(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 June 2013 (13.06.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/084237 Al

(51) International Patent Classification:

Λ *61*K *31/16* (2006.01)	*C07C 233/05* (2006.01)
A61K 31/20 (2006.01)	*C07C 253/00* (2006.01)
A61K 31/225 (2006.01)	*C07C 255/22* (2006.01)
A61P 3/04 (2006.01)	*C07C 51/00* (2006.01)
A61P 3/06 (2006.01)	*C07C 55/02* (2006.01)
A61P 3/08 (2006.01)	*C07C 55/32* (2006.01)
A61P 3/10 (2006.01)	*C07C 67/00* (2006.01)
C07C 231/00 (2006.01)	*C07C 69/34* (2006.01)
C07C 233/04' (2006.01)	

(21) International Application Number:
PCT/IL20 12/0505 11

(22) International Filing Date:
6 December 2012 (06.12.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/568,441 8 December 201 1 (08. 12.201 1) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available):* AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available):* ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

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

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

WO 2013/084237 A1

(54) **Title:** DEUTERATED TETRAMETHYL DIOIC ACIDS, COMPOSITIONS COMPRISING THEM AND USES THEREOF

(57) **Abstract:** This invention relates to deuterated tetramethyl dioic acids, compositions comprising them and uses thereof in the treatment of Metabolic Syndrome and any diseases, disorders or symptoms associated therewith.

DEUTERATED TETRAMETHYL DIOIC ACIDS, COMPOSITIONS COMPRISING THEM AND USES THEREOF

FIELD OF THE INVENTION

This invention relates to deuterated tetramethyl dioic acids, compositions comprising them and uses thereof in the treatment of Metabolic Syndrome and any diseases, disorders or symptoms associated therewith.

BACKGROUND OF THE INVENTION

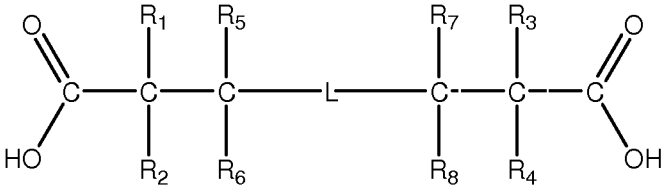
US4634795 discloses long-chain alpha, omega-di-carboxylic acids and derivatives for the treatment of obesity, hyperlipidemia and maturity-onset diabetes. US2002049345 discloses carboxylic acids and derivatives thereof, compositions comprising them for the treatment of obesity, hyperlipidemia and maturity onset diabetes. US2009018199 discloses methods for administering 3,3,14,14-tetramethyl hexadecane-l,16-dioic acid for lowering LDL, VLDL, total cholesterol, triglycerides, insulin resistance and hypertension, and methods for elevating HDL in subjects in need thereof. US4908385 provides a pharmaceutical composition containing at least one alpha-halogenated dicarboxylic acid. US4711896 relates to alpha, omega-dicarboxylic acids and uses thereof as anti-diabetic agents and for lowering the level of plasma lipids. US2002037876 relates to carboxylic acids and derivatives thereof for use in the treatment of metabolic syndrome X.

Isotopes are atoms which have nearly identical properties but which have different masses due to changes in the number of neutrons in their nuclei. Deuterium is an isotope of hydrogen with a nucleus comprising one neutron and one proton. Kinetic isotope effects are the observed changes in the rate of reaction that occur when deuterium is substituted for hydrogen. Deuterium isotope effects result from the greater energy required to break a covalent bond to deuterium versus a covalent bond to hydrogen. One of the challenges of incorporating deuterium into a pharmaceutical composition is the possibility of deuterium/hydrogen exchange within the physiological environment, eviscerating the effect of the compound. Further, when deuterium retards

metabolism at one site, "metabolic shunting" can occur where the suppression of one metabolic pathway promotes metabolism at another site.

SUMMARY OF THE INVENTION

The present invention provides a compound of general formula (I), including any salts, esters, anhydrides or prodrugs thereof:



(I)

wherein

L is a straight or branched C_g-C_{i6} alkylene; optionally interrupted by at least one moiety selected from O, S, NH, C_5-C_{10} cycloalkylene, C_5-C_{10} cycloheteroalkylene, C_6-C_{i8} arylene, C_6-C_{i8} heteroarylene;

each of R_i - R_8 is independently selected from H, D, CH_3 and CD_3; wherein at least one of R_i - R_8 is D or CD_3.

In a compound of the invention, when a particular position is designated as having deuterium, it is understood that the abundance of deuterium at that position is substantially greater than the natural abundance of deuterium, which is 0.015%. A position designated as having deuterium typically has a minimum isotopic enrichment factor that is at least 3340 times greater than the natural abundance of deuterium (i.e., the term "D" or "deuterium" indicates at least 50.1% incorporation of deuterium).

The term *"isotopic enrichment factor"* as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope.

In other embodiments, a compound of the invention has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium), at least 5500 (82.5% deuterium incorporation), at least 6000 (90%

deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

In compounds of the invention any atom not specifically designated as a particular isotope is meant to represent the naturally abundant isotope of that atom. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural abundance isotopic composition. Also unless otherwise stated, when a position is designated specifically as "D" or "deuterium", the position is understood to have deuterium at an abundance that is at least 3340 times greater (i.e., at least 50.1% incorporation of deuterium) than the natural abundance of deuterium, which is 0.015%.

The term *"isotopologue"* refers to a species that has the same chemical structure and formula as a specific compound of this disclosure, with the exception of the positions of isotopic substitution and/or level of isotopic enrichment at one or more positions, e.g., H vs. D.

The term *"compound'* as used herein includes a collection of molecules having an identical chemical structure, except that there may be isotopic variation among the constituent atoms of the molecules. Thus, it will be clear to those of skill in the art that a compound represented by a particular chemical structure containing indicated deuterium atoms, will also contain lesser amounts of isotopologues having hydrogen atoms at one or more of the designated deuterium positions in that structure.

The relative amount of such isotopologues in a compound of this disclosure will depend upon a number of factors including the isotopic purity of deuterated reagents used to make the compound and the efficiency of incorporation of deuterium in the various synthesis steps used to prepare the compound.

In some embodiments, as set forth above, the relative amount of such isotopologues in total will be less than 49.9% of the compound. In other embodiments, the relative amount of such isotopologues in total will be less than 47.5%, less than

40%, less than 32.5%, less than 25%, less than 17.5%, less than 10%, less than 5%, less than 3%, less than 1%, or less than 0.5% of the compound.

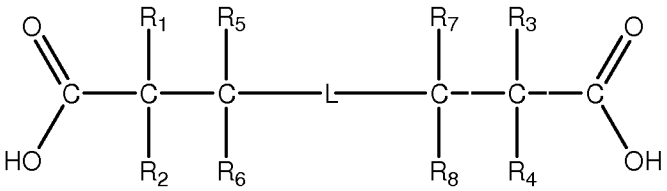
The term *"stable compounds"* as used herein, refers to compounds which possess stability sufficient to allow for their manufacture and which maintain the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., formulation into therapeutic products, intermediates for use in production of therapeutic compounds, isolatable or storable intermediate compounds, treating a disease or condition responsive to therapeutic agents).

In some embodiments, any position in the compound of Formula (I) designated as having D has a minimum deuterium incorporation of at least 50.1% (e.g., at least 52.5%, at least 60%, at least 67.5%, at least 75%, at least 82.5%, at least 90%, at least 95%, at least 97%, at least 99%, or at least 99.5%) at the designated position(s) of the compound of Formula (I). Thus, in some embodiments, a composition comprising a compound of Formula (I) can include a distribution of isotopologues of the compound, provided at least 50.1% of the isotopologues include a D at the designated position(s).

In some embodiments, a compound of Formula (I) is *"substantially free of"* other isotopologues of the compound, e.g., less than 49.9%, less than 25%, less than 10%, less than 5%, less than 2%, less than 1%, or less than 0.5% of other isotopologues are present.

The term *"Cs-Cie alkylene"* is meant to encompass a straight or branched divalent (wherein two hydrogen atoms are removed from the corresponding alkyl) aliphatic hydrocarbon group having between 8 to 16 carbon atoms, which is optionally interrupted (i.e. in between any two carbon atoms of said alkylene group) by at least one moiety selected from -0-, -S-, -NH-, C5-C10 cycloalkylene (i.e. divalent cycloalkane ring), C5-C10 cycloheteroalkylene (i.e. divalent heterocycloalkane ring), C_6-Ci_8 arylene (i.e. divalent aryl ring), C_6-Ci_8 heteroarylene (i.e. divalent heteroaryl ring).

In another aspect the invention provides a compound of general formula (I), including any salts, esters, anhydrides or prodrugs thereof:



(I)

wherein

L is a straight or branched C8-C16 alkylene; optionally interrupted by at least one moiety selected from O, S, NH, C_5-C_{10} cycloalkylene, C_5-C_{10} cycloheteroalkylene, C_6-Ci_8 arylene, C_6-Cig heteroarylene;

each of Ri - R_4 is independently H or D;

each of R_5 - Rg is independently CH_3 or CD_3;

wherein when Ri - R_4 are H, at least one of R_5 - Rg is CD_3; or when R_5 - Rg are CH_3, at least one of Ri - R_4 is D.

Thus, according to the first aspect of the application, at least one of the substituents Ri - Rg comprises a deuterium atom. In some embodiments, at least one of Ri - R_4 is D and each of R_5 - Rg is independently CH_3 or CD_3. In other embodiments, at least one of R_5 - Rg is CD_3 and each of Ri - R_4 is independently H or D. In further embodiments R_5 - Rg are CH_3, and at least one of Ri - R_4 is D.

In some embodiments of a compound of the invention, at least one of said Ri - R_4 is D. In further embodiments, at least one of R_5 - Rg is CD_3. In yet other embodiments, at least one of Ri - R_4 is D and at least one of R_5 - Rg is CD_3.

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

Compound	R_1=R_2=R_3=R_4	R_5=R_6=R_7=R_8
II	D	CH_3
III	H	CD_3
IV	D	CD_3

In other embodiments, a compound of the invention is selected from:

Compound	R_1=R_2	R_3=R_4	R_5=R_6	R_7=R_8
V	D	H	CH_3	CH_3

VI	D	H	CD_3	CHs
VII	D	H	CHs	CDs
VIII	D	H	CDs	CDs
IX	D	D	CDs	CHs

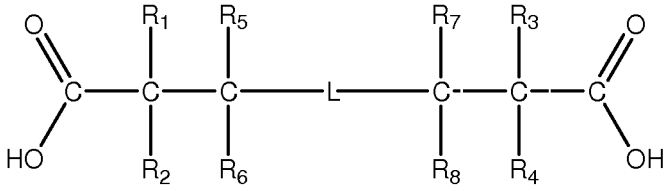
In further embodiments, a compound of the invention is selected from:

Compound	**R_1=R_3**	**R_2=R_4**	**R_5=R_6**	**R_7=R_8**
X	D	H	CH_3	CH_3
XI	D	H	CD_3	CH_3
XII	D	H	CD_3	CD_3

In yet some other embodiments, a compound of the invention is selected from:

Compound	**R_1=R_3**	**R_2=R_4**	**R_5=R_7**	**R_6=R_8**
XIII	D	H	CD_3	CH_3

In a further aspect the invention provides a compound of general formula (I), including any salts, esters, anhydrides or prodrugs thereof:



(I)

wherein

L is a straight or branched C8-Ci_6 alkylene; optionally interrupted by at least one moiety selected from O, S, NH, Cs-Ciocycloalkylene, Cs-Ciocycloheteroalkylene, C_6-Ci8 arylene, C_6-Ci8 heteroarylene;

each of Ri - R_4 is independently CH_3 or CD_3;

each of R_5 - R_8 is independently H or D;

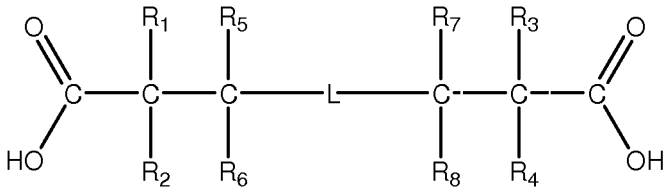
wherein when Ri - R_4 are CH_3, at least one of R_5 - R_8 is D; or when R_5 - R_8 are H, at least one of Ri - R_4 is CD_3.

Thus, according to the first aspect of the application, at least one of the substituents Ri - R_8 comprises a deuterium atom. In some embodiments, at least one of

Ri - R_4 is CD_3 and each of R_5 - Rg is independently H or D. In other embodiments, at least one of R_5 - Rg is D and each of Ri - R_4 is independently CH_3 or CD_3. In further embodiments Ri - R_4 are CH_3, and at least one of R_5 - Rg is D.

In some embodiments of a compound of the invention, at least one of Ri - R_4 is CD_3. In yet further embodiments, at least one of R_5 - Rg is D. In other embodiments, at least one of Ri - R_4 is CD_3 and at least one of R_5 - Rg is D.

In yet a further aspect the invention provides a compound of general formula (I), including any salts, esters, anhydrides or prodrugs thereof:



(I)

wherein

L is a straight or branched Cg-Ci_6 alkylene; optionally interrupted by at least one moiety selected from O, S, NH, Cs-Ciocycloalkylene, Cs-Ciocycloheteroalkylene, C_6-Cig arylene, C_6-Cig heteroarylene;

each of Ri - R_4 is independently CH_3 or CD_3;

each of R_5 - Rg is H;

wherein at least one of Ri - R_4 is CD_3.

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

Compound	**R_1=R_2=R_3=R_4**	**R_5=R_6=R_7=R_8**
XIV	CD_3	H

In some other embodiments, a compound of the invention is selected from:

Compound	**R_1=R_2**	**R_3=R_4**	**R_5=R_6**	**R_7=R_8**
XV	CD_3	CH_3	H	H

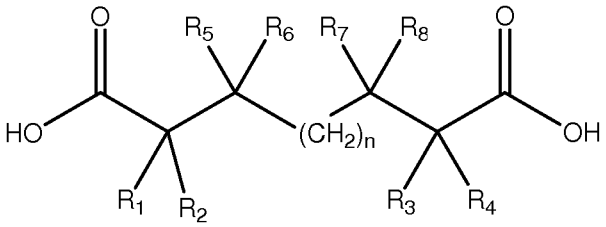
In further embodiments, a compound of the invention is selected from:

Compound	**R_1=R_3**	**R_2=R_4**	**R_5=R_6**	**R_7=R_8**

XVI	CD_3	CHs	H	H

In some embodiments, L is $-(CH_2)_{10}-$. In other embodiments, L is $-(CH_2)_{12}-$.

