H), 7.28-7.24 (m, 1H), 7.16 (dd, $J = 8.9, 2.4$ Hz, 1H), 5.79 (s, 2H), 5.24-5.21 (m, 1H), 4.31 (dd, $J = 12.0, 4.2$ Hz, 2H), 4.11 (dd, $J = 12.0, 6.1$ Hz, 2H), 4.06-4.02 (m, 5H), 3.24-3.20 (m, 2H), 2.57 (s, 3H), 2.42-2.38 (m, 2H), 2.28 (t, $J = 7.5$ Hz, 4H), 1.93-1.88 (m, 2H), 1.58 (t, $J = 7.3$ Hz, 4H), 1.33-1.21 (m, 16H), 1.18 (s, 6H), 0.87 (t, $J = 6.8$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ [ppm] = 176.1, 173.3, 172.9, 172.1, 158.3, 153.3, 133.5, 133.2, 130.2, 129.3, 127.8, 127.3, 123.3, 118.7, 102.6, 80.8, 69.5, 62.1, 55.7, 45.1, 41.9, 34.5, 34.1, 32.8, 31.8, 29.9, 29.2, 29.0, 27.1, 25.1, 25.0, 22.7, 14.2;

AGM-CASI-C6aaGMe-2-TG-octanoate (IV-5b)

[0157] *Synthesis of tert-butyl 6-(benzyloxy)-2,2-dimethylhexanoate (Int-62).* To a stirring solution of *tert*-butyl 2-methylpropanoate (1.19 g, 8.24 mmol) in dry tetrahydrofuran (40 mL) was added LDA (2M in THF/heptane/ethylbenzene, 9.05 mmol, 4.52 mL) dropwise at 0 °C under argon. The reaction mixture was stirred for 30 minutes at 0 °C, then benzyl 4-bromobutyl ether (2.00 g, 8.23 mmol) was added dropwise under argon. The mixture was stirred for 1 hour at 0 °C under argon then allowed to stir at room temperature for 20 hours. The reaction mixture was then slowly poured into ice-cold 2M HCl (100 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organics were washed with saturated brine (250 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a yellow oil. The material was purified by normal phase purification (Biotage Isolera, 120 g SilliCycle cartridge; eluent 0-5% ethyl acetate in heptane over 20 CVs) to afford the desired product (**Int-62**, 532 mg, 21.1% yield) as a colourless oil. MF: C₁₉H₃₀O₃ MW: 306.44; ¹H NMR (400 MHz, CDCl₃): δ [ppm] = 7.36 - 7.25 (m, 5H), 4.49 (s, 2H), 3.46 (t, *J* = 6.6 Hz, 2H), 1.64 - 1.57 (m, 2H), 1.51 - 1.45 (m, 2H), 1.42 (s, 9H), 1.36 - 1.28 (m, 2H), 1.11 (s, 6H);

^{13}C NMR (100 MHz, CDCl_3): δ [ppm] = 177.5, 138.8, 128.5, 127.8, 127.6, 79.7, 73.0, 70.4, 42.8, 40.7, 30.4, 28.2, 25.3, 21.8.

[0158] *Synthesis of 6-(Benzyloxy)-2,2-dimethylhexanoic acid (Int-63).* To a stirring solution of tert-butyl 6-(benzyloxy)-2,2-dimethylhexanoate (520 mg, 1.70 mmol) in dichloromethane (8 mL) was added trifluoroacetic acid (2.98 g, 26.1 mmol, 2.00 mL) at room temperature. The reaction was stirred at room temperature for 3 hours. The reaction mixture was concentrated in vacuo to afford the desired product (**Int-63**, 423 mg, 99.6 % yield) as a yellow oil. MF: $\text{C}_{15}\text{H}_{22}\text{O}_3$ MW: 250.3; ^1H NMR (400 MHz, CDCl_3): δ [ppm] = 10.39 (br s, 1H), 7.37 - 7.26 (m, 5H), 4.53 (s, 2H), 3.49 (t, J = 6.6 Hz, 2H), 1.66 - 1.53 (m, 4H), 1.40 - 1.31 (m, 2H), 1.19 (s, 6H) (Contains possible residual ester, doubling up of C6 portion signals not clear if due to poor peak shape). ^{13}C NMR (100 MHz, CDCl_3): δ [ppm] = 184.8, 138.3, 128.6, 127.9, 127.8, 73.0, 70.2, 42.3, 40.3, 30.1, 25.0, 21.7.

[0159] *Synthesis of 2-((6-(Benzyloxy)-2,2-dimethylhexanoyl)oxy)propane-1,3-diyl dioctanoate (Int-64).* To a stirring solution of 6-(benzyloxy)-2,2-dimethylhexanoic acid (**Int-63**, 550 mg, 2.20 mmol) in dichloromethane (15 mL) was added **Int-11** (757 mg, 2.20 mmol), EDCI (843 mg, 4.40 mmol) and DMAP (537 mg, 4.40 mmol) at room temperature. The reaction was stirred for 18 hours at room temperature. The reaction mixture was concentrated in vacuo. The material purified by normal phase purification (Biotage Isolera, 80 g SilliCycle cartridge; eluent 0-20% ethyl acetate in heptane over 16 CV's) to afford the desired product (**Int-64**, 400 mg, 30.3 % yield) as a colourless oil. MF: $\text{C}_{34}\text{H}_{56}\text{O}_7$ MW: 576.8; UPLC4-MS: (XB BEH 300 C4 20-95%): R_t = 5.37 min, 75.0% (UV), 96.0% (ELSD). MS (ESIpos): m/z = 594.9 $[\text{M}+\text{NH}_4]^+$; ^1H NMR (400 MHz, CDCl_3): δ [ppm] = 7.36 - 7.30 (m, 5H), 5.33 - 5.17 (m, 1H), 4.49 (s, 2H), 4.29 (dd, J = 4.3, 11.9 Hz, 2H), 4.13 (dd, J = 6.0, 11.9 Hz, 2H), 3.45 (t, J = 6.6 Hz, 2H), 2.29 (t, J = 7.6 Hz, 4H), 1.64 - 1.50 (m, 8H), 1.43 - 1.24 (m, 18H), 1.16 (s, 6H), 0.88 (t, J = 6.7 Hz, 6H) (Contains residual 6-(benzyloxy)-2,2-dimethylhexanoic acid, 4% by ELSD, 8.9% w/w calculated by ^1H NMR).

[0160] *Synthesis of 2-((6-Hydroxy-2,2-dimethylhexanoyl)oxy)propane-1,3-diyl dioctanoate (Int-65).* To a stirring solution of 2-((6-(benzyloxy)-2,2-dimethylhexanoyl)oxy)propane-1,3-diyl dioctanoate (**Int-64**, 400 mg, 693 μmol) in ethyl acetate (8 mL) was added Pd/C (74.0 mg, 34.8 μmol , 5% loading on charcoal) at room temperature. The reaction was subjected to vacuum then introduced to a hydrogen atmosphere. The reaction was stirred at room temperature for 18 hours.

