



(43) International Publication Date  
19 July 2012 (19.07.2012)

(10) International Publication Number  
**WO 2012/097144 A1**

- (51) **International Patent Classification:**  
*A01N 37/52* (2006.01) *A61K 31/155* (2006.01)
- (21) **International Application Number:**  
PCT/US2012/021070
- (22) **International Filing Date:**  
12 January 2012 (12.01.2012)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**  
61/461,113 12 January 2011 (12.01.2011) US  
13/348,265 11 January 2012 (11.01.2012) 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, 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, 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, MD, 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 applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

**Published:**

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(54) **Title:** LIPID-LOWERING ANTIDIABETIC AGENT

(57) **Abstract:** A composition which includes a salt of metformin and the use of the composition for treatment of or use in prediabetes, diabetes, lowering triglycerides and/or other conditions in mammals.



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## LIPID-LOWERING ANTIDIABETIC AGENT

## CROSS REFERENCE TO RELATED APPLICATION

The present application claims priority from U.S. Provisional Patent Application No. 61/461,113 filed January 12, 2011 and U.S. Patent Application No. 13/348,265 filed January 11, 2012, the contents of which are herein incorporated by reference.

## BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to salts of poly unsaturated fatty acids with biguanides.

Technical Background

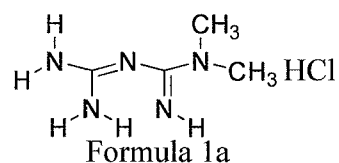
Diabetes mellitus has become pandemic and according to a forecast by the World Health Organization, there will be a sharp increase in the number of diabetic patients by the year 2030. This is an ominous forecast, because managing the long-term complications of diabetes, which include nephropathy, neuropathy, retinopathy, and cardiovascular complications, will have a serious impact on public health budgets. The hallmark of diabetes is chronically elevated blood glucose levels. It is also known that abnormally elevated glucose levels have an adverse impact on glutathione levels in key diabetic tissues. Furthermore, increased oxidative stress and increased production of reactive oxygen species are implicated under hyperglycemic conditions.

In spite of the early discovery of insulin and its subsequent widespread use in the treatment of diabetes, and the later discovery of and use of sulfonylureas, and thiazolidinediones, such as troglitazone, rosiglitazone or pioglitazone, as oral hypoglycemic agents, the treatment of diabetes remains less than satisfactory.

The use of insulin requires multiple daily doses, usually by self-injection. Determination of the proper dosage of insulin requires frequent estimations of the sugar in urine or blood. Treatment of non-insulin dependent diabetes mellitus (type 2 diabetes, NIDDM)

usually consists of a combination of diet, exercise, oral hypoglycemic agents, e.g., thiazolidenediones, and, in more severe cases, insulin. However, the clinically available hypoglycemic agents can either have side effects limiting their use, or an agent may not be effective with a particular patient. In the case of insulin dependent diabetes mellitus (Type I), insulin administration usually constitutes the primary course of therapy.

The biguanide metformin is a known compound approved by the U.S. Food & Drug Administration for the therapeutic treatment of diabetes. The compound and its preparation and use are disclosed, for example, in U.S. Pat. No. 3,174,901. Metformin is orally effective in the treatment of type 2 diabetes. Metformin (N,N-dimethylimidodicarbonimidic diamide) is a biguanide, anti-hyperglycemic agent currently marketed in the United States in the form of its hydrochloride salt 1,1-dimethylbiguanide hydrochloride (Formula 1a).



Metformin hydrochloride can be purchased commercially and can also be prepared, for example, as disclosed in J. Chem. Soc., 1922, 121, 1790.

U.S. Patent US 7,973,073 B2 (Mylari) describes use of metformin R-(+) lipoate as being useful for treating diabetes or diabetic complications.

U.S. Patent Publication 2005/0165102 describes complexes of drugs (metformin being mentioned) with transport moieties (fatty acids being mentioned) to enhance absorption and control delivery of the drugs being used. Among the fatty acid complexing agents mentioned are caprate, laurate, palmitate and oleate.

U. S. Patent Publication 2005/0182029 describes metformin salts of lipophilic acid salts (fatty acids being mentioned), their pharmaceutical formulations, and methods of administering the metformin salts for the treatment of hyperglycemia.