In some embodiments, compounds of the invention are selected from:



Compound	**R_1**	**R_2**	**R_3**	**R_4**	**R_5**	**R_6**	**R_7**	**R_8**	**n**
1	D	D	D	D	CD_3	CD_3	CD_3	CD_3	10
2	D	D	D	D	CH_3	CH_3	CH_3	CH_3	10
3	H	H	H	H	CD_3	CD_3	CD_3	CD_3	10
4	D	D	D	D	CD_3	CD_3	CD_3	CD_3	12
5	D	D	D	D	CH_3	CH_3	CH_3	CH_3	12
6	H	H	H	H	CD_3	CD_3	CD_3	CD_3	12
7	CD_3	CD_3	CD_3	CD_3	H	H	H	H	10
8	CD_3	CD_3	CD_3	CD_3	H	H	H	H	12

including any salts, esters, anhydrides or prodrugs thereof.

The compounds of the present invention, as defined above, may have the ability to crystallize in more than one form, a characteristic, which is known as polymorphism, and it is understood that such polymorphic forms *("polymorphs")* are within the scope of formulae (I). Polymorphism generally can occur as a response to changes in temperature or pressure or both and can also result from variations in the crystallization process. Polymorphs can be distinguished by various physical characteristics known in the art such as x-ray diffraction patterns, solubility, and melting point.

As used herein, the term *"substituted"* refers to substitution with the named substituent or substituents, multiple degrees of substitution being allowed unless otherwise stated.

Certain of the compounds described herein may contain one or more chiral atoms, or may otherwise be capable of existing as two enantiomers or as two or more diastereomers. Accordingly, the compounds of this invention include mixtures of enantiomers as well as purified enantiomers or enantiomerically enriched mixtures. Furthermore, the compounds of this invention include mixtures of diastereomers, as well as purified stereoisomers or diastereomerically enriched mixtures. Also included within the scope of the invention are the individual isomers of the compounds of the invention, as defined above, as well as any wholly or partially mixtures thereof. The present invention also covers the individual isomers of the compounds represented by the formulas above as mixtures with isomers thereof in which one or more chiral centers are inverted.

It is also noted that the compounds of the present invention may form tautomers. It is understood that all tautomers and mixtures of tautomers of the compounds of the present invention, are included within the scope of the compounds of the present invention.

The invention further provides a composition comprising a compound of the invention or any salts, esters, anhydrides or prodrugs thereof.

In some embodiments, said composition of the invention is for use as a medicament.

In a further aspect the invention provides a use of a compound of the invention or any salts, esters, anhydrides or prodrugs thereof, for the preparation of a medicament.

Pharmaceutical compositions or medicaments of the invention may additionally comprise any other suitable substances such as other therapeutically useful substances, diagnostically useful substances, pharmaceutically acceptable carriers or the like.

Pharmaceutical compositions or medicaments of the invention comprise a compound of the subject invention in admixture with pharmaceutically acceptable auxiliaries, and optionally other therapeutic agents. The auxiliaries must be

"acceptable" in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipients thereof.

Pharmaceutical compositions or medicaments of the invention typically include those suitable for oral, rectal, nasal, topical (including transdermal, buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intra-adipose tissue and intradermal) administration or administration via an implant. The compositions may be prepared by any method well known in the art of pharmacy. Such methods include the step of bringing in association compounds used in the invention or combinations thereof with any auxiliary agent. The auxiliary agent(s), also named accessory ingredient(s), include those conventional in the art, such as carriers, fillers, binders, diluents, disintegrants, lubricants, colorants, flavoring agents, anti-oxidants, and wetting agents.

Pharmaceutical compositions or medicaments suitable for oral administration may be presented as discrete dosage units such as pills, tablets, dragees or capsules, or as a powder or granules, or as a solution or suspension. The active ingredient may also be presented as a bolus or paste. The compositions can further be processed into a suppository or enema for rectal administration.

The invention further includes a pharmaceutical composition or medicament, as hereinbefore described, in combination with packaging material, including instructions for the use of the composition for a use as hereinbefore described.

For parenteral administration, suitable compositions include aqueous and non-aqueous sterile injection. The compositions may be presented in unit-dose or multi-dose containers, for example sealed vials and ampoules, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of sterile liquid carrier, for example water, prior to use. For transdermal administration, e.g. gels, patches or sprays can be contemplated. Compositions or formulations suitable for pulmonary administration e.g. by nasal inhalation include fine dusts or mists which may be generated by means of metered dose pressurized aerosols, nebulisers or insufflators.

The exact dose and regimen of administration of the composition will necessarily be dependent upon the therapeutic or nutritional effect to be achieved and may vary with the particular formula, the route of administration, and the age and condition of the individual subject to whom the composition is to be administered.

In some embodiments said medicament or pharmaceutical composition of the invention is administered in a dose of 10 to lOOmg/Kg body weight per day (including doses of 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 and lOOmg/Kg per day). In other embodiments, said medicament or pharmaceutical composition of the invention is administered in a dose of less than 50mg/Kg body weight per day.

The invention also includes any salt of a compound of the invention, including any pharmaceutically acceptable salt, wherein a compound of the invention has a net charge (either positive or negative) and at least one counter ion (having a counter negative or positive charge) is added thereto to form said salt.

The term *"pharmaceutically acceptable salt(s)",* as used herein, means those salts of compounds of the invention that are safe and effective for pharmaceutical use in mammals and that possess the desired biological activity. Pharmaceutically acceptable salts include salts of acidic or basic groups present in compounds of the invention. Pharmaceutically acceptable acid addition salts include, but are not limited to, hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzensulfonate, p-toluenesulfonate and pamoate (i.e., l,l'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. Certain compounds of the invention can form pharmaceutically acceptable salts with various amino acids. Suitable base salts include, but are not limited to, aluminum, calcium, lithium, magnesium, potassium, sodium, zinc, and diethanolamine salts. For a review on pharmaceutically acceptable salts see BERGE ET AL., 66 *J. PHARM. SCI.* 1-19 (1977), incorporated herein by reference.

In some embodiments, said medicament is for the treatment of a Metabolic Syndrome condition in a subject, including any disease, condition, symptom or disorder associated therewith.

The term *"Metabolic Syndrome"* (also known as metabolic syndrome X, cardiometabolic syndrome, syndrome X, insulin resistance syndrome, Reaven's syndrome, and CHAOS) is meant to encompass is a condition of a subject defined by the combination of conditions/disorders/symptoms that, when occurring together, increase the risk of developing cardiovascular disease and/or diabetes.

A subject suffering from Metabolic Syndrome condition is diagnosed with at least three of the below symptoms (Alberti et al, *Circulation* 2009; 120: 1640-1645):

- elevated waist circumference (population- and country-specific; US: Men>102 cm, Women >88cm);
- elevated triglycerides level in the blood (>150mg/dL) or drug treatment for elevated triglycerides;
- reduced HDLcholesterol levels in the blood (<40mg/dl for males and <50mg/dL for females) or drug treatment for reduced HDL-cholesterol;
- elevated blood pressure (systolic >130mmHg and/or diastolic >85 mmHg) or drug treatment for elevated blood pressure;
- elevated fasting glucose levels in the blood (>100mg/dL) or drug treatment for elevated glucose.

Furthermore, it is noted that high-sensitivity C-reactive protein (hs-CRP) is used as a marker to predict coronary vascular diseases in Metabolic Syndrome.

Cconditions/disorders/symptoms associated with Metabolic Syndrome is any one of dyslipidemia, hypertriglyceridemia, diabetes (including type 2 diabetes mellitus (T2DM) and non-insulin dependent diabetes (NIDD) and any symptoms associated therewith), obesity, cancer, hypertension and neurodegeneration.

The symptom associated with T2DM is any one of insulin resistance, hyperglycemia, diabetic dyslipidemia, diabetes macrovascular disease and diabetes microvascular disease. In some , the said condition may be prediabetes.

Where dyslipidemia is concerned, the present invention may be intended for any or all of the following: elevating the plasma level of HDL- cholesterol, for example by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, or even at least 30% or 35% as compared to the level prior to treatment; additionally, the plasma level of HDL-cholesterol may be elevated above at least 30 or 40 mg/DL; further, the invention may comprise maintaining the plasma level of HDL-cholesterol above the level prior to the treatment by the percentages described above and/or above 30 or 40 mg/DL; decreasing the plasma level of LDL-cholesterol for example by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50% or even at least 55 or 60% as compared to the level prior to treatment; additionally, the plasma level of LDL-cholesterol may be decreased below at least 190 mg/DL, at least 160 mg/DL, at least 130 mg/DL or even at least 100 mg/DL; further, the invention may comprise maintaining the plasma level of LDL-cholesterol below the level prior to the treatment by the percentages described above and or below the values described above; decreasing the plasma level of VLDL-cholesterol, for example by at least 5%, at least 10%, at least 20%>, at least 25%>, or even at least 30% or 35%> as compared to the level prior to treatment; further, the invention may comprise maintaining the plasma level of VLDL-cholesterol below the level prior to the treatment by these percentages; decreasing the plasma level of cholesterol, for example by at least 10%), at least 15%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50% or even at least 55 or 60% as compared to the level prior to treatment; additionally, the plasma level of total cholesterol may be decreased below at least 240 mg/DL or at least 200 mg/DL; further, the invention may comprise maintaining the plasma level of total cholesterol below the level prior to the treatment by the percentages described above and/or below the values described above; decreasing the plasma level of triglycerides, for example by at least 7%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50% or even at least 55 or 60% as compared to the level prior to treatment, additionally, the plasma level of triglycerides may be decreased below at least 200 mg/DL or at least 150 mg/DL; further, the invention may comprise maintaining the

plasma level of cholesterol below the level prior to the treatment by the percentages described above and/or below the values described above.

An additional aspect of the present invention concerns the use of a composition of the invention for delaying the onset of non-insulin dependent diabetes mellitus in a human subject susceptible thereto.

In some of these embodiments said disease, condition or disorder associated with Metabolic Syndrome is selected from dyslipidemia, diabetes, obesity, cancer, hypertension, neurodegeneration.

In a further aspect the invention provides a compound as defined hereinabove, or any salts, esters, anhydrides or prodrugs thereof, for use in the treatment of a disease, condition, symptom or disorder associated with Metabolic Syndrome.

In another one of its aspects the invention provides a method of treating a disease, condition, symptom or disorder associated with Metabolic Syndrome in a subject, said method comprising administering to said subject an effective amount of at least one compound as defined hereinabove.

In some embodiments, said medicament is for the treatment of diabetes (including type I and II) in a subject, including a disease, condition, symptom or disorder associated therewith.

BRIEF DESCRIPTION OF THE DRAWINGS

In order to understand the invention and to see how it may be carried out in practice, embodiments will now be described, by way of non-limiting example only, with reference to the accompanying drawings, in which:

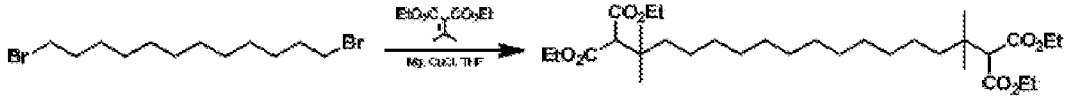
Figs. 1A-1B show the mean plasma levels curves (with S.D.) of compounds 7", 1", 7 and 1 (administered 5mg/kg body weight iv or 50mg/kg body weight po).

Fig. 2 shows the mean plasma levels curves (with S.D.) of compounds 7" and 7 (5mg/kg body weight administered iv).

Fig. 3 shows the 3h-fasting blood glucose (%) of each treatment group at 0, 6 and 12 days of treatment (note that 100% of 3h-Fasting blood glucose equals to 349 ± 17 mg%)

DETAILED DESCRIPTION OF EMBODIMENTS

Example 1: Process for the preparation of l,l,16,16-Tetra(ethoxycarbonyl)-2,2,15,15-tetramethylhexadecane



Reagent	Amount	Mol. Wt.	Mmol	Lot number
1,12-Dibromododecane	14.0 g	328.13	42.7	Aldrich S41671
Magnesium, small turnings	2.19 g	24.31	90.0	Aldrich 15821KH
Tetrahydrofuran	110 mL			Aldrich 22796MMV
Diethyl isopropylidenemalonate	18.0 g	200.23	89.9	Fluka 1191218
Copper(I) chloride	0.150 g	99.00	1.51	Aldrich MKAA0267
3 N Hydrochloric acid	80 mL			Made from Fisher 092605
Heptane	As needed			BDH0904089D
Methyl *tert*-butyl ether	As needed			Aldrich 65396JK
Silica gel	As needed			EMD TA1386285

A 500 mL 3 neck round bottom flask was charged with magnesium turnings (2.19 g). The flask was flushed with nitrogen and anhydrous tetrahydrofuran (100 mL) was added. A solution of 1,12-dibromododecane (14.0 g) in tetrahydrofuran (10 mL) was added dropwise to the magnesium suspension over 20 min. The reaction mixture became warm during the addition. The reaction was stirred at room temperature for 4 h after the addition was complete. The mixture was cooled in an ice bath and copper(I) chloride (0.150 g) was added. Diethyl isopropylidenemalonate (18.0 g) was added dropwise from a syringe over 15 min. The cooling bath was removed and the reaction was allowed to warm to room temperature and stir overnight. The reaction was quenched with 3 N hydrochloric acid (80 mL). Heptane (100 mL) was added and the layers were separated. The aqueous layer was extracted with methyl ieributyl ether (100 mL). The combined organic extracts were filtered through a plug of silica gel (60 mL fritted funnel filled 2/3 full with silica gel). The silica gel was further washed with 1:1 heptane - methyl ieri-butyl ether (100 mL). The filtrate was concentrated under reduced pressure to give a light amber oil. The crude product was distilled using a Kugelrohr apparatus under vacuum (5 mm Hg) with an oven temperature of 180 °C. A small amount of colorless liquid distilled which was predominately unreacted diethyl

isopropylidenemalonate. The residue was allowed to cool to room temperature and was weighed to give l,l,16,16-tetra(ethoxycarbonyl)-2,2,15,15-tetramethylhexadecane (19.6 g, 80.3%).

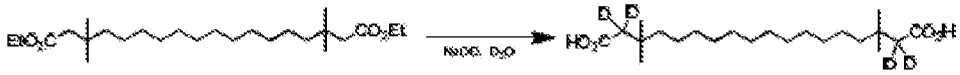
Example 2: Process for the preparation of Diethyl 3,3J6,16-tetramethyl-l,18-octadecanedioate



Reagent	Amount	Mol. Wt.	Mmol	Lot number
1,1,16,16-Tetra(ethoxycarbonyl)-2,2,15,15-tetramethylhexadecane	10.0 g	570.80	17.5	Aptuit 10-163-04-12
Sodium chloride	2.57 g	58.44	44.0	BDH 67573
Sodium bicarbonate	2.21 g	84.01	26.3	Mallinckrodt E23615
Dimethyl sulfoxide	80 mL			Aldrich 26696MJ
DI water	As needed			
Concentrated hydrochloric acid	3 mL			Fisher 092605
Heptane	As needed			BDH080409D
Methyl *tert*-butyl ether	As needed			Aldrich 68396JK
Single Step silica gel cartridge, 160 g	1			Thomson TIC3457393O6211 OA
Dichloromethane	As needed			Burdick & Jackson DB763

A 250 mL round bottom flask was charged with l,l,16,16-tetra(ethoxycarbonyl)-2,2,15,15-tetramethylhexadecane (10.0 g), sodium chloride (2.57 g), sodium bicarbonate (2.21 g) and dimethyl sulfoxide (80 mL). The mixture was heated in a 180 °C oil bath for 24 h. The reaction mixture was cooled to room temperature and was poured into DI water (320 mL) containing concentrated hydrochloric acid (3 mL). The mixture was extracted with 3:1 heptane - methyl ieri-butyl ether (400 mL). The organic layer was washed with DI water (3 x 150 mL). The organic layer was concentrated under reduced pressure to give a brown liquid. The crude product was purified on a Single Step silica gel cartridge (160 g) using 4:1 heptane - dichloromethane as eluent followed by 1:1 heptane - dichloromethane. Fractions that eluted off the column with 1:1 heptane - dichloromethane were combined and concentrated under reduced pressure to give diethyl 3,3,16,16-tetramethyl-l,18-octadecanedioate (4.50 g, 60.2%) as a light yellow liquid.