The reaction mixture was filtered through Celite. The collected organics were concentrated in vacuo to afford the desired product (**Int-65**, 333 mg, 98.7%) as a colourless oil. MF: C₂₇H₅₀O₇ MW: 486.68; UPLC4-MS: (XB BEH 300 C4 20-95%): R_t = 4.39 min, 83.6% (UV), 99.3% (ELSD). MS (ESIpos): m/z = 504.8 [M+NH₄]⁺; ¹H NMR (400 MHz, CDCl₃): δ [ppm] = 5.29 - 5.19 (m, 1H), 4.32 (dd, *J* = 4.2, 11.9 Hz, 2H), 4.13 (dd, *J* = 5.9, 11.9 Hz, 2H), 3.65 - 3.61 (m, 2H), 2.30 (t, *J* = 7.6 Hz, 4H), 1.63 - 1.50 (m, 8H), 1.33 - 1.23 (m, 18H), 1.16 (s, 6H), 0.91 - 0.84 (m, 6H). Exchangeable alcohol signal not observed. (Contains 6.2% w/w by ¹H NMR of residual 6-hydroxy-2,2-dimethylhexanoic acid.)

[0161] *Synthesis of 6-((1,3-Bis(octanoyloxy)propan-2-yl)oxy)-5,5-dimethyl-6-oxohexanoic acid (Int-66).* To a stirring solution of 2-((6-hydroxy-2,2-dimethylhexanoyl)oxy)propane-1,3-diyl dioctanoate (**Int-65**, 330 mg, 678 μmol) in tetrahydrofuran (3.5 mL) was added sodium phosphate monobasic (204 mg, 1.70 mmol), water (3.5 mL), TEMPO (44.0 mg, 282 μmol), sodium chlorite (154 mg, 1.36 mmol, 62.4 μL, 80% purity) and finally sodium hypochlorite (67 μL, 84.1 mg, 170 μmol). The reaction was stirred at room temperature for 18 hours. The reaction mixture was quenched with saturated 2M HCl (25 mL) and extracted with ethyl acetate (3 x 25 mL). The organics were combined and washed with water (75 mL) followed by washing with brine (75 mL). The organic layer was collected and dried over sodium sulfate, filtered and concentrated in vacuo to give a yellow oil. The material purified by normal phase purification (Biotage Isolera, 25 g SiliCycle cartridge; eluent 0-40% ethyl acetate in heptane over 20 CVs) to afford the desired product (244 mg, 72.0% yield) as a colourless oil. MF: C₂₇H₄₈O₈ MW: 500.66; UPLC4-MS: (XB BEH300 C4 20-95%): R_t = 3.52 min, 97.3% (UV), 100.0% (ELSD). MS (ESIpos): m/z = 518.8 [M+NH₄]⁺; ¹H NMR (400 MHz, CDCl₃): δ [ppm] = 5.31 - 5.21 (m, 1H), 4.31 (dd, *J* = 4.2, 11.9 Hz, 2H), 4.13 (dd, *J* = 6.0, 11.9 Hz, 2H), 2.37 - 2.26 (m, 6H), 1.65 - 1.53 (m, 8H), 1.35-1.21 (m, 16H), 1.18 (s, 6H), 0.87 (t, *J* = 6.4 Hz, 6H); Exchangeable carboxylic acid proton not observed; ¹³C NMR (100 MHz, CDCl₃): δ [ppm] = 176.7, 173.5, 69.2, 62.2, 42.4, 39.7, 34.3, 34.2, 31.8, 29.2, 29.0, 25.1, 25.0, 22.7, 20.3, 14.2.

[0162] *Synthesis of AGM-CASI-C6aaGMe-2-TG-octanoate (IV-5b).* To a stirring solution of 6-((1,3-bis(octanoyloxy)propan-2-yl)oxy)-5,5-dimethyl-6-oxohexanoic acid (**Int-66**, 230 mg, 459 μmol) in toluene (5 mL) was added **Int-2** (154 mg, 459 μmol), caesium carbonate (449 mg, 1.38 mmol) and TBAI (85.0 mg, 230 μmol) at room temperature. The reaction was heated to 50 °C and stirred for 3 hours. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with

water (50 mL) followed by brine (50 mL). The organic layer was collected and dried over sodium sulfate, filtered and concentrated in vacuo to give a yellow oil. The material was purified by normal phase purification (Biotage Isolera, 80 g SiliCycle cartridge ; eluent 0-20% ethyl acetate in heptane over 20 CVs) to afford the desired product (256 mg, 69.7% yield) as a colourless oil. MF: $C_{44}H_{65}O_{12}N$ MW: 799.98; UPLC4-MS: (XB BEH300 C4 20 to 95%): $R_t = 5.47$ min, 99.9% (UV), 100.0% (ELSD). MS (ESIpos): $m/z = 818.1$ $[M+NH_4]^+$; 1H NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.74 (d, $J = 9.0$ Hz, 1H), 7.67 (d, $J = 8.1$ Hz, 1H), 7.64 (d, $J = 2.2$ Hz, 1H), 7.35 - 7.30 (m, 1H), 7.29 - 7.22 (m, 1H), 7.16 (dd, $J = 2.4, 8.9$ Hz, 1H), 5.80 (s, 2H), 5.28 - 5.19 (m, 1H), 4.29 (dd, $J = 4.3, 11.9$ Hz, 2H), 4.12 (dd, $J = 6.1, 11.9$ Hz, 2H), 4.07 - 4.00 (m, 5H), 3.26 - 3.19 (m, 2H), 2.57 (s, 3H), 2.39 (t, $J = 6.8$ Hz, 2H), 2.28 (t, $J = 7.5$ Hz, 4H), 1.65 - 1.52 (m, 8H), 1.33 - 1.21 (m, 16H), 1.15 (s, 6H), 0.87 (t, $J = 6.4$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] = 176.6, 173.3, 172.9, 171.9, 158.3, 153.4, 133.5, 133.2, 130.2, 129.3, 127.8, 127.3, 123.3, 118.7, 102.6, 80.7, 69.2, 62.1, 55.7, 45.1, 42.3, 39.6, 34.2, 34.1, 32.8, 31.8, 29.2, 29.0, 27.1, 25.1, 25.0, 22.7, 20.1, 14.2.

Example 3: Lymphatic Transport Assay in Conscious Rats

[0163] The ability of the disclosed lipid prodrugs to be transported to the lymph was assessed in conscious rats. The mesenteric lymph ducts of rats were cannulated to allow for the continual collection of mesenteric lymph. Lipid formulations containing a lipid prodrug were administered to the cannulated rats, lymph was collected, and drug concentrations in the lymph samples were quantified.

[0164] Lipid-based formulations of the compounds of the invention or control compounds were prepared as previously described (Trevaskis, N.L. et al., *Pharmaceutical Research*, 2005, 22(11), 1863-1870, WO 2016/023082, and WO 2017/041139, hereby incorporated by reference).