According to United Kingdom Perspective Diabetes Study (UKPDS) (Clarke et al. Diabetologia, 2005, 48, 868-877), metformin therapy was cost-saving and increased quality-adjusted life expectancy. In the UKPDS, overweight and obese patients randomized to initial therapy with metformin experienced significant reductions in myocardial infarction and diabetes-related deaths. Metformin does not promote weight gain and has beneficial effects on several cardiovascular risk factors. Accordingly, metformin is widely regarded as the drug of choice for most patients with Type 2 diabetes.

Prediabetes is a syndrome. Many patients with type 2 diabetes and with a prediabetic condition known as metabolic syndrome suffer from a variety of lipid disorders including elevated triglycerides. The body uses triglycerides to store fat but high (>200 mg/dl) and very high (>500 mg/dl) triglycerides are associated with atherosclerosis which increases the patients risk of heart attack and stroke.

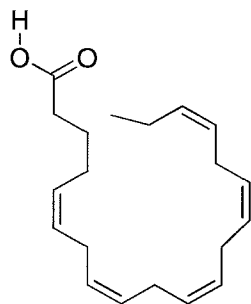
Incipient diabetes with impaired glucose tolerance is another prediabetic condition. Overall, type 2 diabetes and incipient diabetes with impaired glucose tolerance, are intimately intertwined with obesity, hyperlipidemia, including hypertriglyceridemia, and cardiovascular complications including arrhythmia, cardiomyopathy, myocardial infarction, stroke and heart failure. Clinically, pre-diabetes means that blood sugar level is higher than normal, but it's not yet increased enough to be classified as type 2 diabetes. Still, without intervention, prediabetes is likely to become type 2 diabetes over time

Also diabetic patients have impaired circulation which manifests itself in the slow healing of wounds in the foot and lower leg and puts the patient at risk for amputation.

Elevated triglycerides may be lowered by diet and exercise. Niacin and omega-3 fatty acids, commonly known as fish oil, are frequently used in the management of hypertriglyceridemia. Omega-3 fatty acids are unsaturated carboxylic acids which have a terminal double bond three carbons from the methyl terminus, the 3 position. Omega-3 fatty acids are commonly extracted from oily fish like salmon, mackerel and menhaden. They are also extracted from other marine sources like squid and krill. Omega-3 fatty acids are commercially available. The omega-3 fatty acids most commonly extracted

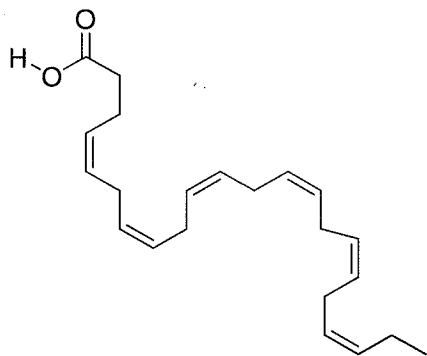
from fish are eicosapentaenoic acid and docosahexaenoic acid. These compounds have been shown to have beneficial effects in treating obesity, arrhythmia, and myocardial infarction and have the structures:

eicosapentaenoic acid



Structure 1

and docosahexaenoic acid:

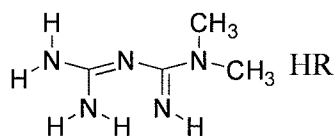


Structure 2

Resolvins are a special class of polyhydroxylated omega-3 fatty acids which possess potent anti-inflammatory and immunoregulatory actions. These biological actions of resolvins are thought to play a significant role in cardiovascular and diabetic conditions.

## SUMMARY OF THE INVENTION

This present invention provides compositions of the formula I:



Wherein HR is an omega-3 polyunsaturated C<sub>16-24</sub> fatty acid optionally substituted with from 1 – 3 hydroxy groups.

The compositions are typically compounds in the form of salts of metformin and an omega-3 polyunsaturated fatty acid (RH) in which the biguanide moiety is protonated and the acid moiety is at least partially in ionic form. In some instances, however, for example depending on the pH of the environment, the composition may be in the form of a mixture of the biguanide and acid components. The invention also provides pharmaceutical compositions comprising compositions of formula I and pharmaceutically acceptable excipients. The invention further provides methods for treating diabetes (especially type 2 diabetes), obesity, cardiac arrhythmia, myocardial infarction and elevated triglycerides. The compounds and compositions of this invention may provide high blood levels of the compositions of structure 1, when administered to patients, preferably by oral administration.