Example 3: Process for the preparation of 3,3J6,16-Tetramethyl-l,18-r2-D2,17-D21octadecanedioic acid (Compound 5)

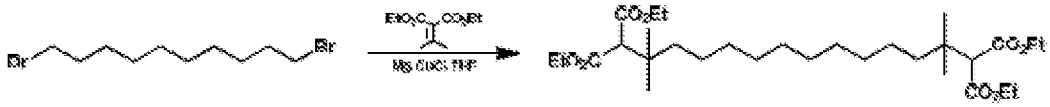


Reagent	Amount	Mol. Wt.	Mmol	Lot number
Diethyl 3,3,16,16-tetramethyl-1,18-octadecanedioate	4.46 g	426.67	10.5	Aptuit 10-163-05-33
Sodium deuteroxide (40% in deuterium oxide)	10 mL			Aldrich MKAA3248
Deuterium oxide	10 mL			Aldrich MKBF3761V
Concentrated hydrochloric acid	As needed			Fisher 992605
Methyl tert-butyl ether	As needed			Aldrich 56395JK
Isopropyl alcohol	As needed			EMD 48121
Ethanol	As needed			EMD 29100480?
Trifluoroacetic acid	2 mL			Aldrich 01113™
DI water	As needed			
Dichloromethane	As needed			Burdick & Jackson DC419
Heptane	As needed			BDH0990408D
Methanol	As needed			BDH0223108
Celite 545	7.0 g			EMD 49685

A 150 ml 316 stainless steel bomb was charged with diethyl 3,3,16,16-tetramethyl-l,18-octadecanedioate (4.46 g), sodium deuteroxide (10 mL, 40% in deuterium oxide) and deuterium oxide (10 mL). The bomb was sealed and was heated in a 200 °C oil bath for 40 h. The bomb was cooled to room temperature and was opened. The liquid contents of the bomb were poured out and acidified with concentrated hydrochloric acid. The aqueous mixture was extracted with methyl ieri-butyl ether (100 mL). Isopropyl alcohol (100 mL) was added to the bomb. A spatula was used to scrape the inside of the bomb to remove the soapy solid. The contents of the bomb were poured out as an amber solution and some solid. Ethanol (100 mL) was added to the bomb. The bomb was again scraped and emptied. The ethanol and isopropyl alcohol washes were combined and trifluoroacetic acid (2 mL) was added. The mixture was stirred until the solid dissolved. The resulting solution was concentrated under reduced pressure to give an oily residue. Methyl ieri-butyl ether (150 mL) and DI water (100 mL) were added. The mixture was vigorously stirred, and then the layers were separated. The methyl ieri-butyl ether layer was combined with the previous methyl ieri-butyl ether extract. The solvent was removed under reduced pressure to give an off white solid. The solid was slurried in dichloromethane (10 mL) and heptane (30 mL). The solid was filtered, washed with heptane (2 x 10 mL) and dried under reduced pressure to give a cream colored solid. The solid was placed in a 1 L Erlenmeyer flask and methanol (500 mL) was added. The mixture was stirred at room temperature for 10 min to give a cloudy solution. The mixture was filtered through Celite 545 (7.0 g) and the solid was washed with methanol (2 x 100 ml). The filtrate was concentrated under reduced pressure to give an off white

solid. The solid was slurried in dichloromethane (10 mL) and heptane (30 mL). The solid was filtered, washed with heptane (10 mL) and dried under high vacuum to give 3,3,16,16-tetramethyl-l,18-[2-D2,17-D2]octadecanedioic acid (3.2684 g, 83.1%) as a white solid.

Example 4: Process for the preparation of l,l,14,14-Tetra(ethoxycarbonyl)-2,2,13,13-tetramethyltetradecane

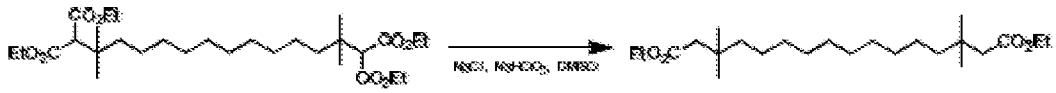


Reagent	Amount	Mol. Wt.	Mmol	Lot number
1,10-Dibromodecane	12.21 g	300.07	40.7	Aldrich 70246DJ
Magnesium, small turnings	2.19 g	24.31	90.0	Aldrich 15621KH
Tetrahydrofuran	110 mL			Aldrich 22796MMV
Diethyl isopropylidenemalonate	18.0 g	200.23	89.9	Fluka 1191218
Copper(I) chloride	0.150 g	99.00	1.51	Aldrich MKAA0267
3 N Hydrochloric acid	80 mL			Made from Fisher 982605
Heptane	As needed			BDH8904080
Methyl *tert*-butyl ether	As needed			Aldrich 66396JK
Silica gel	As needed			EMD TA1366285

A 500 mL 3 neck round bottom flask was charged with magnesium turnings (2.19 g). The flask was flushed with nitrogen and anhydrous tetrahydrofuran (100 mL) was added. A solution of 1,12-dibromododecane (14.0 g) in tetrahydrofuran (10 mL) was added dropwise to the magnesium suspension over 20 min. The reaction mixture got warm during the addition. The reaction was stirred at room temperature for 4 h after the addition was complete. The mixture was cooled in an ice bath and copper(I) chloride (0.150 g) was added. Diethyl isopropylidenemalonate (18.0 g) was added dropwise from a syringe over 15 min. The cooling bath was removed and the reaction was allowed to warm to room temperature and stir overnight. The reaction was quenched with 3 N hydrochloric acid (80 mL). Heptane (100 mL) was added and the layers were separated. The aqueous layer was extracted with methyl ieributyl ether (100 mL). The combined organic extracts were filtered through a plug of silica gel (60 mL fritted funnel filled 2/3 full with silica gel). The silica gel was further washed with 1:1 heptane - methyl ieri-butyl ether (100 mL). The filtrate was concentrated under reduced pressure to give a light amber oil. The crude product was distilled using a Kugelrohr apparatus under vacuum (5 mm Hg) with an oven temperature of 180 °C. A small amount of colorless liquid distilled which was predominately unreacted diethyl isopropylidenemalonate. The residue was allowed to cool to room temperature and was

weighed to give l,l,14,14-tetra(ethoxycarbonyl)-2,2,13,13-tetramethyltetradecane (15.9 g, 72.1%).

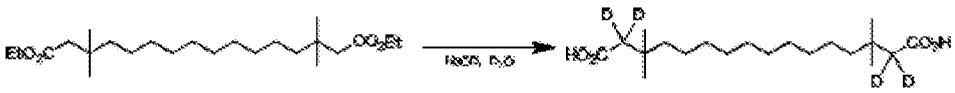
Example 5: Process for the preparation of Diethyl 3,3J4,14-tetramethyl-l,16-hexadecanedioate



Reagent	Amount	Mol. Wt.	Mmol	Lot number
1,1,14,14-Tetra(ethoxycarbonyl)-2,2,13,13-tetramethyltetradecane	15.9 g	542.74	29.3	Aptuit 10-163-10-33
Sodium chloride	4.36 g	58.44	74.7	BDH 67573
Sodium bicarbonate	3.75 g	84.01	44.6	Mallinckrodt E23615
Dimethyl sulfoxide	135 mL			Aldrich 26696MJ
DI water	As needed			
Concentrated hydrochloric acid	5 mL			Fisher 892605
Heptane	As needed			BDH090409D
Methyl *tert*-butyl ether	As needed			Aldrich 66396JK
Single Step silica gel cartridge, 160 g	1			Thomson TIC3457393O8211 OA
Dichloromethane	As needed			Burdick & Jackson DB763

A 250 mL round bottom flask was charged with l,l,14,14-tetra(ethoxycarbonyl)-2,2,13,13-tetramethyltetradecane (15.9 g), sodium chloride (4.36 g), sodium bicarbonate (3.75 g) and dimethyl sulfoxide (135 mL). The mixture was heated in a 180 °C oil bath for 42 h. The reaction mixture was cooled to room temperature and was poured into DI water (500 mL) containing concentrated hydrochloric acid (5 mL). The mixture was extracted with 3:1 heptane - methyl ieri-butyl ether (400 mL). The organic layer was washed with DI water (3 x 150 mL). The organic layer was concentrated under reduced pressure to give a brown liquid. The crude product was purified on a Single Step silica gel cartridge (160 g) using 3:2 heptane - dichloromethane as eluent. Fractions that contained product were combined and concentrated under reduced pressure to give diethyl 3,3,14,14-tetramethyl-l,16-hexadecanedioate (4.00 g, 34.2%) as a light yellow liquid.

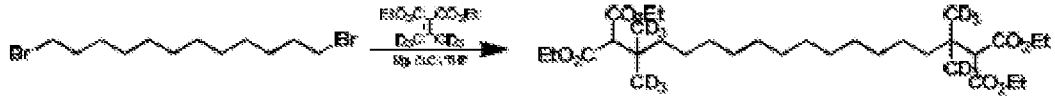
Example 6: Process for the preparation of 3,3J4,14-Tetramethyl-l,16-r2-D2,15-D21hexadecanedioic acid (Compound 2)



Reagent	Amount	Mol. Wt.	Mmol	Lot number
Diethyl 3,3,14,14-tetramethyl-1,16-tetradecanedioate	4.00 g	398.62	10.0	Aptuit 10-163-01-32
Sodium deuteroxide (40% in deuterium oxide)	12 mL			Aldrich MKAA3249
Deuterium oxide	12 mL			Aldrich MKBF3761V
Methyl tert-butyl ether	As needed			Aldrich 6839-JK
Ethanol	As needed			EMD 201004607
Trifluoroacetic acid	4 mL			Aldrich 01113[illegible]
DI water	As needed			
Dichloromethane	As needed			Burdick & Jackson DC419
Heptane	As needed			BDH0904390
Methanol	As needed			BDH0223108
Celite 545	5.0 g			EMD 49085

A 150 ml 316 stainless steel bomb was charged with diethyl 3,3,14,14-tetramethyl-l,16-tetradecanedioic acid (4.00 g), sodium deuteroxide (12 mL, 40% in deuterium oxide) and deuterium oxide (12 mL). The bomb was sealed and was heated in a 200 °C oil bath for 48 h. The bomb was cooled to room temperature and then opened. The soapy solid was broken up with a spatula so the aqueous contents of the bomb could be poured out. Four 50 mL portions of ethanol were used to wash the waxy solids out of the bomb. The ethanol washes were combined and trifluoroacetic acid (4 mL) was added. The mixture was stirred for 30 min until the solid dissolved. The resulting solution was concentrated under reduced pressure to give an oily residue. Methyl ieri-butyl ether (150 mL) and DI water (100 mL) were added. The mixture was vigorously stirred, and then the layers were separated. The methyl ieri-butyl ether layer was concentrated under reduced pressure to give a white solid. The solid was slurried in dichloromethane (10 mL) and heptane (20 mL). The solid was filtered, washed with heptane (10 mL) and dried under reduced pressure to give a white solid. The filtrate was concentrated under reduced pressure to give a solid. Both solids were placed in a 1 L Erlenmeyer flask and methanol (300 mL) was added. The mixture was stirred at room temperature for 10 min to give a slightly cloudy solution. The mixture was filtered through Celite 545 (5.0 g) and the solid was washed with methanol (100 ml). The filtrate was concentrated under reduced pressure to give an off white solid. The solid was slurried in dichloromethane (10 mL) and heptane (30 mL). The solid was filtered, washed with heptane (10 mL) and dried under high vacuum to give 3,3,14,14-tetramethyl-l,16-[2-D2,15-D2]tetradecanedioic acid (2.3371 g, 67.4%) as a white solid.

Example 7: Process for the preparation of 1,1,16,16,-Tetra(ethoxycarbonyl)2,2,15,15,-rD121tetramethylhexadecane



Reagent	Amount	Mol. Wt.	Mmol	Lot number
1,12-Dibromododecane	5.32 g	328.13	16.2	Aldrich S41871
Magnesium, small turnings	0.88 g	24.31	36.0	Aldrich 15621KH
Tetrahydrofuran	45 mL			Aldrich 22796MMV
Diethyl [D_6]isopropylidenemalonate	7.00 g	206.27	33.9	Aptuit 10-163-02-04
Copper(I) chloride	75 mg	99.00	0.76	Aldrich MKAA0287
3 N Hydrochloric acid	40 mL			Made from Fisher 092605
Heptane	As needed			BDH0904090
Methyl tert-butyl ether	As needed			Aldrich 68396JK
Silica gel	As needed			EMD TA1368285

A 250 mL round bottom flask was charged with magnesium turnings (0.88 g). The flask was flushed with nitrogen and anhydrous tetrahydrofuran (40 mL) was added. A solution of 1,12-dibromododecane (5.32 g) in tetrahydrofuran (5 mL) was added dropwise to the magnesium suspension over 15 min. The reaction mixture became warm during the addition. The reaction was stirred at room temperature for 4 h after the addition was complete. The mixture was cooled in an ice bath and copper(I) chloride (0.150 g) was added. Diethyl [D6]isopropylidenemalonate (7.0 g) was added dropwise from a syringe over 5 min. The cooling bath was removed and the reaction was allowed to warm to room temperature and to stir overnight. The reaction was quenched with 3 N hydrochloric acid (40 mL). Heptane (50 mL) was added and the layers were separated. The aqueous layer was extracted with methyl ieri-butyl ether (50 mL). The combined organic extracts were filtered through a plug of silica gel (60 mL fritted funnel filled half full with silica gel). The silica gel was further washed with methyl ieri-butyl ether (100 mL). The filtrate was concentrated under reduced pressure to give a golden oil. The crude product was distilled using a Kugelrohr apparatus under vacuum (5 mm Hg) with an oven temperature of 180 °C. A small amount of colorless liquid distilled which was predominately unreacted diethyl isopropylidenemalonate. The residue was allowed to cool to room temperature and was weighed to give 1,1, 16,1 6-tetra(ethox ycarbonyl)-2,2,15, 15-[D12]tetramethylhexadecane (8.2 g, 87%).