[0165] In brief, either 1 or 2 mg of test compound (prodrug or agomelatine), 40 mg oleic acid and 25 mg Tween 80 were mixed in a glass vial and incubated at 37 °C for 12–18 h to equilibrate. An aqueous phase consisting of 2 mL phosphate buffered saline (PBS, pH 7.4) was subsequently added to the lipid phase.

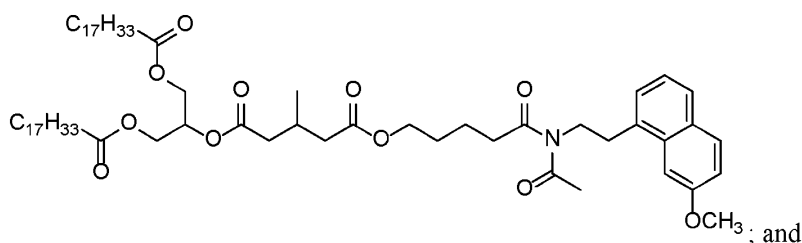
[0166] The formulation was emulsified by ultrasonication using a probe sonicator in bursts (10 seconds on, 10 seconds off) for 2 min at RT, ensuring that the temperature remained below 40 °C.

Alternatively, some prodrugs were formulated in a SEDDS formulation, where prodrug was dissolved in a preformed mixture of 27% Peceol, 48% Cremophor RH40, 25% Sesame Oil, and then dispersed 1:4 in DI water.

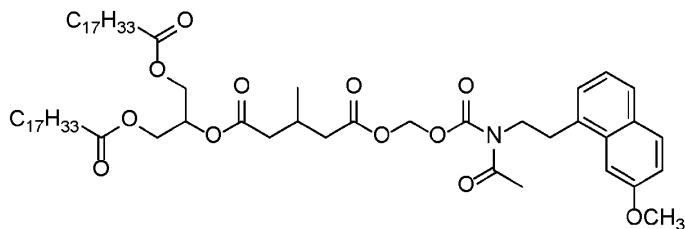
The above quantities can be scaled and prepared in batch. The formulation concentrations were verified by HPLC-MS or HPLC-UV assay.

[0167] Male Sprague-Dawley (SD) rats (~240-320 g) were maintained on a standard diet with free access to water. The rats were anesthetized, and cannulas were inserted surgically into the duodenum (for rehydration) and the mesenteric lymph duct (for lymph collection). Post-surgery, rats were recovered and re-hydrated for overnight via an intraduodenal infusion of normal saline with heparin (100IU) at 1.0 mL/h, with the saline infused at the same rate for the remainder of the experiment. Prodrug in formulation (2 mL per animal) was dosed via oral gavage, and lymph was collected continuously for up to 24 hr into pre-weighed tubes. 0.5 M EDTA-K2 was added into the sample tube at the rate of 1:50 (anticoagulation: lymph fluid). The collection tubes were changed periodically, and lymph flow measured gravimetrically. The aliquots of lymph were stored frozen at -80 °C prior to assay.

[0168] Lymph samples were thawed immediately prior to the assay. The samples were first treated with a lipase (such as porcine pancreatic lipase) or exposed to an appropriate hydrolytic condition (e.g., acidic or basic environment) to liberate agomelatine prior to measurement. The concentration of agomelatine in each lymph sample was determined by HPLC-MS. The percentage of lymphatic transport was calculated from the measured concentration in the lymph sample to the volume of lymph collected. The percentage of lymphatic transport for certain prodrugs is shown in **Table 3**. In this assay, AGM-FSI5-C5bMe-2-TG-oleate has the structure:



AGM-CASI-C5bMe-2-TG-oleate has the structure:



[0169] As evidenced in **Table 5**, disclosed lipid prodrugs resulted in significant increases in lymphatic transport (26-77%); 700-1800X greater than agomelatine alone.

Table 5: Lymphatic Transport of AGM Prodrugs in Rats

Compound	% Dose in Lymph	Approximate Fold Change Compared to AGM
AGM (Agomelatine)	0.04*	1
AGM-CASI-C5bcPr-2-TG-oleate (II-2a)	72*	1800
AGM-CASI-C5bbGMe-2-TG-oleate (II-1a)	61*	1500
AGM-CASI-C5bbGMe-2-TG-octanoate (II-1b)	57*	1400
AGM-FSI5-C5bMe-2-TG-oleate	77*	1900
AGM-CASI-C5bMe-2-TG-oleate	26*	700
AGM-CASI-C6bbGMe-TG-octanoate (II-7b)	12**	300
AGM-CASI-C7bbGMe-2-TG-octanoate (II-8b)	22**	550
AGM-CASI-C8bbGMe-2-TG-octanoate (II-9b)	16**	400
AGM-CASI-C10bbGMe-2-TG-octanoate (II-10b)	9**	225
AGM-CASI-C8b'b'bbMe-2-TG-octanoate (III-1b)	43**	1075
AGM-CASI-C8a'a'aaMe-2-TG-octanoate (IV-1b)	54**	1350
AGM-CASI-C10a'a'aaMe-2-TG-octanoate (IV-2b)	40**	1000

*formulated in oleic acid/Tween 80 formulation.

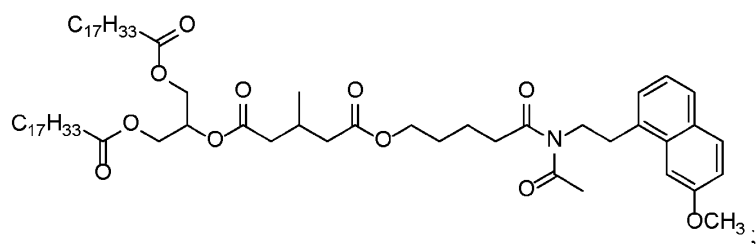
**formulated in SEDDS formulation (27% Peceol, 48% Cremophor RH40, 25% Sesame Oil)

Example 4: *In vitro* Release of Agomelatine from Prodrugs in Plasma

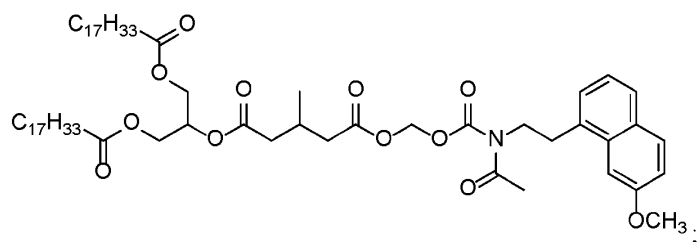
[0170] In order to probe the release of agomelatine from its respective prodrug in systemic circulation, prodrugs were incubated with human plasma and supplemented with lipoprotein lipase (LPL). LPL is a key enzyme required for hydrolysis of lipoprotein-associated triglycerides in systemic circulation and is expected to be involved in the lipolysis of re-esterified prodrugs in plasma. This occurs via the lipolysis of fatty acids at the sn-1 and sn-3 position of the prodrug, prior to the release of the active agent (e.g., agomelatine) from the sn-2 position via esterase

hydrolysis. *In vivo*, LPL is active in plasma and is tethered to the luminal surface of vascular endothelial cells. To better mimic the physiological conditions, plasma was supplemented with LPL.