Particularly useful compounds are those wherein HR is a fatty acid of 20 or 22 carbon atoms with four or five unsaturated bonds in addition to the required omega-3 unsaturated bond such as 4,7,10,13,16, 19 docosahexaenoic acid, 5, 8, 11, 14 eicosapentanoic acid and resolvins derived from these acids such as the 5, 12, 18 trihydroxy eicosapentanoic acid known as resolvin E1, the 15, 18 dihydroxy eicosapentanoic acid, known as resolvin E2, the 7, 8, 17 trihydroxy docosahexaenoic acid known as resolvin D1, and its 7,16, 17 trihydroxy eipmer known as resolvin D2, the 4,11,17 trihydroxy docosahexaenoic acid known as resolvin D3 and the 4,5, 17 trihydroxy docosahexaenoic acid known as resolvin D4.

The invention relates to a compound of formula I which is a salt of metformin and an omega-3 polyunsaturated fatty acid and is meant to include any polymorphs, solvates, and

hydrates thereof.

In one preferred embodiment, RH is a resolving. In the most preferred embodiment, RH is eicosapentaenoic acid or docosahexaenoic acid.

Compounds of the present invention can be considered as designer dual-acting drugs and additionally possess a means for improving the bioavailability of their component moieties as a result of their high degree of water solubility.

In certain embodiments, the invention relates to a mixture of metformin or a pharmaceutically acceptable salt thereof, (e.g., hydrochloride, succinate, fumarate) with an omega-3 polyunsaturated fatty acid (RH), or a pharmaceutically acceptable salt thereof. In one preferred embodiment, RH is a resolvin. In the most preferred embodiment, RH is eicosapentaenoic acid or docosahexaenoic acid.

The present invention provides a pharmaceutical composition of the invention comprising compound of formula I and a pharmaceutically-acceptable carrier, vehicle or diluent.

The pharmaceutical composition may, for example, be in a form suitable for oral administration as a tablet, capsule, pill, powder, sustained release formulation, solution, suspension, for parenteral injection as a sterile solution, suspension or emulsion. Such compositions and methods for their preparation may be found, for example, in 'Remington's Pharmaceutical Sciences', 19th Edition (Mack Publishing Company, 1995). The pharmaceutical composition may be in unit dosage forms suitable for single administration of precise dosages. The pharmaceutical composition will include a conventional pharmaceutical carrier or excipient and an active compound.

Formulations suitable for oral administration include solid formulations such as tablets, capsules containing particulates, liquids, or powders, lozenges (including liquid-filled lozenges), chews, multi- and nano-particulates, gels, solid solution, liposome, films, ovules, sprays and liquid formulations.

Tablet dosage forms typically also include a disintegrant (such as sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinised starch and sodium alginate) a binder (such as microcrystalline cellulose, gelatin, a sugar, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinised starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose) and a lubricant (such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulfate). A diluent such as lactose, mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dehydrate) may also be present. Compositions of the invention may also be administered for example as capsules made, for example, from gelatin or hydroxypropylmethylcellulose .

Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet. The compositions of the invention may also be used in fast-dissolving, fast- disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, 11 (6), 981-986, by Liang and Chen (2001).

Other formulations will be apparent to those skilled in the art.

The invention further provides methods for treatment or lowering the risk of developing conditions such as diabetes, especially type 2 diabetes, prediabetes, obesity, arrhythmia, myocardial infarction and stroke by administering therapeutically effective amounts of compositions of formula I. Such compositions may also be used to lower triglyceride levels in a subject and so have a role in treatment of diabetes exacerbated with high triglyceride levels. Suitable dosages may be determined by conventional means.

The triglyceride lowering efficacy of the compounds of the present invention can be determined in animal models according to the procedure described by Sidika et al in Journal of Lipid Research, 1992, 33, 1-7.



The following example describes a diabetic rat model that may be used for determination of conditions leading to a method for treatment and prevention of post-ischemic damage of the heart and heart tissue.