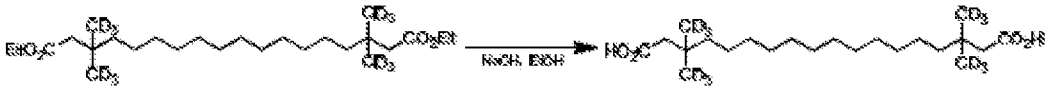
Example 8: Process for the preparation of Diethyl 3,3J4,14-rD121tetramethyl-l,18-octadecanedioiate



Reagent	Amount	Mol. Wt.	Mmol	Lot number
1,1,16,16-Tetra(ethoxycarbonyl)-2,2,15,15-[D12]tetramethylhexadecane	8.2 g	582.87	14.1	Aptuit 10-163-06-34
Sodium chloride	2.07 g	58.44	35.2	BDH 87573
Sodium bicarbonate	1.77 g	84.01	21.0	Mallinckrodt E23615
Dimethyl sulfoxide	65 mL			Aldrich 26695MJ
DI water	As needed			
Concentrated hydrochloric acid	3 mL			Fisher 092605
Heptane	As needed			BDH030409D
Methyl *tert*-butyl ether	As needed			Aldrich 86396JK
Single Step silica gel cartridge, 160 g	1			Thomson TIC3457383O6211 DA
Dichloromethane	As needed			Burdick & Jackson DB763

A 250 mL round bottom flask was charged with 1,1, 16,1 6-tetra(ethoxycarbonyl)-2,2,15,15-[D12]tetramethylhexadecane (8.2 g), sodium chloride (2.07 g), sodium bicarbonate (1.77 g) and dimethyl sulfoxide (65 mL). The mixture was heated in a 180 °C oil bath for 50 h. The reaction mixture was cooled to room temperature and was poured into DI water (250 mL) containing concentrated hydrochloric acid (3 mL). The mixture was extracted with 2:1 heptane - methyl ieri-butyl ether (300 mL). The organic layer was washed with DI water (3 x 150 mL). The organic layer was concentrated under reduced pressure to give a brown liquid. The crude product was purified on a Single Step silica gel cartridge (160 g) using 3:2 heptane - dichloromethane as eluent. Fractions that contained product were combined and concentrated under reduced pressure to give diethyl 3,3,16,16-[D12]tetramethyl-l,18-octadecanedioate (3.10 g, 50.2%) as an orange liquid.

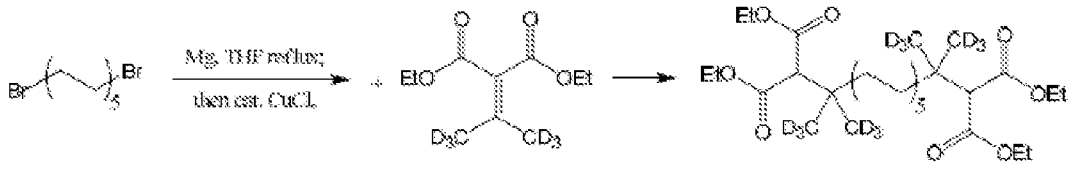
Example 9: Process for the preparation of 3,3J6,16-rD121Tetramethyl-l,18-octadecanedioic acid (Compound 6)



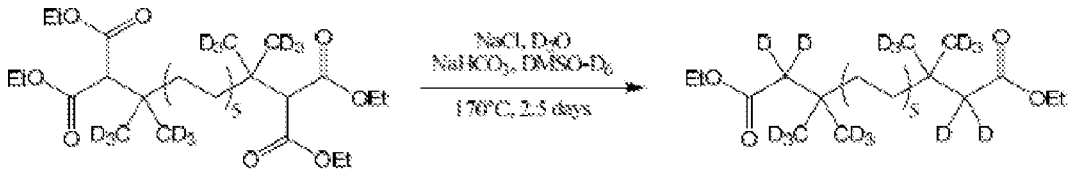
Reagent	Amount	Mol. Wt.	Mmol	Lot number
Diethyl 3,3,16,16-[D_{12}]tetramethyl-1,18-octadecanedioate	3.10 g	438.75	7.07	Aptuit 10-163-07-28
Sodium hydroxide	1.75 g	40.0	43.8	Fisher 081317
Ethanol	70 mL			EMD 201004807
DI water	200 mL			
Concentrated hydrochloric acid	10 mL			Fisher 092605
Methyl *tert*-butyl ether	As needed			Aldrich 66396JK
Dichloromethane	As needed			Burdick & Jackson DC419
Heptane	As needed			BDH0804090
Methanol	As needed			BDH0223108
Silica gel	As needed			EMD TA1366265
Celite 545	4.8 g			EMD 49085

A 250 mL round bottom flask was charged with diethyl 3,3,16,16-[D12]dimethyl-l,18-octadecanedioate (3.10 g), sodium hydroxide (1.75 g) and ethanol (70 mL). The mixture was heated in a 80 °C oil bath overnight. The reaction was allowed to cool to room temperature. Most of the ethanol was removed under reduced pressure. DI water (100 mL) was added and the mixture was acidified with concentrated hydrochloric acid (10 mL). The solid that formed was filtered and washed with DI water (100 mL). The solid was dissolved in 3% methanol in dichloromethane (100 mL). The solution was passed through a plug of silica gel (60 mL fritted funnel filled 2/3 full). The silica gel was further eluted with 3% methanol in dichloromethane (300 mL). The filtrate was concentrated under reduced pressure to give a yellow solid. The solid was suspended in methyl tert-butyl ether (5 mL) and heptane (25 mL). The solid was filtered, washed with heptane (2 x 5 mL) and dried under reduced pressure. The solid was placed in a 500 mL Erlenmeyer flask and methanol (250 mL) was added. The mixture was stirred for 10 min at room temperature giving a cloudy solution. The solution was filtered through a pad of Celite 545 (4.8 g), and the Celite was further washed with methanol (100 mL). The filtrate was concentrated under reduced pressure to give an off white solid. The solid was suspended in dichloromethane (5 mL) and heptane (15 mL). The solid was filtered, washed with heptane (10 mL) and dried under high vacuum to give 3,3,16,16-[D12]tetramethyl-l,18-octadecanedioic acid (1.5740 g, 58.2%) as a white solid.

Example 10: Process for the preparation of 3,3J4,14-rD161Tetramethyl-l,16-hexadecanedioic acid (Compound 1) and 3,3J4,14-rD121Tetramethyl-l,16-hexadecanedioic acid (Compound 3):

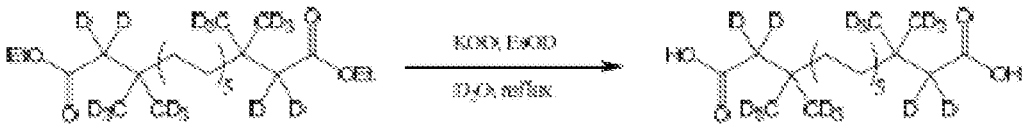


A 1L, 3-neck, round bottom flask equipped with a magnetic stir bar, reflux condenser, addition funnel, and thermometer was flushed with nitrogen for 30 min. Into the flask was charged magnesium turnings (5.82 g, 239 mmoles), anhydrous THF (208 mL), and a single iodine crystal to initiate the reaction. A solution of 1,10-dibromodecane (34.2 g, 114 mmoles) in anhydrous THF (90 mL) was prepared. A portion of this solution (~5 mL) was added to the reaction. The mixture was heated to a mild reflux (65 °C) using a temperature-controlled oil bath and was held at reflux until the yellow color of 12 had disappeared (-30 min). The remaining solution was added dropwise over -30 min, maintaining a gentle reflux. The reaction was refluxed for an additional 2 h. The reaction was cooled to -2°C (ice/water/C0 $_2$ bath), CuCl(s) (0.79 g, 8.0 mmoles) was added in a single portion, and the mixture was stirred for additional 10 min. A solution of diethyl isopropylidenemalonate (dimethyl-D6) (47.0 g, 228 mmoles) in anhydrous THF (50 mL) was added to the reaction dropwise at a rate to keep the temperature ≤ 5°C. After addition was completed, the reaction mixture was allowed to warm to ambient temperature and stirred overnight. The reaction was cooled to 0°C, and then a solution of 12N HCl(aq) (174 mL) in water (261 mL) was added in a slow stream maintaining the internal temperature below 20°C. The mixture was extracted with Et_20 (1 x 250 mL; 3 x 100 mL), and the combined Et_20 extracts were washed with sat. NaHC0 $_3$(aq) (3 x 150 mL) and sat. NaCl(aq) (1 x 150 mL). The Et_20 layer was dried with MgS0 $_4$, filtered, and concentrated *in vacuo* to a crude oil (62.7 g) which was purified by flash chromatography (silica gel, EtOAc/hexanes gradient) to afford compound 1 and compound 3 precursor tetraester (D12) (35.2 g, 56% yield) as a colorless oil.



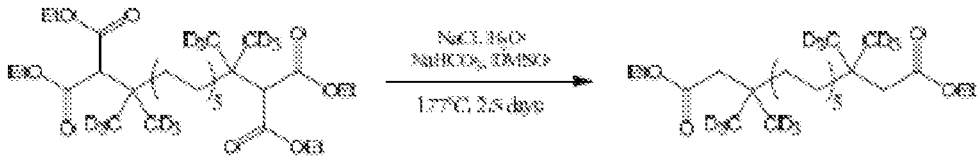
Compound 1 precursor tetraester (D12) (34.0 g, 61.3 mmoles), DMSO-D6 (268 mL), D_20 (9.2 mL, 457 mmoles), NaCl(s) (8.9 g, 152 mmoles), and $NaHC0_3$(s) (7.7 g, 91.7 mmoles) were charged into a 500-mL round bottom flask equipped with a magnetic stir bar, reflux condenser (with no coolant flow) and an internal thermometer. A temperature-controlled oil bath was used for heating. With stirring, the flask was heated in the oil bath set to 177°C. The reaction was heated for 48 hours until complete by TLC. TLC control: ten drops of the reaction was shaken with 30 drops (0.6 mL) of 0.1M HCl(aq) and 0.5 mL of Et_20. TLC of the Et_20 layer (10% EtOAc/ hexanes; visualization with $KMn0_4$ stain). At intermediate stages of the reaction, a mixture of tetraester, triester (see below) and desired diester was observed.

The reaction flask was allowed to cool to room temperature and was poured into of 1M HCl(aq) (1.1 L) and extracted with Et_20 (4 x 500 mL). The Et_20 extracts were combined and washed with water (1 x 500 mL) and saturated NaCl(aq) (1 x 500 mL). The Et_20 layer was dried with $MgS0_4$, filtered, and concentrated *in vacuo* to an orange oil (24.6 g). The crude oil was chromatographed on silica gel using a EtOAc/hexanes gradient to obtain compound 1 Diester (D16) (18.2 g, 72% yield) as a colorless oil.

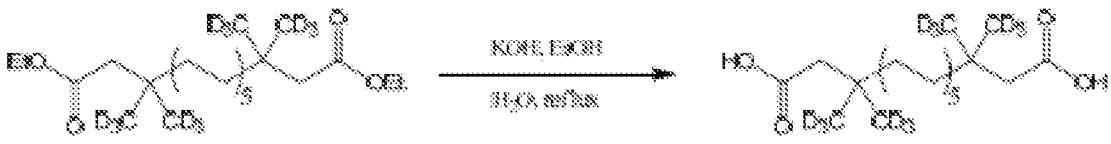


In a 1-L round bottom flask equipped with a magnetic stir bar, reflux condenser, and a nitrogen line, compound 1 diester (D16) (11.2 g, 27 mmoles) and EtOD (504 mL) were stirred to a solution. 35% KOD/D_20 (97 g, 596 mmoles) was added, and the solution was refluxed for 3 h. Fifteen drops of the reaction was shaken with 15 drops of 1M HCl(aq) and 0.5 mL of Et_20. TLC of the Et_20 layer (silica gel plate; 10% EtOAc/hexanes mobile phase; visualization with $KMn0_4$ stain) showed the diester was consumed. The cooled overnight reaction was concentrated *in vacuo* to a thick oil which was dissolved in water (100 mL) and acidified with 12% $DC1/D_20$ (-150 mL) until the

supernatant was acidic. The precipitated solid was collected by filtration and washed with a small amount of H_20 (2 x 5 mL). The solids were briefly air dried on the filter and then *in vacuo* at 40°C overnight. The off-white solid was dissolved in hot ethanol-D6 (100 mL). D_20 (60 mL) was added slowly, and the resulting suspension was left overnight to complete crystallization. The white solid was filtered-off, washed with 50% EtOH(aq) (2 x 25 mL). The solids were dried *in vacuo* at 40°C to constant weight for to afford compound 1 (D16) (9.0 g; 93% yield) as a white solid which passed all release testing (HPLC chemical purity, mp, GCMS IE, 1HNMR, 13CNMR, KF).



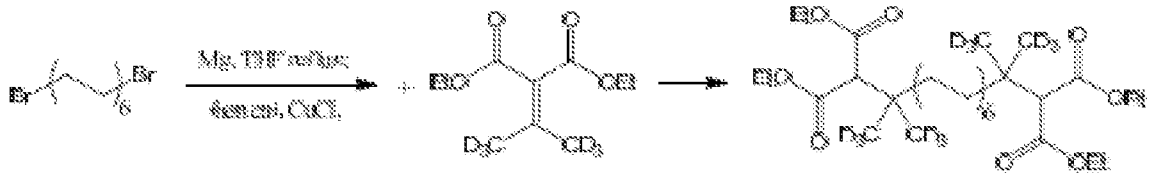
Compound 3 precursor tetraester (D12) (14.0 g, 25.2 mmoles), DMSO (110 mL), H20 (3.4 mL, 189 mmoles), NaCl(s) (3.7 g, 63.1 mmoles), and $NaHC0_3$(s) (3.2 g, 37.8 mmoles) were placed in a 250-mL round bottom flask equipped with a magnetic stir bar, reflux condenser (with no coolant flow) and an internal thermometer. A temperature-controlled oil bath was used for heating. With stirring, the flask was heated in the oil bath set to 177°C. The reaction was heated for 2.5 days until complete by TLC. The reaction mixture was poured into 440 mL of 1M HCl(aq) and extracted with Et_20 (4 x 200 mL). The Et_20 extracts were combined and washed with water (1 x 200 mL) and saturated NaCl(aq) (1 x 200 mL). The Et_20 layer was dried with $MgS0_4$, filtered, and concentrated *in vacuo* to an orange oil (10.8 g). The crude oil was chromatographed on silica gel using a EtOAc/hexanes gradient to obtain compound 3 Diester (D12) (7.8 g, 75% yield) as a colorless oil.