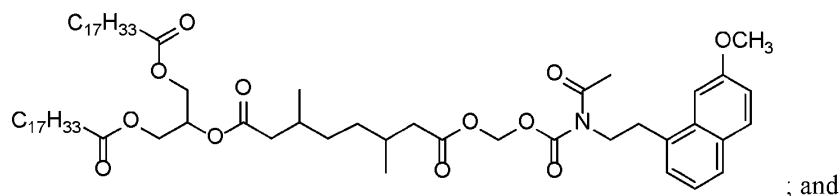
[0171] 40 μ M of a prodrug is incubated with human plasma containing 200-12,000 units/mL of LPL (LPL concentration is determined experimentally based on the units needed to generate maximum monoglyceride concentration after the reaction is initiated). Samples are incubated for 0-180 minutes at 37°C. Reaction is quenched with 1:1:1 MeCN:MeOH:IPA (0.1% formic acid) spiked with internal standard(s), vortexed, and centrifuged at 4000xg for 10 minutes to precipitate proteins. The supernatant is analyzed by LC-MS/MS and potential hydrolysis products are detected, namely the monoglyceride form, the acid form, and the free agomelatine. The concentration of free agomelatine is calculated using a standard curve of agomelatine. The results for the human plasma experiment are summarized in **Table 4**. Release is shown as the percentage of free agomelatine in solution at the 180 min timepoint. In this assay, AGM-FSI5-C5bMe-2-TG-oleate has the structure:



AGM-CASI-C5bMe-2-TG-oleate has the structure:

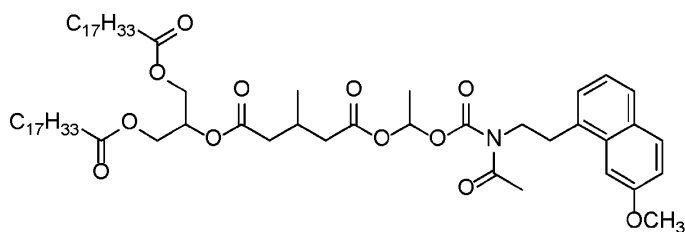


AGM-CASI-C8b' bMe-2-TG-oleate has the structure



; and

AGM-CMSI-C5bMe-2-TG-oleate has the structure:



[0172] As shown in **Table 6**, prodrugs II-1a, II-2a, and II-4a resulted in high levels of free agomelatine in human plasma supplemented with LPL. For reference, the groups refer to the following percentages of agomelatine in solution: A: >25%, B: 5-25%, C: 1-4.99%, D: <1%.

Table 6: *In vitro* Release of Agomelatine from Lipid Prodrugs in human plasma

Compound	Percentage of Agomelatine in Solution
AGM-CASI-C5bcPr-2-TG-oleate (II-2a)	A
AGM-CMSI-C5bbGMe-2-TG-oleate (II-3a)	C
AGM-CMSI-C5bMe-2-TG-oleate	A
AGM-CASI-C5bbGMe-2-TG-oleate (II-1a)	A
AGM-FSI5-C5bMe-2-TG-oleate	A
AGM-CASI-C5bMe-2-TG-oleate	A
AGM-CASI-C8b'bMe-2-TG-oleate	A
AGM-CASI-C5bcBu-2-TG-oleate (II-4a)	A
AGM-CASI-C5bcPn-2-TG-oleate (II-5a)	B
AGM-CASI-C5bcHx-2-TG-oleate (II-6a)	C
AGM-CASI-C5aaGMe-2-TG-octanoate (IV-4b)	A
AGM-CASI-C6bbGMe-TG-octanoate (II-7b)	A
AGM-CASI-C6aaGMe-2-TG-octanoate (IV-5b)	A
AGM-CASI-C7bbGMe-2-TG-octanoate (II-8b)	A
AGM-CASI-C8bbGMe-2-TG-octanoate (II-9b)	A
AGM-CASI-C10bbGMe-2-TG-octanoate (II-10b)	A
AGM-CASI-C8b'b'bbMe-2-TG-octanoate (III-1b)	A
AGM-CASI-C8b'b'bbMe-2-TG-oleate (III-1a)	A
AGM-CASI-C8a'a'aaMe-2-TG-octanoate (IV-1b)	A
AGM-CASI-C10a'a'aaMe-2-TG-octanoate (IV-2b)	A
AGM-CASI-C12a'a'aaMe-2-TG-octanoate (IV-3b)	B

Example 5: *In vitro* Monoglyceride Stability Evaluation with Monoacylglyceride Lipase

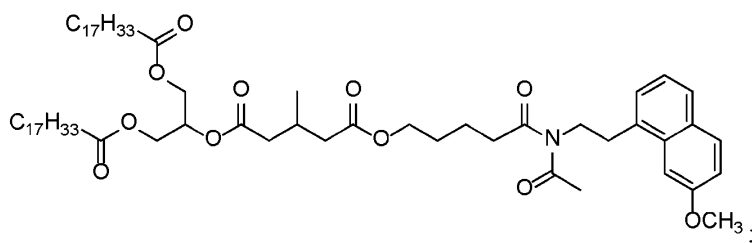
[0173] The stability of each prodrug monoglyceride was evaluated in the presence and absence of recombinant human monoacylglyceride lipase (rhMAGL). 50 μ M of each prodrug was incubated in 10 mg/mL bovine serum albumin (BSA) supplemented with lipoprotein lipase (LPL, 300 units/mL) and rhMAGL (0-0.5 μ g/mL). The amount of MAGL may be adjusted based on the observed activity. The reactions were initiated with the addition of each prodrug and incubated at 37 °C for 0-180 minutes. Aliquots were removed from these samples at 30, 60, 120, and 180 minutes and the reaction was quenched with the addition of cold acetonitrile (1:3 sample:ACN). The plate was then vortexed and centrifuged. The resultant supernatant was transferred to a 96 well plate, diluted in 0.1% formic acid water (1:3 supernatant:0.1% formic acid water) and samples were analyzed by LC-MS. Monoglyceride stability was evaluated using the following equations.

$$[0174] \text{ LPL MG Ratio} = \frac{\text{MG Peak Area at 180 minutes for LPL only}}{\text{MG Peak area at 30 minutes for LPL only}}$$