Spontaneously diabetic Bio-Bred (BB/W) rats from the colony maintained at the University of Massachusetts Medical Center, Worcester, were used in this study. BB/W rats were chosen for the current study because the BB/W rats have been considered a useful model of autoimmune human insulin-dependent diabetes DM). Like human IDDM, spontaneous diabetes appears during adolescence, with an abrupt clinical onset characterized by weight loss, hyperglycemia, hypoinsulinemia, and ketonuria. As in the case of human diabetics, pathological changes in retina, myocardium, liver, kidney, bone metabolism and peripheral nerves have all been well documented in BB rats, as described in *Diab. Metab. Rev.*, 8:9 (1992). The BB/W rats were 3 to 4 months old and weighed about 300 to 350 g. The BB/W rats received daily insulin, which was discontinued 24 h prior to performing the isolated heart perfusion studies, leading to a hyperglycemic state. The rats were acutely diabetic, receiving  $2.02 \pm 0.04$  units of insulin daily, and had been diabetic for at least  $12 \pm 3$  days. The mean blood glucose levels in these diabetic rats were  $386 \pm 24$  mg/dL. The age-matched non-diabetic controls had mean blood glucose levels of  $92 \pm 12$  mg/dL.

#### Isolated Perfused Heart Model

This example describes an isolated perfused rat heart model used in development of the invention. Studies are performed using an isovolumic isolated rat heart preparation. Acutely diabetic male BB/W rats and non-diabetic age-matched (3 to 4 months old) control are pretreated with heparin (1000 u; IP), followed by sodium pentobarbital (65 mg/kg; IP). After deep anaesthesia is achieved as determined by the absence of a foot reflex, the hearts are rapidly excised and placed into iced saline. The arrested hearts are retrograde perfused in a non-recirculating model through the aorta within 2 minutes following their excision. Left ventricular developed pressure (LVDP) is determined using a latex balloon

in the left ventricle with high pressure tubing connected to a pressure transducer. Perfusion pressure is monitored using high pressure tubing off the perfusion line. Hemodynamic measurements are recorded on a 4-channel Gould recorder. The system has two parallel perfusion lines with separate oxygenators, pumps and bubble traps, but common temperature control allows rapid change perfusion media. The hearts are perfused using an accurate roller pump. The perfusate consists of 118 mM NaCl, .47 mM KCl, 12 mM CaCl<sub>2</sub>, 12 mM MgCl<sub>2</sub>, 25 mM NaHCO<sub>3</sub>, and the substrate 11 mM glucose. The perfusion apparatus is tightly temperature-controlled, with heated baths being used for the perfusate and for the water jacketing around the perfusion tubing to maintain heart temperature at  $37 \pm 0.5$  °C under all conditions. The oxygenated perfusate in the room temperature reservoir is passed through 25 ft. of thin-walled silicone tubing surrounded by distilled water at 37 °C saturated with 95% oxygen. The perfusate then enters the water-jacketed (37 °C) tubing leading to the heart through a water jacketed bubble trap. This preparation provides excellent oxygenation that routinely has been stable for 3 to 4 hours.

#### Model for Zero-/low Ischemia

This example describes a procedure used for study of zero-flow ischemia in diabetic control, diabetic treated, non-diabetic treated and control isolated hearts. Diabetic control (DC) diabetic treated (DZ) normal (C) control and normal treated (CZ) hearts are subjected to 20 minutes of normoxic perfusion followed by 20 minutes of zero-flow ischemia where the perfusate flow is completely shut off, followed by 60 minutes of reperfusion. Hearts are treated with 10 µM metformin eicosapentaenoate. In the metformin eicosapentaenoate treated diabetic group (DZ), hearts are subjected to 10 minutes of normoxic perfusion with normal Krebs-Henseleit buffer and 10 minutes of normoxic perfusion with Krebs-Henseleit buffer containing 10 µM metformin eicosapentaenoate. The hearts are then subjected to 20 minutes of zero-flow ischemia followed by 60 minutes of reperfusion. In order to avoid any variability in reperfusion conditions, both DC and DZ hearts are reperfused with normal Krebs-Henseleit buffer.

### Model for Low-flow Ischemia

This example describes a procedure used for study of low-flow ischemia in diabetic controls, diabetic treated, non-diabetic treated and non-diabetic control isolated hearts. Diabetic control hearts (DC) are subjected to 20 minutes of normoxic perfusion at a flow rate of 12.5 mL/minute followed by 30 minutes of low-flow ischemia where the perfusate flow is slowed down to 1.25 mL/min, that is about 10% of normal perfusion, followed by 30 minutes of reperfusion at a normal flow rate (12.5 mL/min). In the metformin eicosapentaenoate treated diabetic or non-diabetic groups (DZ or CZ), hearts are subjected to 10 minutes of normoxic perfusion (flow rate 12.5 mL/min) with normal Krebs-Henseleit buffer and 10 minutes of normoxic perfusion with Krebs-Henseleit buffer containing 10  $\mu$ M metformin eicosapentaenoate. The hearts are subjected to 30 minutes of low-flow ischemia (flow rate 1.25 mL/min) and 30 minutes of reperfusion at normal flow rate (12.5 mL/min).