In a 1-L round bottom flask equipped with a magnetic stir bar, reflux condenser, and a nitrogen line, COMPOUND 3 diester (D12) (7.5 g, 18.3 mmoles), EtOH (337.5 mL), and water (37.5 mL) were stirred to a solution. 85% KOH (26.6 g, 402 mmoles) was added in a single portion and the resulting mixture was refluxed for 3 h. Fifteen drops of

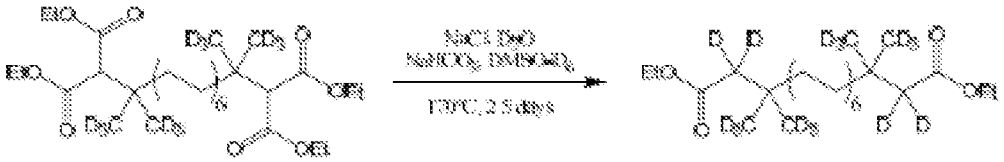
the reaction was shaken with 15 drops of 1M HCl(aq) and 0.5 mL of Et_20 . TLC of the Et_20 layer (silica gel plate; 10% EtOAc/hexanes mobile phase; visualization with KMn04 stain) showed the diester was consumed. The cooled overnight reaction was concentrated *in vacuo* to an orange oil which was dissolved in water (75 mL) and acidified with 4N HC1 (-110 mL). The precipitated solid was collected by filtration and washed with a small amount of H_20 (2 x 5 mL). The solids were briefly air dried on the filter and then *in vacuo* at 40°C overnight. The off-white solid (6.9 g) was dissolved in hot ethanol (70 mL). The yellow solution was treated with charcoal (~1 g) and filtered through a pad of Celite. To the colorless solution was added water (50 mL), and the resulting slurry was left overnight to complete crystallization. The solid was collected by filtration, washed with 50% EtOH(aq) (2 x 25 mL) and dried *in vacuo* at 40°C to constant weight to afford compound 3 (D12) (6.2 g; 95% yield) as a white solid which passed all release testing (HPLC chemical purity, mp, GCMS IE, 1HNMR, 13CNMR, KF).

Example 11: Process for the preparation of 3,3J6,16-rD161Tetramethyl-l,18-octadecanedioic acid (compound 4)

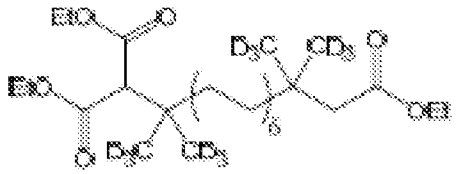


A 500-mL, 3-neck, round bottom flask equipped with a large magnetic stir bar, reflux condenser, thermometer, and a nitrogen inlet was flushed with nitrogen for 30 min. Into the flask was charged magnesium turnings (2.65 g, 109 mmoles), anhydrous THF (105 mL), and iodine crystals (-5-10 mg). The yellow mixture was heated to reflux (65°C) using a temperature-controlled oil bath and was held at reflux until the yellow color of 12 had diminished (-30 min). A solution of 1,12-dibromododecane (16.2 g, 49.4 mmoles) in anhydrous THF (30 mL) was prepared. A portion of this solution (-4 mL) was added to the reaction, and heating was continued until evidence of reaction was seen (gas evolution, increased rate of reflux). The remaining solution was added dropwise over -30 min, maintaining a gentle reflux. The reaction was refluxed for an additional 2 h. The reaction was cooled in an ice/salt bath (to -10°C), CuCl(s) (0.35 g, 3.5 mmoles) was added, and the mixture was stirred for 15 min. A solution of diethyl

isopropylidenemalonate (dimethyl-D6) (21.4 g, 104 mmoles) in anhydrous THF (22 niL) was added to the reaction dropwise at a rate to keep the temperature ≤ 5°C (15-20 min). After an additional 5 min, the cold bath was removed. After the reaction temperature had risen to 15°C, the reaction was stirred an additional 1 h. The reaction was cooled to 0°C, and then a solution of 12N HCl(aq) (77 mL) in water (116 mL) was added in a slow stream. The mixture was extracted four times with Et20 (1 x 190 mL; 3 x 125 mL), and the combined Et20 extracts were washed with sat. NaHC03(aq) (2 x 125 mL), water (1 x 125 mL), and sat. NaCl(aq) (1 x 125 mL). The Et20 layer was dried with MgS04, filtered, and concentrated *in vacuo* to a crude oil (29.6 g), which was purified by flash chromatography (silica gel, EtOAc/hexanes gradient) to afford compound 4 precursor tetraester (D12) (15.8 g, 55% yield) as a pale, yellow oil.

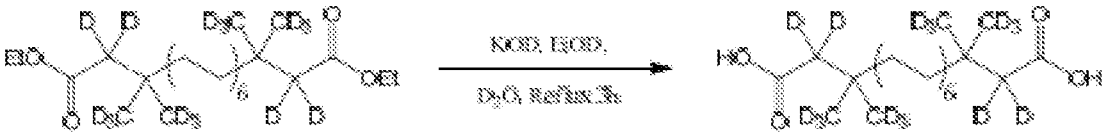


A 250-mL round bottom flask was equipped with a magnetic stir bar, reflux condenser (with no coolant flow) and an internal thermometer. A temperature-controlled oil bath was used for heating. Into the flask was charged compound 4 tetraester (D12) (15.8 g, 27.1 mmoles), DMSO-D6 (124 mL), D_20 (3.7 mL, 204 mmoles), NaCl(s) (4.0 g, 68.4 mmoles), and NaHC03(s) (3.4 g, 40.5 mmoles). With stirring, the flask was heated in the oil bath set to 180°C. The reaction start time was noted when the internal temperature of the reaction rose to ≥ 154°C. The reaction was heated for 2.5 days. Ten drops of the reaction was shaken with 30 drops (0.6 mL) of 0.1M HCl(aq) and 0.5 mL of Et_20 . TLC of the Et_20 layer (10% EtOAc/ hexanes; visualization with $KMn0_4$ stain) showed the reaction was complete. At intermediate stages of the reaction, a mixture of tetraester, triester (below) and desired diester was observed.



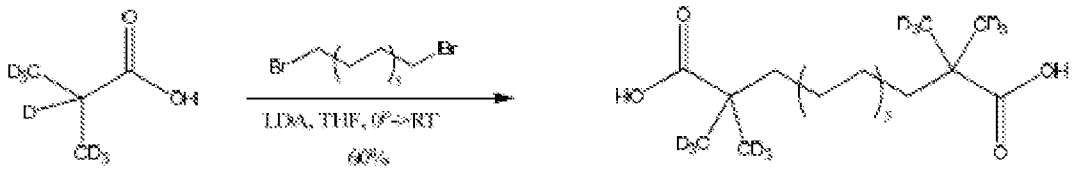
The reaction was allowed to cool to room temperature. The reaction was diluted with 0.1M HCl(aq) (500 mL) and extracted with Et_20 (3 x 230 mL). The Et_20 extracts were

combined and washed with water (1 x 150 mL) and saturated NaCl(aq) (1 x 150 mL). The Et_20 layer was dried with MgS04, filtered, and concentrated *in vacuo* to an orange oil (11.1 g). The crude oil was chromatographed on silica gel using a DCM/hexanes gradient to obtain compound 4 Diester (D16) (8.8 g, 73% yield) as a pale, yellow oil. 1HNMR integration (in CDC13/TMS) revealed that the methylenes alpha to the ester carbonyls were > 90% enriched with deuterium.



In a 500-mL round bottom flask equipped with a magnetic stir bar, reflux condenser, and a nitrogen line, compound 4 diester (D16) (8.8 g, 19.9 mmoles) and EtOD (250 mL) were stirred to a solution. 38% KOD/D_20 (66 g, 440 mmoles) was added, and the solution was refluxed for 3 h. Fifteen drops of the reaction was shaken with 15 drops of 1M HCl(aq) and 0.5 mL of Et20. TLC of the Et_20 layer (silica gel plate; 7.5 mL DCM + 2.5 mL hexanes + 1 mL EtOH mobile phase; visualization with KMn04 stain) showed the diester was consumed. The cooled reaction was diluted with D_20 (100 mL) and concentrated *in vacuo* until solids began to form. The mixture was stirred, and 12% $DC1/D_20$ was added portionwise (110 mL total) until the supernatant was acidic. The resulting warm mixture was stirred until it had cooled to room temperature. The mixture was filtered, and the solids were washed with H_20 (3 x 50 mL). The solids were dried *in vacuo* at 40°C for 2 h. The solids were dissolved in MTBE (175 mL), and the solution was stirred with $MgS0_4$(s) and activated carbon (0.8 g) for 30 min. The slurry was filtered, and the filtrate was concentrated *in vacuo* to a white solid (7.4 g). The solid was dissolved in EtOH (100 mL) with warming to 50°C. With stirring, DI water (50 mL) was added slowly, and the resulting slurry was stirred for 1.5 h. The slurry was filtered, and the solids were washed with 50% EtOH(aq) (50 mL). The solids were dried *in vacuo* at 40°C for 3 h to afford compound 4 (D16) (7.2 g; 93% yield) as a white solid which passed all release testing (HPLC chemical purity, mp, GCMS IE, 1HNMR, 13CNMR, KF).

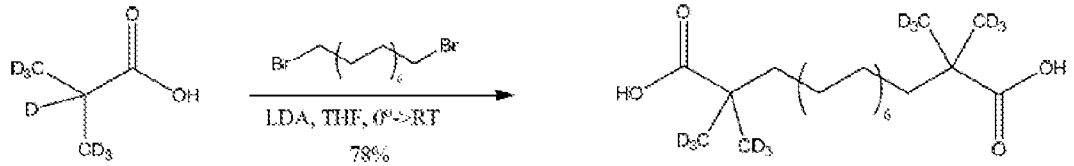
Example 12: Process for the preparation of 2,2,15,15-Tetramethyl(D12)-hexadecanedioic acid (compound 7)



A 250-mL round bottom flask was equipped with a large magnetic stir bar, an internal temperature probe, and a nitrogen line. The apparatus was flushed thoroughly with nitrogen. Into the flask, lithium diisopropylamide solution (2.0M in heptanes/THF/ethylbenzene from Aldrich; 48 mL, 96 mmol) and anhydrous THF (40 mL) were charged. The solution was cooled to 0-5 °C with stirring. 85% Isobutyric acid (isopropyl-D7; contains 15wt% ethyl ether; 5.2 g; 46 mmol) was added dropwise. The reaction was stirred for 5 min, the cold bath was removed, and the reaction was stirred an additional 1.5h. The reaction was cooled to 0-5°C. A solution of 1,12-dibromododecane (5.7 g, 17.4 mmol) in anhydrous THF (15 mL) was added rapidly, and the reaction was stirred for 5 min. The cooling bath was removed, and the reaction was stirred at room temperature (15-20°C) for 15-20 h. The disappearance of 1,12-dibromododecane was confirmed by silica gel TLC (100% hexanes eluent; KMn04(aq) visualization). The reaction was cooled to 0°C. 12% HCl(aq) (55 mL) was added slowly with swirling. Toluene (55 mL) was added, and the mixture was swirled until all solids had dissolved. The phases were separated, and the aqueous layer was extracted twice with toluene (30 mL each). The organic layers were combined and diluted to -220 mL with toluene. The organic solution was washed with deionized water (65 mL), washed with saturated NaCl(aq) (65 mL), dried with MgS04(s), filtered and concentrated *in vacuo* to a solid (8 g). The solid was taken up in hexanes (40 mL) and heated to 60°C. Insolubles were removed by filtration, and the filtrate was concentrated *in vacuo* to a solid. The solid was taken up in hexanes (40 mL) and heated to 60°C to dissolve. The solution was stirred and allowed to cool slowly to room temperature. The resulting slurry was stirred for 2 h and then allowed to stand overnight. The slurry was filtered, and the solids were washed with hexanes (2 x 20 mL). The solid was airdried to obtain an off-white solid (4.3 g, 71% yield; impure compound 7 (D12) by HPLC analysis). The solid was dissolved in EtOH (22 mL) with warming to 45-50°C. With

stirring, deionized water (22 mL) was added portionwise. The heating bath was removed, and the resulting slurry was stirred for 6h. The slurry was filtered, and the solids were washed with 50% EtOH(aq) (25 mL). The solids were dried *in vacuo* at 40°C for 16h to obtain compound 7 (D12) (4.2 g, 69% yield) as a white solid.

Example 13: Process for the preparation of 2,2,17,17-Tetramethyl(D12)-octadecanedioic acid (compound 8)



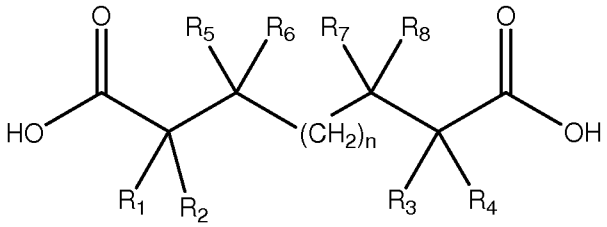
A 250-mL round bottom flask was equipped with a large magnetic stir bar, an internal temperature probe, and a nitrogen line. The apparatus was flushed thoroughly with nitrogen. Into the flask, lithium diisopropylamide solution (2.0M in heptanes/THF/ethylbenzene from Aldrich; 57 mL, 114 mmol) and anhydrous THF (46 mL) were charged. The solution was cooled to 0-5 °C with stirring. 85% Isobutyric acid (ISOPROPYL-D7; contains 15wt% ethyl ether; 6.3 g; 56.3 mmol) was added dropwise. The reaction was stirred for 5 min, the cold bath was removed, and the reaction was stirred an additional 1.5h. The reaction was cooled to 0-5°C. A solution of 1,14-dibromotetradecane (7.4 g, 20.8 mmol) in anhydrous THF (15 mL) was added rapidly, and the reaction was stirred for 5 min. The cooling bath was removed, and the reaction was stirred at room temperature (15-20°C) for 15-18 h. The disappearance of 1,14-dibromotetradecane was confirmed by silica gel TLC (100% hexanes eluent; $KMnO_4$(aq) visualization). The reaction was cooled to 0°C. 12% HCl(aq) (65 mL) was added slowly with swirling. Toluene (65 mL) was added, and the mixture was swirled until all solids had dissolved. The phases were separated using a separatory funnel. The aqueous layer was extracted twice with toluene (30 mL each). The organic layers were combined and were diluted to ~300 mL with toluene. The organic solution was washed with deionized water (100 mL), washed with saturated NaCl(aq) (100 mL), dried with $MgSO_4$(s), filtered and concentrated *in vacuo* to a solid (7.9 g). The solid was taken up in hexanes (55 mL) and heated to 60°C to dissolve. The solution was stirred and allowed to cool slowly to room temperature. The resulting slurry was stirred for 2 h and then allowed to stand overnight. The slurry was filtered, and the solids were washed

with hexanes (20 niL). The solid was air-dried to obtain an off white solid (6.4 g, 80% yield; impure compound 8 (D12) by HPLC analysis). The solid was dissolved in EtOH (33 mL) with warming to 40-45 °C. With stirring, deionized water (33 mL) was added portionwise. The heating bath was removed, and the resulting slurry was stirred for 6h. The slurry was filtered, and the solids were washed with 50% EtOH(aq) (25 mL). The solids were dried *in vacuo* at 40°C for 16h to obtain compound 8 (D12) (6.2 g, 78% yield) as a white solid.