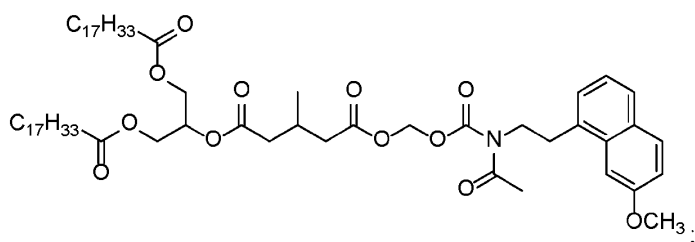
$$[0175] \text{ rhMAGL MG Ratio} = \frac{\text{MG Peak Area at 180 minutes for LPL and rhMAGL}}{\text{MG Peak Area at 30 minutes for LPL and rhMAGL}}$$

$$[0176] \text{ MG Stability} = ((\text{rhMAGL MG Ratio} - (1 - \text{LPL MG Ratio})) * 10$$

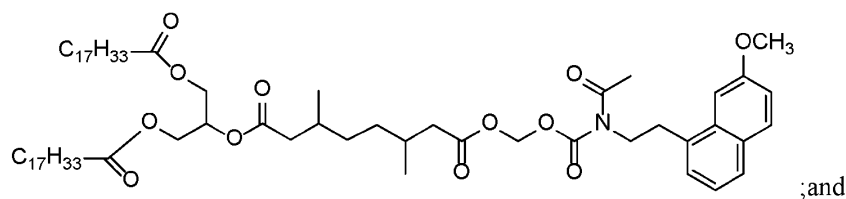
[0177] In this assay, AGM-FSI5-C5bMe-2-TG-oleate has the structure:



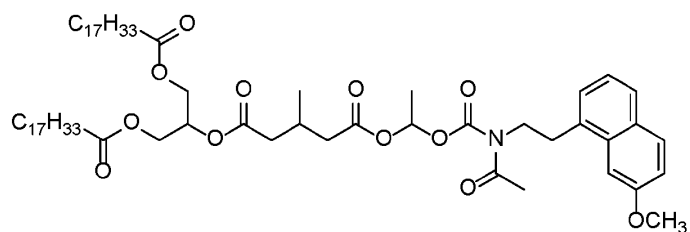
AGM-CASI-C5bMe-2-TG-oleate has the structure:



AGM-CASI-C8b'bMe-2-TG-oleate has the structure:



AGM-CMSI-C5bMe-2-TG-oleate has the structure:



The monoglyceride stability of lipid prodrugs of agomelatine is shown in **Table 7**. Stability is scored on a scale of -10 to 10, with 10 representing 100% monoglyceride remaining (*i.e.*, highest stability) and -10 representing 100% monoglyceride loss (*i.e.*, lowest stability). If analytical testing artifacts yield a score above 10, the score is indicated as a 10.

Table 7: Monoacylglyceride Stability of Lipid Prodrugs

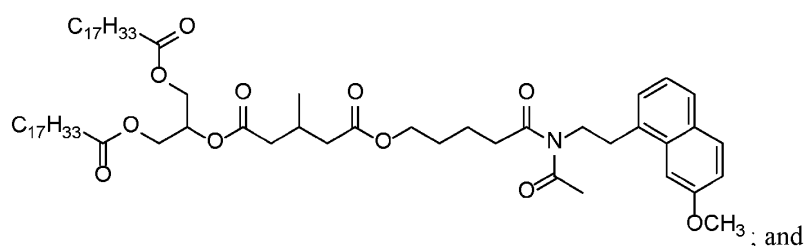
Compound	Monoacylglyceride Stability
AGM-CASI-C5bcPr-2-TG-oleate (II-2a)	6
AGM-CMSI-C5bbGMe-2-TG-oleate (II-3a)	10
AGM-CMSI-C5bMe-2-TG-oleate	5
AGM-CASI-C5bbGMe-2-TG-oleate (II-1a)	10
AGM-FSI5-C5bMe-2-TG-oleate	9
AGM-CASI-C5bMe-2-TG-oleate	5
AGM-CASI-C8b'bMe-2-TG-oleate	5
AGM-CASI-C6bbGMe-2-TG-octanoate (II-7b)	10
AGM-CASI-C5aaGMe-2-TG-octanoate (IV-4)	4
AGM-CASI-C6aaGMe-2-TG-octanoate (IV-5)	9
AGM-CASI-C7bbGMe-2-TG-octanoate (II-8b)	8
AGM-CASI-C8bbGMe-2-TG-octanoate (II-9b)	-7
AGM-CASI-C10bbGMe-2-TG-octanoate (II-10b)	-10
AGM-CASI-C8b'b'bbMe-2-TG-oleate (III-1a)	10
AGM-CASI-C8a'a'aaMe-2-TG-octanoate (IV-1b)	10
AGM-CASI-C10a'a'aaMe-2-TG-octanoate (IV-2b)	6
AGM-CASI-C12a'a'aaMe-2-TG-octanoate (IV-3b)	8

Example 6: Pharmacokinetic Studies in Non-human Primates

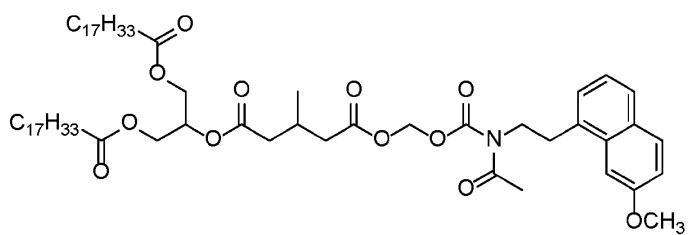
[0178] To determine the plasma exposure after oral dosing in non-human primates, cynomolgus monkeys were held in a large animal research facility prior to the study. The monkeys were fasted for 12h up to 30 min prior to the administration. In fed-state studies, monkeys received ~20 g of high fat food (~50% caloric value from fat) administered by hand, followed by 10 mL water to aid in swallowing. Food (120 g standard diet) was returned 4h post-dosing. Water was available ad libitum throughout the study. Agomelatine as a solid was filled into gelatin capsules for oral administration or dissolved in 25% hydroxypropyl-beta-cyclodextrin with mixing and intermittent sonication over 30 minutes and filtered (0.22 µm filter) before IV dosing or dosing by oral gavage. Prodrugs were formulated in a SEDDS formulation (27% Peceol, 48% Cremophor RH40, 25% Sesame Oil dispersed 1:4 in water).

[0179] Formulations in capsules were administered to the NHPs by placing the capsules as far posterior to the pharynx as possible, closing the mouth, and rubbing the throat to stimulate swallowing. Subsequently, 50 mL of water was administered orally via syringe. Alternatively, the formulation may be dispersed in a suitable volume of water (e.g. 1:4 lipid excipient to water) and administered by oral gavage tube, which is then flushed with 50 mL of water after delivery. Monkeys were dosed at a 1 mg/kg agomelatine equivalent for the prodrugs.