Animal models to determine the effects of compounds of the invention on diabetes and complications of diabetes have been reviewed by Tirabassi et al., *ILAR Journal*, 2004, 45, 292-302. Antidiabetic activity may also be tested according to protocols described in the following patents: United States Patent Nos. 4,340,605; 4,342,771; 4,367,234; 4,617,312; 4,687,777 and 4,703,052. Additional references relevant to this application include the following: French Patent 2796551 and United States Published Patent Application No. 20030220301.

The present invention is exemplified by the following non-limiting examples.

#### EXAMPLE 1

Preparation of [amino(imino)methyl]amino}(dimethylamino)methaniminium (5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenoate

N,N-dimethylimidodicarbonimidic diamide. N,N-dimethylimidodicarbonimidic diamide hydrochloride (4.01 g, 24.3 mmol) was dissolved in 1N sodium hydroxide (24.2 mL,

24.2 mmol) and stirred at room temperature for 30 minutes. The solution was concentrated in vacuo and to the residue was added ethanol (80 mL). The mixture was carefully concentrated to azeotropically remove water. To the resulting solid was added EtOH (60 mL) and the suspension was filtered to remove precipitated NaCl. The filtrate was concentrated and the resulting solid was placed on high vacuum overnight to yield 3.18 g (102%) of metformin as a white solid.

{[Amino(imino)methyl]amino}(dimethylamino)methaniminium (5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenoate. Metformin free base (2.67 g, 20.7 mmol) was dissolved in acetonitrile (100 mL) and the resulting solution was filtered through a medium frit to remove a small amount of NaCl that precipitated. To the filtrate was added dropwise at room temperature (over a 5 minute period) a solution of (5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenoic acid (5.40 g, 17.8 mmol) in acetonitrile (30 mL). A white solid precipitated immediately upon addition of the acid. The reaction flask was covered in foil to protect it from light. The mixture was stirred for one hour at room temperature and was then chilled to 0 °C for 1 hour, and then filtered under an atmosphere of nitrogen. The resulting solid was washed with 50 mL acetonitrile and then quickly transferred to a foil-covered round bottom flask and placed under high vacuum. The material was left under high vacuum overnight to yield 6.5 (84%) of the title compound of Example 1 as a light tan solid; MP 121-124 °C (with decomposition); <sup>1</sup>H NMR (400 MHz, MeOD) δ 5.36 (m, 10 H), 3.03 (s, 6 H), 2.84 (m, 8 H), 2.18 (m, 2 H), 2.10 (m, 4 H), 1.66 (m, 2 H), 0.97 (t, J=7.57 Hz, 3 H); MS (ESI-) for C<sub>20</sub>H<sub>24</sub>O<sub>2</sub> *m/z* 301.2 (M-H)<sup>-</sup>.

## EXAMPLE 2

Preparation of {[amino(imino)methyl]amino}(dimethylamino)methaniminium (4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoate

N,N-dimethylimidodicarbonimidic diamide. N, N-dimethylimidodicarbonimidic diamide hydrochloride (4.06 g, 24.5 mmol) was dissolved in 1N sodium hydroxide (24.5 mL, 24.5 mmol) and stirred at room temperature for 30 minutes. The solution was concentrated in vacuo and to the residue was added ethanol (80 mL). The mixture was carefully concentrated to azeotropically remove water. To the resulting solid was added (60 mL)

and the suspension was filtered to remove precipitated sodium chloride. The filtrate was concentrated and the resulting solid was placed on high vacuum overnight to yield 3.22 g (102%) of N,N-dimethylimidodicarbonimidic diamide as a white solid.

{[amino(imino)methyl]amino}(dimethylamino)methaniminium  
(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoate.