Example 14: Stability of compounds of the invention

The objective of this stability study is to measure the chemical and isotopic stability of the compounds shown below as solutions in DMSO/phosphate buffered saline solution over a 48 hour period, with time points at 2, 4, 24 and 48 hours.

Compounds:



Compound	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	n
1/T1	D	D	D	D	CD_3	CD_3	CD_3	CD_3	10
2/T2	D	D	D	D	CH_3	CH_3	CH_3	CH_3	10
3/T3	H	H	H	H	CD_3	CD_3	CD_3	CD_3	10
4/T4	D	D	D	D	CD_3	CD_3	CD_3	CD_3	12
5/T5	D	D	D	D	CH_3	CH_3	CH_3	CH_3	12
6/T6	H	H	H	H	CD_3	CD_3	CD_3	CD_3	12
7/T7	CD_3	CD_3	CD_3	CD_3	H	H	H	H	10
8/T8	CD_3	CD_3	CD_3	CD_3	H	H	H	H	12

General Procedure

A 1 mg/niL stock solution (~55mL) of deuterated compound in DMSO was prepared. A measured volume of stock (7.5mL) was dispensed in to each of seven vials. To each vial was added a measured volume of PBS (aq) (3.0mL), and each vial was agitated to mix. The vials were then placed in a thermostatically-controlled oven set to 37°C. At each

time-point (Oh, 2h, 4h, 24h, 48h) a vial was drawn from the oven. To the vial was added MTBE (9.0mL), and the mixture was stirred vigorously for 5 min. The layers were separated, and the MTBE layer was agitated with DI water (3.75mL) for 1 min. The layers were separated. The MTBE layer was dried with MgS04 for >lh, and then filtered through a PTFE syringe filter into a tared vial. The solution was concentrated in vacuo to a solid residue, and the mass of the residue was calculated and recorded. To the residue a measured volume of MeOH was added to make (theoretically) a 2.5mg/mL solution. In this case, 3.00mL MeOH was added to each vial which theoretically contained 7.5mg of compound. The content of each solution was measured by quantitative HPLC analysis (by comparison to a standard of known concentration). The MeOH solutions were then recovered, concentrated in vacuo to a solid, and then analyzed by GCMS to determine isotopic enrichment as the methyl ester derivatives.

Results

HPLC analyses of each sample were carried out; an assay against a freshly prepared standard to determine the recovery and an area percent analysis to determine the chemical purity of the recovered material with respect to similar compounds.

Compound **1/Tl** (P 16) **Stability** Data

Stock Preparation		
Mass of Sample:	55.9	mg
Vol DMSO:	56.0	mL
Stock Concentration:	0.998	mg/mL

Sample ID	Concentrated Mass	HPLC Assay	Corrected Mass Recovery	HPLC Area Percentage	GC/MS IE
T1-0h	10.3mg	66.5%	6.9mg	98.1%	98.3%
T1-2h	10.9mg	64.5%	7.0mg	97.2%	98.2%
T1-4h	10.0mg	70.1%	7.0mg	97.8%	98.2%
T1-24h	7.8mg	89.3%	7.0mg	97.6%	98.3%
T1-48h	8.1mg	86.3%	7.0mg	97.5%	98.3%
			Original Sample	100.0%	98.3%

The results for Compound 1/Tl show that the analyte was recovered in over 90% yield with a chemical purity of around 97% with respect to related substances detectable in the HPLC system. No disenrichment of the product was observed throughout the time period of the study.

Compound 2/T2 (P4) Stability Data **Batch # 16-163-13-13**

Stock Preparation			
	Mass of Sample:	59.5	mg
	Vol DMSO:	60.0	mL
	Stock Concentration:	0.992	mg/mL

Sample ID	Concentrated Mass	HPLC Assay	Corrected Mass Recovery	HPLC Area Percentage	GC/MS IE
T2-0h	10.3mg	67.4%	6.9mg	94.9%	97.9%
T2-2h	10.4mg	65.1%	6.8mg	95.5%	98.0%
T2-4h	11.0mg	62.4%	6.9mg	95.4%	98.0%
T2-24h	8.2mg	86.0%	7.0mg	95.2%	98.0%
T2-48h	2.5mg*	280.4%*	7.0mg	96.0%	98.0%
T2-96h	9.2mg	76.8%	7.1mg	96.1%	98.0%
			Original Sample†	97.0%	

The results for Compound 2/T2 show that the analyte was recovered in approximately 90% yield with a chemical purity of around 96% with respect to related substances detectable in the HPLC system. No disenrichment of the product was observed throughout the time period of the study.

Compound 3/T3 (D12) Stability Data **Batch # PR-22093**

Stock Preparation:			
	Mass of Sample:	60.4	mg
	Vol DMSO:	60.0	mL
	Stock Concentration:	1.007	mg/mL

Sample ID	Concentrated Mass	HPLC Assay	Corrected Mass Recovery	HPLC Area Percentage	GC/MS IE
T3-0h	21.4mg	33.3%	7.1mg	98.0%	99.9%
T3-2h	18.9mg	38.4%	7.3mg	98.8%	99.9%
T3-4h	22.4mg	32.4%	7.3mg	98.4%	99.9%
T3-24h	16.1mg	46.0%	7.4mg	98.6%	99.9%
T3-48h	14.4mg	50.2%	7.2mg	98.5%	99.9%
			Original Sample†	100.0%	

The results for Compound 3/T3 are very similar to those obtained for Compound 2. The material was recovered at about 95% yield and area percent chemical purity was between 98% and 99% for all samples through the study. No disenrichment was observed.

Compound 4/T4 (D16) Stability Data

Stock Preparation:		
Mass of Sample:	52.8	mg
Vol DMSO:	52.5	mL
Stock Concentration:	1.006	mg/mL

Sample ID	Concentrated Mass	HPLC Assay	Corrected Mass Recovery	HPLC Area Percentage	GC/MS IE
T4-0h	10.0mg	70.9%	7.1mg	97.2%	98.6%
T4-2h	10.7mg	65.9%	7.1mg	97.8%	98.4%
T4-4h	11.0mg	53.8%	5.9mg	97.5%	98.4%
T4-24h	7.2mg	93.8%	6.8mg	96.5%	98.4%
T4-48h	9.0mg	77.6%	7.0mg	97.5%	98.3%
			Original Sample	99.2%	98.3%

The results for Compound 4/T4 were essentially the same as those for Compound 1.

Compound 5/T5 (D4) Stability Data **Batch #** **10-163-14-19**

Stock Preparation:		
Mass of Sample:	56.5	mg
Vol DMSO:	56.0	mL
Stock Concentration:	1.009	mg/mL

Sample ID	Concentrated Mass	HPLC Assay	Corrected Mass Recovery	HPLC Area Percentage	GC/MS IE
T5-0h	12.7mg	57.0%	7.2mg	98.4%	96.3%
T5-2h	16.5mg	44.6%	7.4mg	98.0%	95.9%
T5-4h	16.0mg	46.3%	7.4mg	98.5%	96.0%
T5-24h	7.8mg	95.3%	7.4mg	98.4%	96.0%
T5-48h	3.4mg	213.8%	7.3mg	98.0%	95.5%
T5-96h	9.2mg	79.8%	7.3mg	98.7%	96.1%
			Original Sample	100.0%	

The results for Compound 5/T5 are very similar to those obtained for the other Compound compounds. The material was recovered at about 95% yield and area percent chemical purity was between 98% and 99% for all samples through the study. No disenrichment was observed, although it appears that this compound was slightly disenriched when compared with the other compounds in the set.

Compound 6/T6 (D12) Stability Data		Batch #	**10-163-15-18**
Stock Preparation:			
	Mass of Sample:	**55.8**	**mg**
	Vol DMSO:	**56.0**	**ml**
	Stock Concentration:	**0.998**	**mg/mL**

Sample ID	Concentrated Mass	HPLC Assay	Corrected Mass Recovery	HPLC Area Percentage	GC/MS IE
T6-0h	18.2mg	39.0%	7.1mg	98.4%	99.2%
T6-2h	21.8mg	33.1%	7.2mg	98.6%	99.0%
T6-4h	19.5mg	35.6%	6.9mg	97.9%	99.1%
T6-24h	18.1mg	39.8%	7.2mg	98.5%	99.0%
T6-48h	12.0mg	59.6%	7.1mg	98.7%	99.1%
			Original Sample	100.0%	

The results for Compound 6/T6 are very similar to those of the other compounds. The material was recovered at about 95% yield and area percent chemical purity was between 98% and 99% for all samples through the study. No disenrichment was observed.

Compound 7/T7 (D12) **Stability** Data

Stock Preparation			
	Mass of Sample:	41.8	mg
	Vol DMSO:	42.0	mL
	Stock Concentration:	0.995	mg/mL

Sample ID	Concentrated Mass	HPLC Assay	Corrected Mass Recovery	HPLC Area Percentage	GC/MS IE
T7-0h	5.0mg	89.4%	4.5mg	96.8%	99.9%
T7-2h	4.5mg	101.6%	4.6mg	95.4%	99.9%
T7-4h	4.9mg	91.6%	4.5mg	95.8%	99.9%
T7-24h	4.9mg	92.3%	4.5mg	96.9%	99.9%
T7-48h	5.5mg	82.2%	4.5mg	96.7%	99.9%
			Original Sample	99.5%	99.9%

The results for Compound 7/T7 show that the analyte was recovered in approximately 90% yield with a chemical purity of around 96% with respect to related substances detectable in the HPLC system. No disenrichment of the product was observed throughout the time period of the study.

Compound 8/T8 (P 12) Stability Data

Stock Preparation:		
Mass of Sample:	39.6	mg
Vol DMSO:	40.0	mL
Stock Concentration:	0.990	mg/mL

Sample ID	Concentrated Mass	HPLC Assay	Corrected Mass Recovery	HPLC Area Percentage	GC/MS IE
T8-0h	6.9mg	60.0%	4.1mg	95.1%	99.9%
T8-2h	6.0mg	68.7%	4.1mg	94.3%	99.9%
T8-4h	7.3mg	56.9%	4.2mg	94.1%	99.9%
T8-24h	6.4mg	66.8%	4.3mg	96.0%	99.9%
T8-48h	9.3mg	47.7%	4.4mg	97.2%	99.9%
			Original Sample	100.0%	99.9%

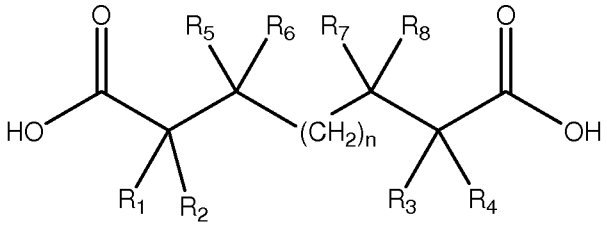
The results for Compound 8/T8 are very similar to those obtained for Compound 7. The material was recovered at about 85% yield and area percent chemical purity was around 95% for all samples through the study. No disenrichment was observed.

Conclusion

Based on the data shown above, there appeared to be no chemical degradation of the compounds studied during the timescale of the study (48h). No disenrichment of any of the compound was observed during the time course of the study.

Example 15: Comparative oral bioavailability study

The pharmacokinetic properties and the oral bioavailability were investigated for the following comparative compounds:



Compound	Ri	R_2	R_3	R_4	R_5	R_6	R_7	R_8	n
1	D	D	D	D	CDs	CDs	CDs	CDs	10
1"	H	H	H	H	CHs	CHs	CHs	CHs	10
7	CD_3	CDs	CDs	CDs	H	H	H	H	10
7"	CHs	CHs	CHs	CHs	H	H	H	H	10

Definitions:

$t_{½}$ Apparent terminal elimination half-life $\{t_{½}=\ln(2)/\lambda_z)$

tmax Time of maximum plasma concentration measured (Cmax)

Cmax Maximum plasma concentration measured, occurring at tmax

AUCinf Area under the plasma concentration-time curve from time zero (the time of dosing) extrapolated to infinity

Co Back-extrapolated concentration at time zero (only for IV administration)

Vc Central volume of distribution (only for IV administration)

Vss Volume of distribution estimated for the steady state phase

CI Total body clearance (only for IV administration)

$MRTi_{nf}$ Mean residence time

F Oral bioavailability (AUCpo*doseiv)/(AUCiv*dosepo)*100

The plasma concentrations of the test items were measured by LC/MS/MS method following single intravenous and oral administration at the doses of 5 mg/kg body weight and 50 mg/kg body weight, respectively. Following intravenous administration small inter-individual variability was observed. Following i.v administration, the highest plasma concentrations were measured at the first sampling time-point (5 minutes) followed by a biphasic continuous decrease. Following oral administration, t(he absorption process was prolonged and showed high individual variability. The variability was smaller for the deuterated analogues than for the non-deuterated compounds. The peaks (tmax) occurred at 4 hours post-dose for each Compound 1 and Compound 7 treated rats. Contrary, t_{max} varied from 0.5 to 12 hours for the Compound 7" and Compound 1" administered animals. The pharmacokinetic parameters were calculated using non-compartmental analysis. All plasma level curves were characterized well since the extrapolated parts were small and the fit of the terminal phases was good. The peak concentrations, t_{max} and the apparent terminal elimination half-lives ($t_{½}$) were the followings:

Compound	Mean CV(%)				
	5 mg/kg iv dose		50 mg/kg po dose		
	Co [µg/ml]	tl/2 [h]	Cmax |^g/ml]	tmax [h]	tl/2 [h]
7"	74.6 (6.9%)	2.18 (19.1%)	143 (41.3%)	8 (50.0%)	2.22 (9.9%)
1"	56.1 (6.2%)	2.68 (6.0%)	103 (24.2%)	3.5 (79.5%)	2.43 (57.6%)
1	67.0 (8.8%)	2.81 (28.5%)	114 (19.6%)	4 (0%)	4.29 (15.7%)
7	64.3 (16.9%)	2.14 (2.6%)	151 (29.0%)	4 (0%)	6.64 (50.3%)

All experimental compound analogues showed small volume of distribution (Vc: 67.2-89.4 mg/kg; Vss: 97.3-143 ml/kg) (approximately equal to total blood volume), and clearance (CI: 23.2-42.0 h*µg/πl).