[0180] After oral administration, blood samples (0.6 mL) were taken via venipuncture of the cephalic vein or other suitable sample site at -5 minutes up to 120 hours post-dosing. Blood samples were collected in K2EDTA tubes prefilled with sufficient inhibitor solutions such that the final concentration of each inhibitor after sample collection was 40 µg/mL of orlistat and 100 µM of JZL-184, GR148672X, and Rivastigmine inhibitors. Plasma was separated by centrifugation and stored at -80°C prior to analysis. As a comparative control or to allow for the calculation of bioavailability, agomelatine was administered via oral gavage or by infusion/injection. In this assay, AGM-FSI5-C5bMe-2-TG-oleate has the structure:



AGM-CASI-C5bMe-2-TG-oleate has the structure:



[0181] As shown in **Table 9**, prodrugs of the instant disclosure resulted in an increase in plasma exposure of agomelatine as measured by AUC. Notably, when agomelatine alone was administered orally, no agomelatine was detected in the plasma (ND = not detected). The representative Formula I compounds tested exhibited AUC values ranging from 104 to 288 nmol*h/L (**Table 7**).

Table 9: Plasma Exposure of Agomelatine in NHPs

Compound	AUC (nmol*h/L)
AGM-CASI-C5bcPr-2-TG-octanoate (II-2b)	104
AGM-CASI-C5bbGMe-2-TG-octanoate (II-1b)	207
AGM-FSI5-C5bMe-2-TG-oleate	Not Detected
AGM-CASI-C5bMe-2-TG-oleate	52
Agomelatine (AGM)	Not Detected
AGM-CASI-C7bbGMe-2-TG-octanoate (II-8b)	194
AGM-CASI-C8b'b'bbMe-2-TG-oleate (III-1a)	288*
AGM-CASI-C8a'a'aaMe-2-TG-octanoate (IV-1b)	156

*Delivered dose was 2.9x lower than the standard dose for other prodrugs (equivalent 1 mg/kg agomelatine) due to material limitations. The resulting AUC was dose adjusted to the equivalent of 1 mg/kg agomelatine during data processing.

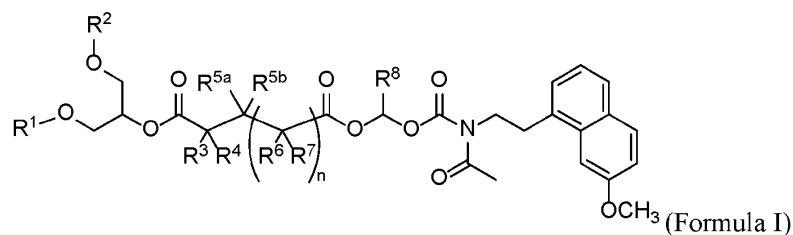
Other Embodiments

[0182] While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the invention that come within known or customary practice within the art to which the invention pertains and may be applied to the essential features hereinbefore set forth, and follows in the scope of the claims. Other embodiments are within the claims.

Claims

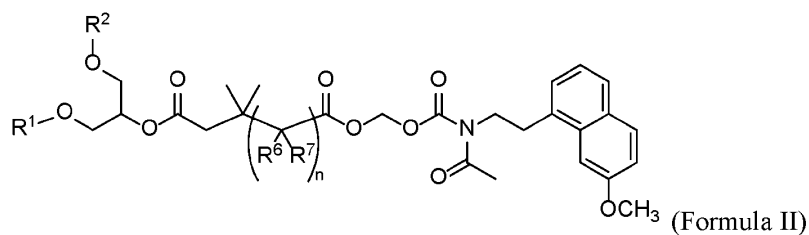
We claim:

1. A compound of Formula I:



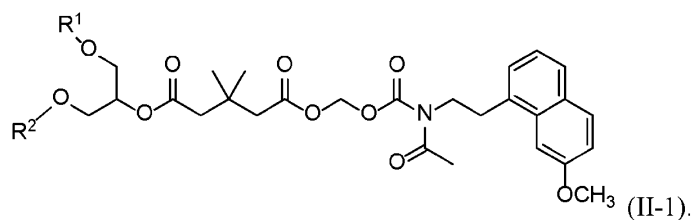
wherein R^1 and R^2 are each independently hydrogen or a residue of a C_2 - C_{28} fatty acid;
 R^3 and R^4 are each independently hydrogen or C_1 - C_4 alkyl;
 R^{5a} and R^{5b} are each independently hydrogen, C_1 - C_4 alkyl, or are taken together with the carbon to which they are attached form a C_3 - C_8 cycloalkyl;
 R^6 and R^7 are each independently at each occurrence hydrogen or C_1 - C_4 alkyl;
 n is 1-10; and
 R^8 is hydrogen or C_1 - C_{10} alkyl.

2. The compound of claim 1, wherein the compound has the Formula II:

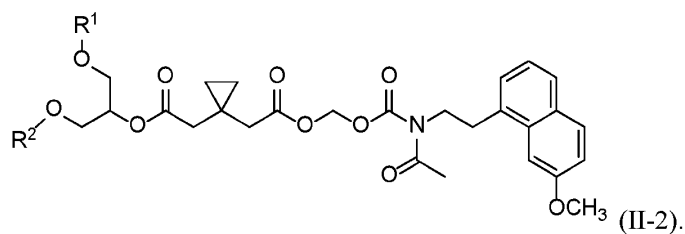


wherein R^1 and R^2 are each independently hydrogen or a residue of a C_2 - C_{28} fatty acid;
 R^6 and R^7 are each independently at each occurrence hydrogen or C_1 - C_4 alkyl; and
 n is 1-10.

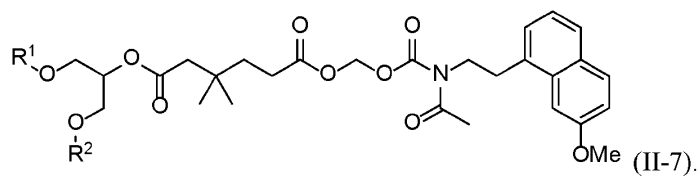
3. The compound of claim 2, wherein the compound is compound (II-1):



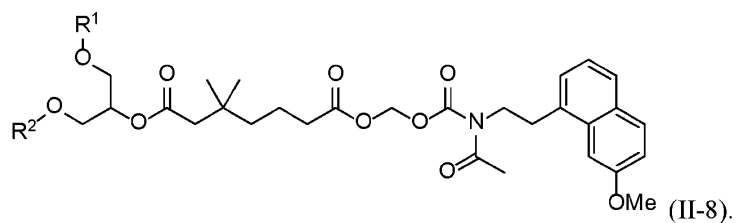
4. The compound of claim 2, wherein the compound is (II-2):



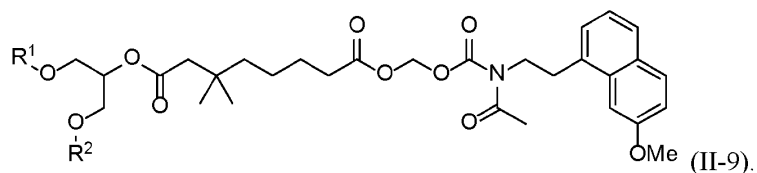
5. The compound of claim 2, wherein the compound is (II-7):