N,N-Dimethylimidodicarbonimidic diamide (968 mg, 7.61 mmol) was dissolved in acetonitrile (36 mL) and the resulting solution was filtered through a medium frit to remove a small amount of sodium chloride that precipitated. To the filtrate was added dropwise at room temperature (over a 5 minute period) a solution of (4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16, 19-hexaenoic acid (**2**) (2.00 g, 6.09 mmol) in acetonitrile (35 mL). A white solid precipitated immediately upon addition of the acid. The reaction flask was covered in foil to protect it from light. After stirring for 1 h at room temperature, the mixture was chilled to 0 °C for 1 h, and then filtered under an atmosphere of nitrogen. The solid was washed with 50 mL ice-cold acetonitrile and then quickly transferred to a foil-covered round bottom flask and placed under high vac. The material was left under high vacuum overnight to yield 2.54 g (91%) of **1** as a light tan solid. The material was found to be air and light sensitive, and was therefore stored in an amber vial under nitrogen: MP 124-127 °C (turned brown); <sup>1</sup>H NMR (400 MHz, MeOD) 5.36 (m, 12 H), 3.03 (s, 6 H), 2.85 (m, 10 H), 2.37 (m, 2 H), 2.19 (m, 2 H), 2.09 (m, 2 H), 0.97 (t, *J*=7.57 Hz, 3 H); MS (ESI-) for C<sub>22</sub>H<sub>32</sub>O<sub>2</sub> *m/z* 327.3 (M-H).

### EXAMPLE 3

Preparation of {[amino(imino)methyl]amino}(dimethylamino)methaniminium  
(5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenoate.

N,N-dimethylimidodicarbonimidic diamide.

Metformin hydrochloride (331.25 g, 2 moles) was weighed into a 4000 mL beaker containing a stir bar. 1N KOH (1980 mL, 1.998 moles) was added, the beaker was covered, and the mixture was stirred for 2 h. The solids were collected by vacuum

filtration, and the filtrate was concentrated to a damp solid. Isopropanol (500 mL) was added and after brief swirling, the mixture was concentrated. The residual white solid was dried for 16 h in a vacuum oven (yield: 269.08 g).

{[Amino(imino)methyl]amino}(dimethylamino)methaniminium (5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenoate.

Metformin free base (50.10 g, 0.366 mole) was weighed into a 4000 mL beaker containing a stir bar. CH<sub>3</sub>CN (2000 mL) was added and the mixture was rapidly stirred until all metformin had dissolved. A fine white solid was removed by vacuum filtration (Notes 10,11). After ~30 min, the hazy filtrate was vacuum filtered through the same medium, and the clear filtrate was transferred to a 5000 mL 3-necked round bottom flask, which was fitted with a complete stir shaft assembly, N<sub>2</sub> inlet and addition funnel and bubbler. The funnel was charged with a solution of eicosapentaenoic acid (100.01 g, 0.324 mole) in acetonitrile (500 mL) which was added drop-wise over 70 min. After stirring for 2h, the flask was fitted with a N<sub>2</sub> balloon, sealed, and placed in the refrigerator over-night. The off-white solid was collected by vacuum filtration and washed with acetonitrile (500 mL). The damp solid was transferred to a pyrex dish, which was stored in a vacuum oven for 24 h. The oven was vented with nitrogen gas, and the beige solid was coarsely ground in a mortar with pestle then transferred to an amber jar that had been flushed with N<sub>2</sub> to obtain the compound of Example 3 (yield: 130.49 g).

#### EXAMPLE 4

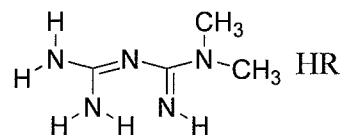
The solubility of the compound of Example 1 in water was compared with that of eicosapentaenoic acid (EPA).

Measurement of the water solubility of the test compounds is accomplished by using methods well known to those skilled in the art. Specifically, to a weighed amount of the test compound of Example 1 distilled water is added in small portions until a clear solution is obtained. The total volume of the solution is measured. The water solubility is calculated by dividing the weight of the salt, in mg, by the volume of the solution, in mL.

The water solubility of the compound of Example 1 when measured using the above technique, was determined to be 50 mg/ml. Likewise, the water solubility of EPA was found to be < 0.2 mg/mL. The compound of Example 1 is therefore, at least, 250 times more soluble in water than EPA itself. This is a clear indication of an unexpectedly high degree of bioavailability of the compositions of the invention. Highly water soluble medicinal preparations, when administered orally, result in efficient absorption of such preparations from the gastrointestinal tract into systemic circulation. Such preparations permit rapid absorption into the blood stream resulting in a high concentration of the active agent in the blood. Furthermore, water soluble preparations are especially suitable for parenteral administration, for example, intravenous administration.