Following administration of the same intravenous or oral dose among the 1, 1", 7, 7" compounds, compound 7 showed the highest total exposure:

Compound	Mean CV(%)	
	AUC_{inf} [h*µg/ml]	
	5 mg/kg iv	50 mg/kg po
7"	128 (13.4%)	1586 (28.3%)
1"	124 (23.6%)	863 (29.4%)
1	137 (19.3%)	1246 (11.1%)
7	218 (14.9%)	2221 (36.8%)

The oral bioavailability of all analogues indicated good absorption The oral bioavailability for the investigated compounds were the following:

Compound	Mean (CV%)
	F [%]
7"	124 (28.3)
1"	69.6 (29.4)
1	91.0 (11.1)
7	102 (36.8)

The deuterated/non-deuterated ratios were calculated for the most important pharmacokinetic parameters. After 5 mg/kg intravenous dosing the kinetic parameters of Compound 1" and Compound 1 did not show biologically relevant differences. For Compound 7 the tendency of the slower elimination already could be observed which resulted in higher total exposure, longer mean residence time and smaller clearance compared to its non-deuterated analogue.

Deuterated/ Non Deuterated ratio	**For AUC_{inf} (hr*µg/ml)**	**For Cl (ml/hr/kg)**	**For MRT_{inf} (hr)**
5mg/kg iv dose	[%]		
1/1"	110	89	100
7/7"	170	58	168

Following 50 mg/kg oral administration the absorption did not show differences since the peak concentrations were almost equal for the deuterated and the non-deuterated analogues. Increased total exposure and the prolonged mean residence time were obtained for both Compound 1 and Compound 7 due to the slower elimination. The effect was more expressed for Compound 7 than for Compound 1.

Deuterated/ Non Deuterated ratio	**For $t_{1/2}$ (hr)**	**For C_{max} (µg/ml)**	**For AUC_{inf} (hr*µg/ml)**	**For MRT_{inf} (hr)**
50mg/kg po dose	[%]			
1/1"	177	111	144	115
7/7"	300	106	140	133

Preparation of vehicle

The vehicle for oral administration was prepared in advance. Preparation: 1 g of carboxymethylcellulose sodium salt was dissolved in 100 ml of Humaqua. The vehicle was prepared at least 2 days prior to formulation of the test items. The vehicle was stored in a refrigerator when not in use.

Preparation of the dose forms

Intravenous formulation The required amount of test item was weighed on an analytical balance, transferred into a suitable vial. The test item was dissolved in the required volume of N,N-dimethylacetamide (40% of the final volume). Dissolution of

the test item was facilitated by gentle mixing by vortex. The solution was diluted with the suitable volume of PEG400 (40% of the final volume) then Salsol A (20% of the final volume). The final concentration of the test item in the solution was 5 mg/ml. The formulations were prepared freshly on the day of administration.

Oral dose form: The required amount of test item was weighed on an analytical balance, transferred into a test tube and mixed with the suitable volume of 1% CMC to achieve the final concentration of 25 mg/ml. The suspension was sonicated twice in bath sonicator for 30 min at 40C (each round), and left overnight at room temperature. On the following day, the suspension was sonicated again (bath sonicator, 30 min, 40oC) and further homogenized in a glass/glass homogenizer trying to reaching an homogenous suspension. In spite of the above procedure the quality (homogeneity) of the suspension was not perfect. The suspension was stored at room temperature till administration.

Animal specification

Species / Strain rat / Wistar (Crl:(WI)BR rats)

Number of animals: 24 males (at least 32 for cannulation*)

Body weights at arrival: 250-270 g

Acclimatization: at least five days

Experimental Study

Cannulation

After the acclimatization period, rats were equipped with a jugular vein cannula under isoflurane anesthesia. The following day the animals were used for the study. In the morning the rats were checked for health status and blood sampling before assigning them into the experimental group. If the cannula did not function properly, the animal was left out from the experiment.

Plasma concentrations

Following intravenous administration small inter-individual variability was observed. The highest plasma concentrations were measured at the first sampling time-point (5 minutes). Then the concentrations decreased continuously. In the semi-logarithmic curves biphasic decrease could be seen. Following oral administration the absorption

process was prolonged and showed high individual variability. The variability was smaller for the deuterated analogues than for the non-deuterated compounds. The peaks occurred at 4 hours post-dose for each Compound 1 and Compound 7 treated rats. Contrary, tmax varied from 0.5 to 12 hours for the Compound 7" and Compound 1" administered animals.

Pharmacokinetic evaluation

The terminal elimination phase was defined on the basis of the last 3-5 measured concentration except rat A4. The good regression data indicated that the reliable terminal half-lives could be determined. For rat A4 the peak concentration occurred at 12 hours post-dose, thus only 1 later time point was available for calculation of the half-life. All experimental compound analogues showed small distribution volume. The central volume of distribution (Vc: 67.2-89.4 mg/kg) was approximately equal to the total blood volume. The volume of distribution estimated for the steady state situation (Vss: 97.3-143 ml/kg) remained also small compared to the total extracellular fluid volume (-300 ml/kg). The clearance was also very small for all experimental compound analogues. The smallest clearance was obtained for Compound 7: 23.2 ml/h/kg. Thus, the longest mean residence time was also observed for Compound 7: 4.2h and 11.8h following intravenous and oral administration, respectively.

Conclusions

Pharmacokinetic properties of Compound 7" and Compound 1" were compared to those of their deuterated analogues, Compound 7 and Compound 1, respectively. The mean plasma level curves (with S.D.) for the pairs are shown in **Figs. 1A - IB** and **Fig. 2.**

The deuterated/non-deuterated ratios were calculated for the most important pharmacokinetic parameters. After 5 mg/kg intravenous dosing the kinetic parameters of Compound 1" and Compound 1 did not show biologically relevant differences.

Although the calculated apparent terminal elimination half life for Compound 7 did not differ from that of Compound 7", the plasma level curve already indicated the tendency of the slower elimination which resulted in higher total exposure, longer mean residence time and smaller clearance compared to its non-deuterated analogue.

Following 50 mg/kg oral administration the absorption did not show differences since the peak concentrations were almost equal for the deuterated and the non-deuterated analogues. Implementation of deuterium atoms into the molecules resulted in increased total exposure and the prolonged mean residence time for both Compound 1 and Compound 7 due to the slower elimination. The effect was more expressed for Compound 7 than for Compound 1.

Example 16: Comparative *in vivo* efficacy studies

Animal model:

Male db/db Mouse Model. Age of animal at start of treatment: 10-llweeks. Animals per treatment group: 6-7 mice per each group.

Treatment groups:

Vehicle control: (1% CMC in water).

Positive control: Rosiglitazone, 25 mg/kg.

Group I: Compound 7", 12.5 mg/kg.

Group II: Compound 7", 25 mg/kg.

Group III: Compound 7, 12.5 mg/kg.

Group IV: Compound 7, 25 mg/kg.

Duration of treatment: 15 days.

Study Summary:

1. Dosing: Animals are 10-11 weeks of age and were allowed to acclimate 1-2 weeks. After acclimation, animals were entered to the study and were gavaged daily for a duration of 15 days.

2. Formulation: compounds were formulated with CMC in 1% water. Formulation also involve sonication and vortexing before use.

3. Body Weight: Body weight was followed throughout the study to monitor animal health.

4. Fasting Glucose Levels: 3h-Fasting glucose levels were measured on tail blood of all the animals on days 0, 6, 12, and 16 (not shown) of the study using glucose sticks (Proforma).

5. Triglycerides: Blood samples are collected on all animals on termination of the study, and analyzed for triglycerides.

6. Insulin Levels: Blood samples are collected on all animals on termination of the study, and analyzed for plasma insulin using RIA.

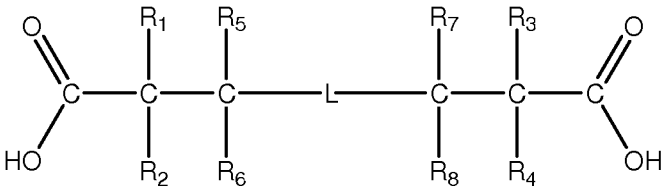
7. Necropsy: Animals are sacrificed after 15 days of drug treatment. Gross pathology evaluation of the liver is assessed at the time of necropsy.

Results:

Fig. 3 shows the 3h-fasting blood glucose (%) of each treatment group at 0, 6 and 12 days of treatment (note that 100% of 3h-Fasting blood glucose equals to 349 ± 17 mg%). The results show that treatment Group IV (Compound 7, 25mg) showed greater efficacy as compared with Rosiglitazone (the current state of the art treatment for Diabetes), achieving higher rate of decrease in glucose levels to normalized plasma levels (less than 110 mg% of glucose). Furthermore, the efficacy of treatment Group III (Compound 7, 25mg dose) exceeds that of both treatment Groups I and II (Compound 7").

CLAIMS:

1. A compound of general formula (I), including any salts, esters, anhydrides or prodrugs thereof:



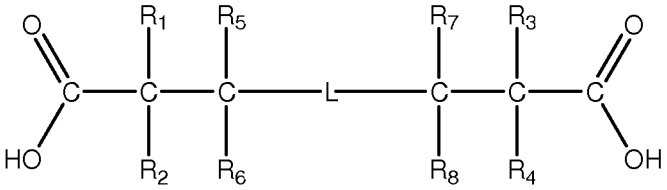
(I)

wherein

L is a straight or branched C8-Ci 6 alkylene; optionally interrupted by at least one moiety selected from O, S, NH, Cs-Ciocycloalkylene, Cs-Ciocycloheteroalkylene, C_6-Ci8 arylene, C_6-Ci8 heteroarylene;

each of Ri - R_8 is independently selected from H, D, CH_3 and CD_3; wherein at least one of Ri - R_8 is D or CD_3.

2. A compound of general formula (I), including any salts, esters, anhydrides or prodrugs thereof:



(I)

wherein

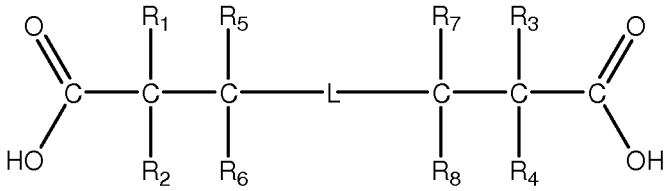
L is a straight or branched C8-C16 alkylene; optionally interrupted by at least one moiety selected from O, S, NH, Cs-Ciocycloalkylene, Cs-Ciocycloheteroalkylene, C_6-Ci8 arylene, C_6-Ci8 heteroarylene;

each of Ri - R_4 is independently H or D;

each of $_{R\,5}$ - R_8 is independently CH_3 or CD_3;

wherein when Ri - R_4 are H, at least one of $_{R\,5}$ - R_8 is CD_3; or when $_{R\,5}$ - R_8 are CH_3, at least one of Ri - R_4 is D.

3. A compound of general formula (I), including any salts, esters, anhydrides or prodrugs thereof:



(I)

wherein

L is a straight or branched C_9-C_{16} alkylene; optionally interrupted by at least one moiety selected from O, S, NH, Cs-Ciocycloalkylene, Cs-Ciocycloheteroalkylene, C_6-C_{18} arylene, C_6-C_{18} heteroarylene;

each of R_1 - R_4 is independently CH_3 or CD_3;

each of R_5 - R_8 is independently H;

wherein at least one of R_1 - R_4 is CD_3.

4. A compound according to claims 1 or 2, wherein at least one of R_1 - R_4 is D.

5. A compound according to claims 1 or 2, wherein at least one of R_5 - R_8 is CD_3.

6. A compound according to claims 1 or 3, wherein at least one of R_1 - R_4 is CD_3.

7. A compound according to claims 1 or 3, wherein at least one of R_5 - R_8 is D.

8. A compound according to any one of claims 1 to 8, wherein L is $-(CH_2)_{10}-$.

9. A compound according to any one of claims 1 to 8, wherein L is $-(CH_2)_{12}-$.

10. A compound according to claims 1 or 2, wherein at least one of R_1 - R_4 is D and at least one of R_5 - R_8 is CD_3.

11. A compound according to claims 1 or 3, wherein at least one of R_1 - R_4 is CD_3 and at least one of R_5 - R_8 is D.

12. A compound according to claims 1 or 2, wherein:

Compound	$R_1=R_2=R_3=R_4$	$R_5=R_6=R_7=R_8$
II	D	CH_3
III	H	CD_3
IV	D	CD_3

13. A compound according to claims 1 or 2, wherein:

Compound	$R_1=R_2$	$R_3=R_4$	$R_5=R_6$	$R_7=R_8$
V	D	H	CH_3	CH_3
VI	D	H	CD_3	CH_3
VII	D	H	CH_3	CD_3
VIII	D	H	CD_3	CD_3
IX	D	D	CD_3	CH_3

14. A compound according to claims 1 or 2, wherein:

Compound	$R_1=R_3$	$R_2=R_4$	$R_5=R_6$	$R_7=R_8$
X	D	H	CH_3	CH_3
XI	D	H	CD_3	CH_3
XII	D	H	CD_3	CD_3

15. A compound according to claims 1 or 2, wherein:

Compound	$R_1=R_3$	$R_2=R_4$	$R_5=R_7$	$R_6=R_8$
XIII	D	H	CH_3	CH_3

16. A compound according to claims 1 or 3, wherein:

Compound	$R_1=R_2=R_3=R_4$	$R_5=R_6=R_7=R_8$
XIV	CD_3	H

17. A compound according to claims 1 or 3, wherein:

Compound	R1-R2	R3-R4	R5-R6	R7-R8
XV	CD_3	CH_3	H	H

18. A compound according to claims 1 or 3, wherein:

Compound	R_1=R_3	R_2=R_4	R_5=R_6	R_7=R_8
XVI	CD_3	CH_3	H	H

19. A composition comprising a compound according to any one of claims 1 to 18 or any salts, esters, anhydrides or prodrugs thereof.

20. A composition according to claim 19, for use as a medicament.

21. A composition according to claim 20, wherein said medicament is administered in a dose of 10 to lOOmg/Kg per day.

22. A composition according to claim 20, wherein said medicament is administered in a dose of less than 50mg/Kg per day.

23. Use of a compound according to any one of claims 1 to 18 or any salts, esters, anhydrides or prodrugs thereof, for the preparation of a medicament.

24. Use according to claim 23, wherein said medicament is for the treatment of any disease, condition, symptom or disorder associated with Metabolic Syndrome.

25. Use according to claim 24, wherein said disease, condition or disorder associated with Metabolic Syndrome is selected from dyslipidemia, diabetes, obesity, cancer, hypertension and neurodegeneration.

26. A compound according to any one of claims 1 to 18 or any salts, esters, anhydrides or prodrugs thereof, for use in the treatment of a disease, condition, symptom or disorder associated with Metabolic Syndrome.

27. A compound according to claim 26, wherein said disease, condition or disorder associated with Metabolic Syndrome is selected from dyslipidemia, diabetes, obesity, cancer, hypertension and neurodegeneration.

28. A method of treating a disease, condition, symptom or disorder associated with Metabolic Syndrome in a subject, said method comprising administering to said subject an effective amount of at least one compound as defined in any one of claims 1 to 18.

29. A method according to claim 28, wherein said disease, condition or disorder associated with Metabolic Syndrome is selected from dyslipidemia, diabetes, obesity, cancer, hypertension and neurodegeneration.