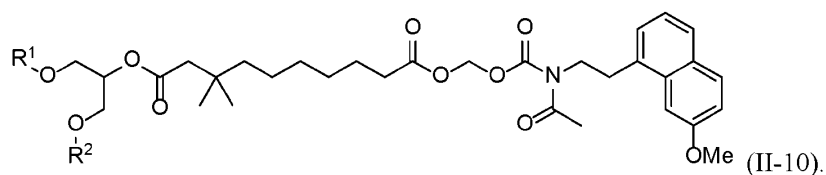
6. The compound of claim 2, wherein the compound is (II-8):



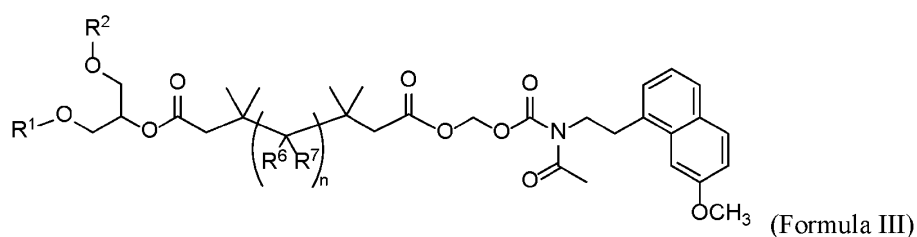
7. The compound of claim 2, wherein the compound is (II-9):



8. The compound of claim 2, wherein the compound is (II-10):

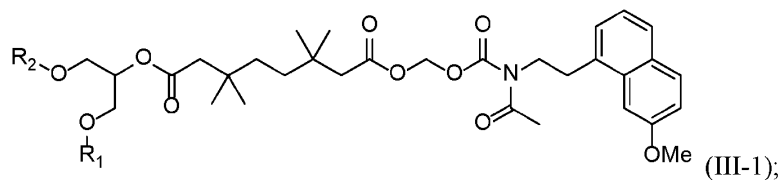


9. The compound of claim 1, wherein the compound has the Formula III:



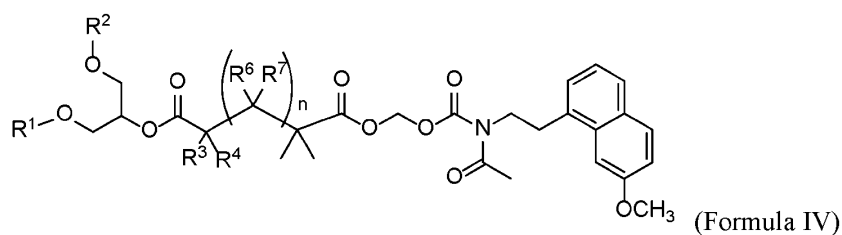
wherein R^1 and R^2 are each independently hydrogen or a residue of a C_2 - C_{28} fatty acid;
 R^6 and R^7 are each independently at each occurrence hydrogen or C_1 - C_4 alkyl; and
 n is 1-10.

10. The compound of claim 9, wherein the compound is (III-1):



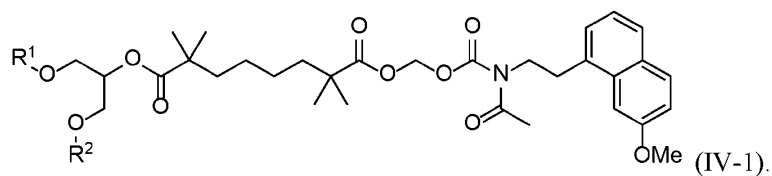
where R^1 and R^2 are octanoate [$-C_7H_{15}-C(O)-$] or oleate [$-C_{17}H_{33}-C(O)-$].

11. The compound of claim 1, wherein the compound has the Formula IV:

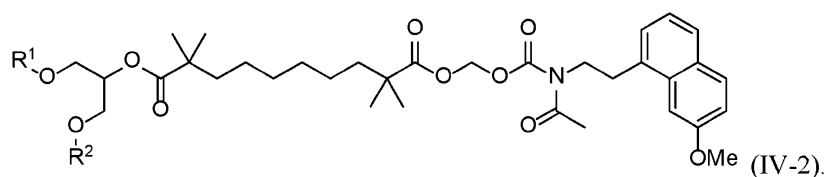


wherein R^1 and R^2 are each independently hydrogen or a residue of a C_2 - C_{28} fatty acid;
 R^3 and R^4 are each independently hydrogen or C_1 - C_4 alkyl;
 R^6 and R^7 are each independently at each occurrence hydrogen or C_1 - C_4 alkyl; and
 n is 1-10.

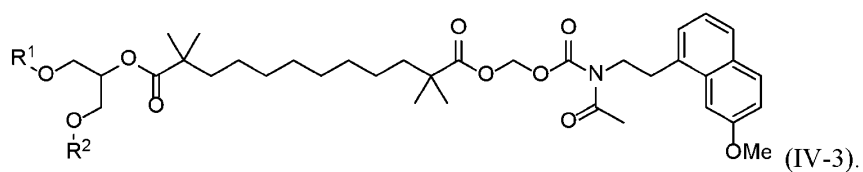
12. The compound of claim 11, wherein the compound is (IV-1):



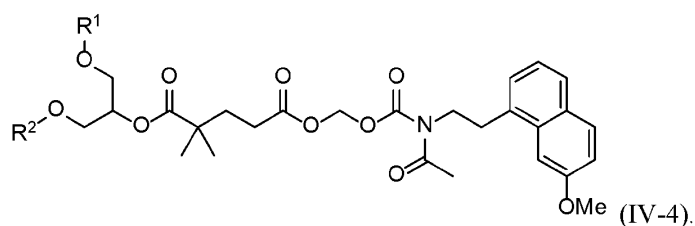
13. The compound of claim 11, wherein the compound is (IV-2):



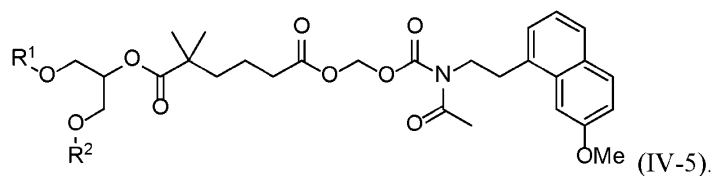
14. The compound of claim 11, wherein the compound is (IV-3):



15. The compound of claim 11, wherein the compound is (IV-4):



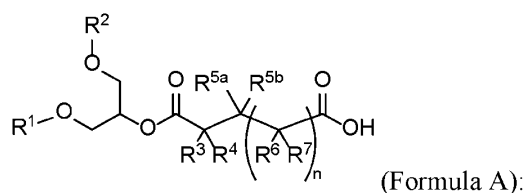
16. The compound of claim 11, wherein the compound is (IV-5):



17. A pharmaceutical composition comprising a compound as described in any one of the preceding claims and a pharmaceutically acceptable carrier.
18. A method of treating a disorder in a subject, wherein the disorder is a bipolar and related disorder, a depressive disorder, an anxiety disorder, or a trauma- and stressor-related disorder, comprises administering a therapeutically effective amount of a compound as described in any one of claims 1-16 or the pharmaceutical composition of claim 17 to effectively treat the disorder in the subject.
19. A compound as described in any one of claims 1-16 for use in treating a disorder in a subject, wherein the disorder is a bipolar and related disorder, a depressive disorder, an anxiety disorder, or a trauma- and stressor-related disorder.