What is claimed is:

1. A composition of structure I, which is a salt of metformin



I

with at least one polyunsaturated fatty acid represented by RH or a mixture of metformin and at least one acid RH or a pharmaceutically acceptable solvate or hydrate thereof.

2. The composition of Claim 1 in which the polyunsaturated fatty acid RH is an omega-3 fatty acid.
3. A composition of claim 1 wherein RH is an omega-3 polyunsaturated C<sub>16-24</sub> fatty acid optionally substituted with from 1 – 3 hydroxy groups
4. A composition as claimed in claim 2 or 3 wherein RH is a fatty acid of 20 or 22 carbon atoms with a total of 4 or 5 unsaturated linkages in the fatty acid chain in addition to the omega-3 unsaturated bond.
5. A composition of claim 1, wherein RH is selected from the group consisting of resolvins D1, D2, D3, D4, E1, and E2.
6. The composition of Claim 1 in which the polyunsaturated fatty acid RH is eicosapentaenoic acid.
7. The composition of Claim 1 in which the polyunsaturated fatty acid is docosahexaenoic acid.
8. A composition according to Claim 1, wherein R is a mixture of polyunsaturated fatty acids.



9. The mixture of Claim 8 in which the polyunsaturated fatty acid comprises a mixture of eicosapentaenoic acid and docosahexaenoic acid.
10. A pharmaceutical composition comprising a compound according to any of claims 1 - 9 and a pharmaceutically acceptable carrier, vehicle or diluent.
11. A kit comprising: a) a unit dosage form comprising the compound of any of claims 1 - 10; b) instructions on how to use the kit; and c) at least one container for holding the unit dosage forms.
12. A method for treating a condition in a mammal selected from diabetes, elevated triglycerides, prediabetes, obesity, cardiac arrhythmia, cardiomyopathy or myocardial infarction, comprising administering a therapeutically effective amount of a compound according to any of claims 1 - 10.
13. A composition according to claim 1 for treating a condition in a mammal selected from diabetes, elevated triglycerides, prediabetes, obesity, cardiac arrhythmia, cardiomyopathy or myocardial infarction.
14. Use of a composition according to claim 1 for preparation of a medicament for treating a condition in a mammal selected from diabetes, elevated triglycerides, prediabetes, obesity, cardiac arrhythmia, cardiomyopathy or myocardial infarction.
15. A method for the manufacture of the composition of Claim 1 comprising: a) freshly preparing the free base of metformin from a suitable metformin salt; and b) reacting the freshly prepared free base of metformin with eicosapentaenoic acid, docosahexaenoic acid or a mixture thereof at a temperature between about 1 degree C. and about 60 degree C.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/21070

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A01N 37/52; A61K 31/155 (2012.01)

USPC - 514/635

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)

USPC -514/635

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
USPC - 424/450; 514/558 (see search terms below)Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
PubWest, Google Patent, Google Scholar, WiPO (resolvin, polyunsaturated, fatty, omega, acid, metformin, diabetes, salt, docosahexaenoic, reacting, eicosapentaenoic, free, base, biguanides, structure, dimethylbiguanide, dimethylimidodicarbonimidic, diamide, mylari, diaminomethylidene)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2006/0159746 A1 (TROUP et al.) 20 July 2006 (20.07.2006) entire document, especially para [0009], [0011], [0020]-[0021], [0069]; claim 2	1-9, 13-15
Y	US 2009/0054513 A1 (WEBSTER et al.) 26 February 2009 (29.02.2009) entire document, especially para [0008], [0047]-[0049]	1-9, 13-15
Y	US 2010/0105773 A1 (SMITH et al.) 29 April 2010 (29.04.2010) entire document, especially para [0012], [0014], [0020]	2-5
Y	US 2008/0260819 A1 (FLEMING et al.) 23 October 2008 (23.10.2008) entire document, especially para [0002], [0018], [0022]	15

☐ Further documents are listed in the continuation of Box C.

\* 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

"&amp;" document member of the same patent family

Date of the actual completion of the international search

17 April 2012 (17.04.2012)

Date of mailing of the international search report

08 MAY 2012

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents  
P.O. Box 1450, Alexandria, Virginia 22313-1450

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PCT OSP: 571-272-7774

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/21070

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

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

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3. ☒ Claims Nos.: 10-12  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

### Remark on Protest

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