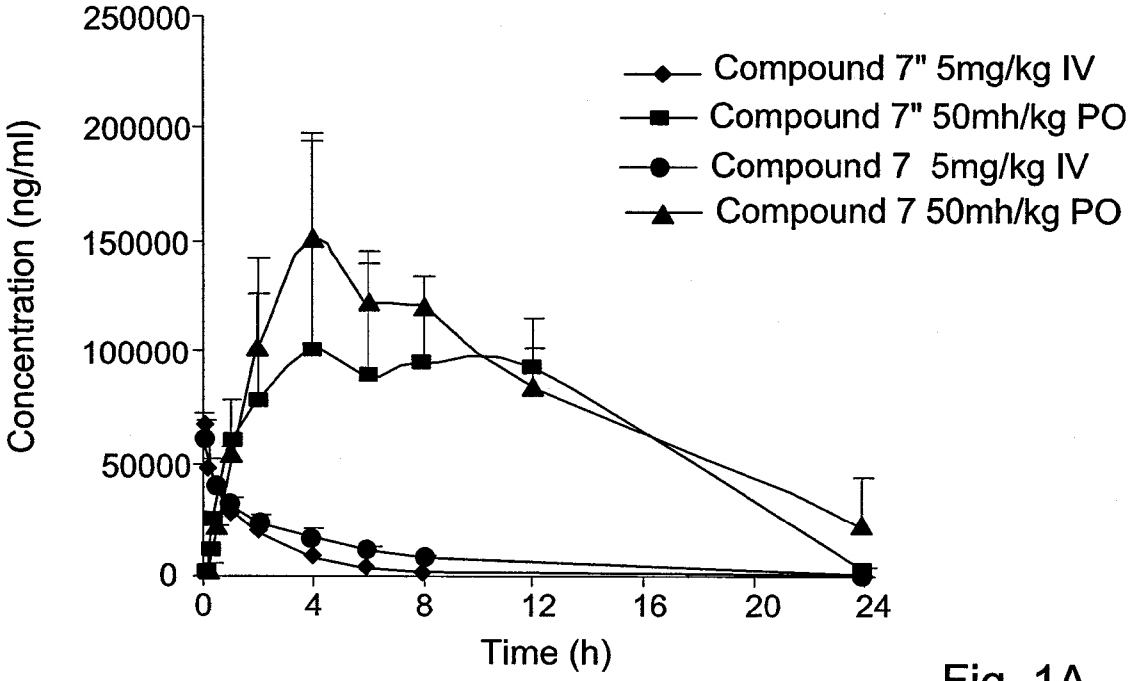

250000
200000
150000
100000
50000
0
Concentration (ng/ml)
0
4
8
12
16
20
24
Time (h)
Compound 7" 5mg/kg IV
Compound 7" 50mh/kg PO
Compound 7 5mg/kg IV
Compound 7 50mh/kg PO

Fig. 1A

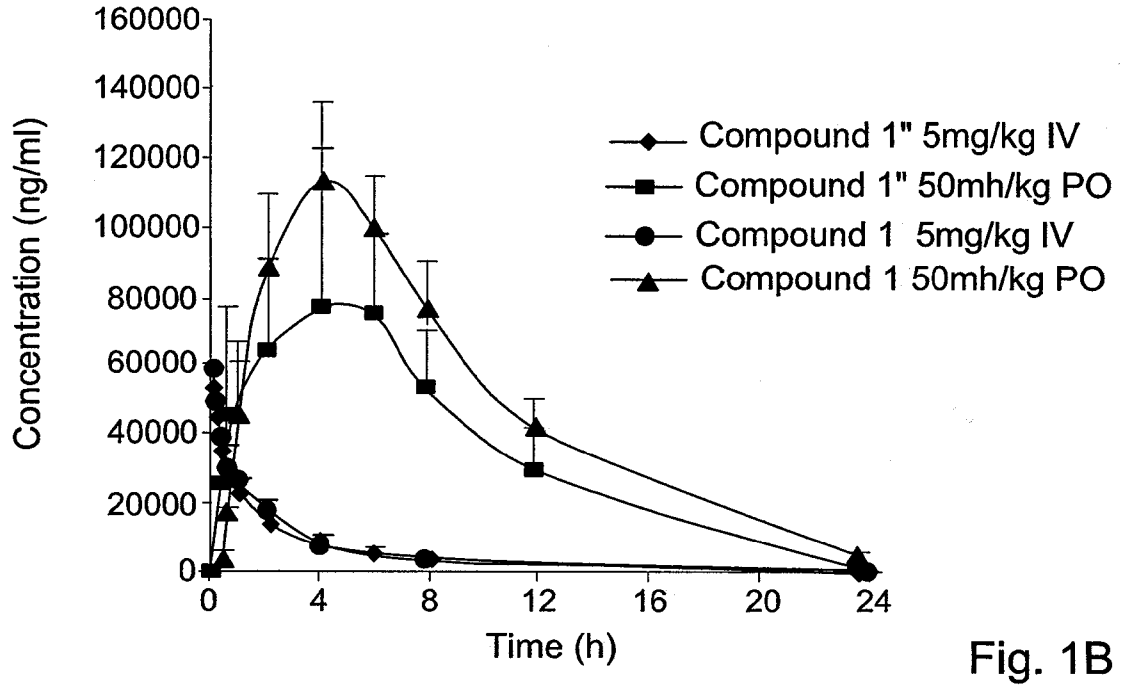

160000
140000
120000
100000
80000
60000
40000
20000
0
Concentration (ng/ml)
0
4
8
12
16
20
24
Time (h)
Compound 1" 5mg/kg IV
Compound 1" 50mh/kg PO
Compound 1 5mg/kg IV
Compound 1 50mh/kg PO

Fig. 1B

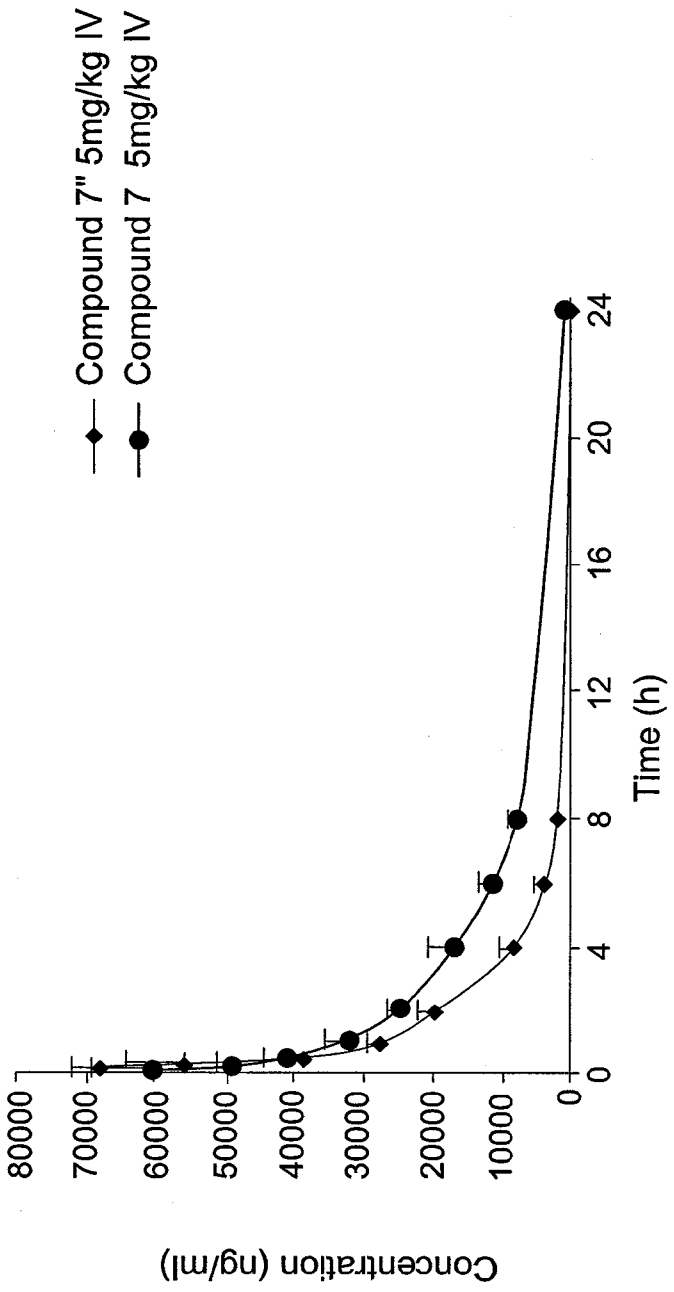

Compound 7" 5mg/kg IV
Compound 7 5mg/kg IV
Concentration (ng/ml)
80000
70000
60000
50000
40000
30000
20000
10000
0
0
4
8
12
16
20
24
Time (h)

Fig. 2

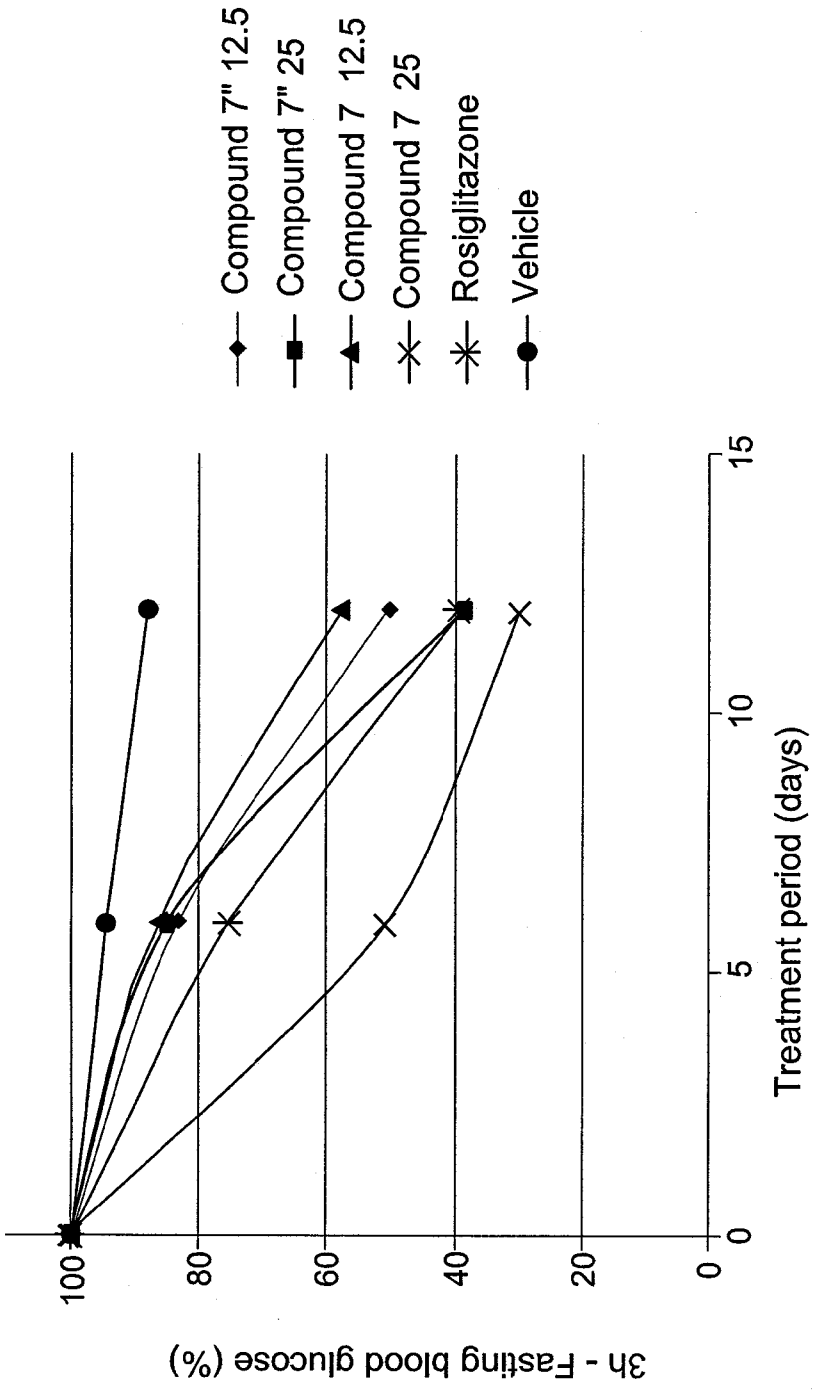

Compound 7" 12.5
Compound 7" 25
Compound 7 12.5
Compound 7 25
Rosiglitazone
Vehicle
3h - Fasting blood glucose (%)
100
80
60
40
20
0
0
5
10
15
Treatment period (days)

Fig. 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL2012/050511

A. CLASSIFICATION OF SUBJECT MATTER

See extra sheet.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC (2013.01) A61K 31/16, A61K 31/20, A61K 31/225, A61P 3/04, A61P 3/06, A61P 3/08, A61P 3/10, C07C 231/00, C07C 233/04, C07C 233/05, C07C 253/00, C07C 255/22, C07C 51/00, C07C 55/02, C07C 55/32, C07C 67/00, C07C 69/34

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

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

Databases consulted: THOMSON INNOVATION, Google Patents, CAPLUS, REGISTRY
Search terms used: deuterium , isotop , effect , covalent bond

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4634795 A EPIS SA [CH] 06 Jun 1987 (1987/06/06) abstract , col. 1-3 , claim 1. cited in the application	1-29
Y	WO 2012028106 A1 ASCEPION PHARMACEUTICALS INC [CN]; JIANG SHAN [US]; GAO XIAOYONG [CN]; WANG QISHAN [CA] 08 Mar 2012 (2012/03/08) para. [10]	1-29

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

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 Mar 2013	12 Mar 2013

Name and mailing address of the ISA;	Authorized officer
Israel Patent Office Technology Park, Bldg.5, Malcha, Jerusalem, 9695101, Israel	VALKOV Karina
Facsimile No. 972-2-5651616	Telephone No. 972-2-5651777

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IL2012/050511

Patent document cited search report	Publication date	Patent family member(s)	Publication Date
US 4634795 A	06 Jun 1987	CA 1260952 A1	26 Sep 1989
		DE 3272373 D1	04 Sep 1986
		EP 0081930 A1	22 Jun 1983
		EP 0081930 B1	30 Jul 1986
		IL 64542 D0	31 Mar 1982
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		JP 5001251 B	07 Jan 1993
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		JP 7080762 B	30 Aug 1995
		US 4634795 A	06 Jan 1987
		US 4689344 A	25 Aug 1987
WO 2012028106 A1	08 Mar 2012	WO 2012028106 A1	08 Mar 2012

International application No.
PCT/IL2012/050511

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (2013.01) A61K 31/16, A61K 31/20, A61K 31/225, A61P 3/04, A61P 3/06, A61P 3/08, A61P 3/10, C07C 231/00, C07C 233/04, C07C 233/05, C07C 253/00, C07C 255/22, C07C 51/00, C07C 55/02, C07C 55/32, C07C 67/00, C07C 69/34