20. The method of claim 18, or the use of claim 19, wherein the disorder is a bipolar and related disorder.
21. The method or use of claim 20, wherein the bipolar disorder is bipolar I disorder or bipolar II disorder.
22. The method of claim 18, or the use of claim 19, wherein the disorder is a depressive disorder.
23. The method or use of claim 22, wherein the depressive disorder is a major depressive disorder (MDD), persistent depressive disorder (PDD), or an unspecified mood disorder.
24. The method of claim 18, or the use of claim 19, wherein the disorder is an anxiety disorder.
25. The method or use of claim 24, wherein the anxiety disorder is a separation anxiety disorder, a specific phobia, a social anxiety disorder, a panic disorder, or a generalized anxiety disorder (GAD).
26. The method of claim 18, or the use of claim 19, wherein the disorder is a trauma- and stressor-related disorders.
27. The method or use of claim 26, wherein the trauma- and stressor-related disorder is a posttraumatic stress disorder (PTSD), acute stress disorder, or adjustment disorder.
28. The method or use of any one of claims 18-27, wherein the subject is a pediatric subject.

29. The method or use of any one of claims 18-27, wherein the subject is an adolescent subject.
30. The method or use of any one of claims 18-27, wherein the subject is an adult subject.
31. The method or use of any one of claims 18-27, wherein the subject is a geriatric subject.
32. The method or use of any one of claims 18-31, wherein the compound is selected from the group consisting of Compounds II-1, II-2, II-7, II-8, II-9, II-10, III-1, IV-1, IV-2, IV-3, IV-4, and IV-5.
33. The method or use of claim 32, wherein the compound is administered to a subject QD.
34. The method or use of claim 32, wherein the compound is administered to a subject QHS.
35. A compound of Formula A



or a salt thereof, wherein:

R^1 and R^2 are each independently a residue of a C_2 - C_{28} fatty acid;

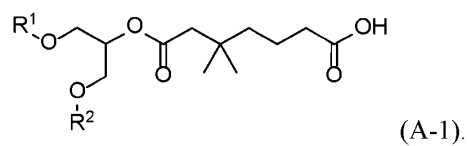
R^3 and R^4 are each independently hydrogen or C_1 - C_4 alkyl;

R^{5a} and R^{5b} are hydrogen, C_1 - C_4 alkyl, or are taken together with the carbon to which they are attached form a C_3 - C_8 cycloalkyl;

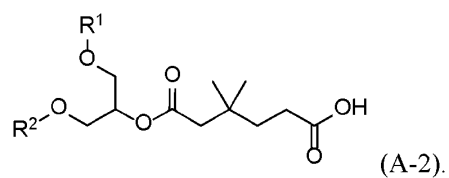
R^6 and R^7 are each independently at each occurrence hydrogen or C_1 - C_4 alkyl; and

n is 1-10.

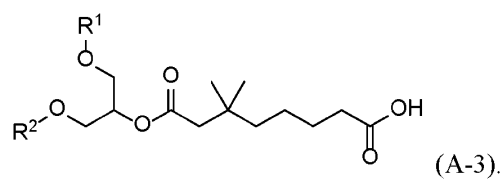
36. The compound of claim 35, wherein the compound is (A-1):



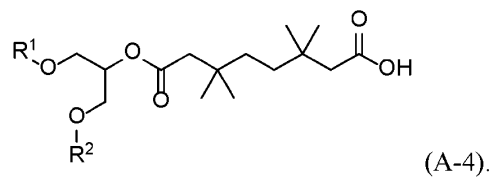
37. The compound of claim 35, wherein the compound is (A-2):



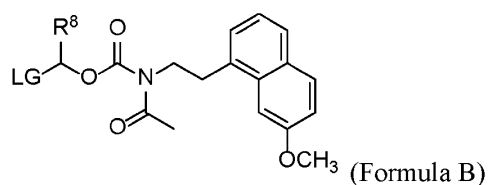
38. The compound of claim 35, wherein the compound is (A-3):



39. The compound of claim 35, wherein the compound is (A-4):



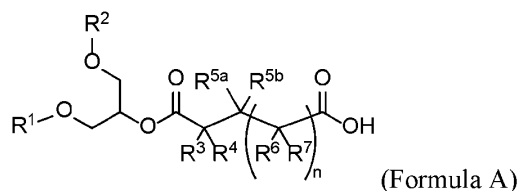
40. A compound of Formula B:



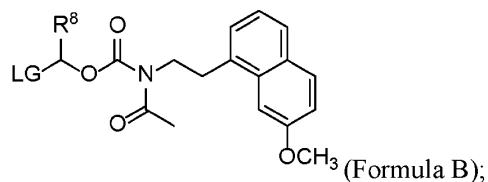
wherein R^8 is hydrogen; and
 LG is a leaving group.

41. A method of making a compound as described in any one of claims 1-16, the method comprising:

reacting a compound of Formula A

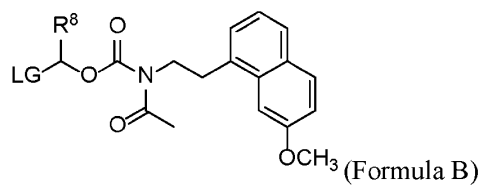


or a salt thereof, with a compound of Formula B

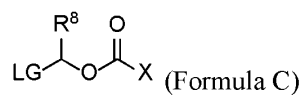


wherein R^1 and R^2 are each independently a residue of a C_2 - C_{28} fatty acid;
 R^3 and R^4 are each independently hydrogen or C_1 - C_4 alkyl;
 R^{5a} and R^{5b} are each independently hydrogen, C_1 - C_4 alkyl, or are taken together with the carbon to which they are attached form a C_3 - C_8 cycloalkyl;
 R^6 and R^7 are each independently at each occurrence hydrogen or C_1 - C_4 alkyl;
 n is 1-10;
 R^8 is hydrogen or C_1 - C_{10} alkyl; and
 LG is a leaving group.

42. A method of making a compound of Formula B:



the method comprising the step of reacting agomelatine or a salt thereof with a compound of Formula C



wherein R⁸ is hydrogen;

X is halo; and

LG is a leaving group.

43. The method of claim 42, wherein the agomelatine salt is an alkali metal salt.
44. The method of claim 43, wherein the salt is a lithium salt.
45. The method of any one of claims 42 to 44, wherein LG is chloro- and/or wherein X is chloro-.

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.: 18, 20-34 because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).	