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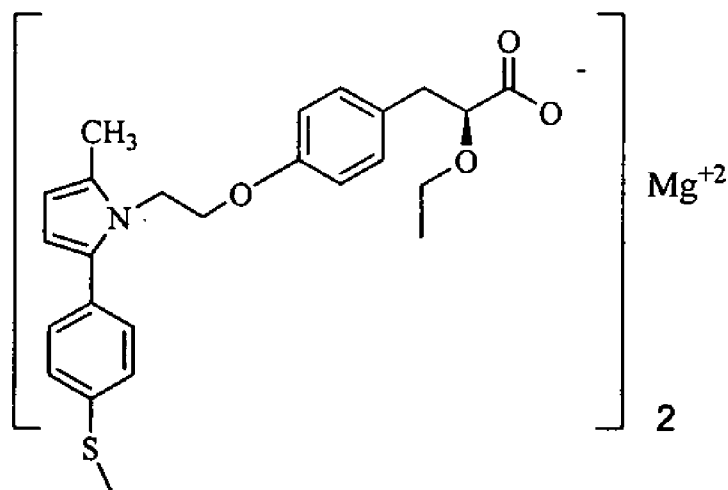
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(54) Title: SAROGLITAZAR MAGNESIUM FOR THE TREATMENT OF CHYLOMICRONEMIA SYNDROME -



Formula (1)

(57) Abstract: The present invention relates to the use of Saroglitazar Magnesium of formula (1), for the treatment of, or the prevention, delay of progression, or treatment of a disease or condition which is selected from chylomicronemia syndrome, familial chylomicronemia syndrome and Type V hyperlipoproteinemia. The present invention further relates to the use of a pharmaceutical composition comprising Saroglitazar Magnesium for the prevention, delay of progression, or treatment of a disease or condition which is selected from chylomicronemia syndrome, familial chylomicronemia syndrome and Type V hyperlipoproteinemia.



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SAROGLITAZAR MAGNESIUM FOR THE TREATMENT OF CHYLOMICRONEMIA SYNDROME

FIELD OF INVENTION

5 The present invention relates to the use of Saroglitazar Magnesium of formula (1), for the treatment of, or the prevention, delay of progression, or treatment of a disease or condition which is selected from chylomicronemia syndrome, familial chylomicronemia syndrome and Type V hyperlipoproteinemia. The present invention further relates to the use of a pharmaceutical composition comprising Saroglitazar Magnesium for the prevention, delay of
10 progression, or treatment of a disease or condition which is selected from chylomicronemia syndrome, familial chylomicronemia syndrome and Type V hyperlipoproteinemia.

BACKGROUND OF INVENTION

Hyperlipidemia, or the presence of elevated levels of lipids in the bloodstream, can take the
15 form of hypercholesterolemia (elevated cholesterol), hypertriglyceridemia (elevated triglyceride) or a combination of the two. Hypercholesterolemia, which can further be subdivided, is typically associated with increased risk of atherosclerosis cardiovascular disease. Hypertriglyceridemia occurs when the body's production or intake of triglyceride exceeds the body's ability to metabolize or remove the triglyceride from the blood stream. The most severe
20 form of hypertriglyceridemia is chylomicronemia (also called hyperchylomicronemia), and is associated with an increased risk of pancreatitis. Chylomicrons are lipoprotein particles that carry absorbed dietary fat from the gut to other body tissues via the bloodstream, and are typically present only during meal times. Chylomicronemia is defined as having the presence of chylomicrons in the blood stream during times of fasting, and is typically associated with total
25 plasma triglyceride levels above 1000 mg/dL.

The chylomicronemia syndrome refers to a set of clinical complications associated with high chylomicron levels. Typically, patients with the chylomicronemia syndrome have markedly elevated fasting triglyceride levels (1000-2000 mg/dL), with profound excursions (up to 5000
30 mg/dL and higher) following oral fat intake. The massively elevated plasma triglyceride levels are associated with a number of clinical findings and complications including recurrent episodes

of pancreatitis, deposition of triglycerides in the skin in the form of eruptive xanthomas, hepatosplenomegaly, a milky pink appearance of the blood vessels in the back of the eye (lipemia retinalis), and mild neuro-cognitive deficits.

- 5 The chylomicronemia syndrome can be further sub divided into two groups based on ultracentrifugation of lipoprotein species (see “A system for phenotyping hyper lipoproteinemia”, Fredrickson D. S., Lees R. S. Circulation, 1965 March; 31, pp. 321-327). Fredrickson classification Type I, also known as the familial chylomicronemia syndrome (FCS), patients have accumulation of only chylomicrons in the bloodstream whereas Fredrickson
10 classification Type V, also known as Type V hyperlipoproteinemia, patients have accumulation of both chylomicrons and very low density lipoproteins (V LDL) in the bloodstream.

The familial chylomicronemia syndrome (FCS or Type I hyperlipoproteinemia) is caused by a homozygous or compound heterozygous defect in the clearance of chylomicrons from the
15 bloodstream. The most common cause of FCS is a defect in lipoprotein lipase (LPL), the protein that hydrolyzes triglycerides carried on chylomicrons. Other causes of FCS include defects in apolipoprotein CH (apoCII, a co activator of LPL) or glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1, an anchoring protein of LPL).

- 20 Type 1 patients are usually identified by early onset as youth of hypertriglyceridemia and pancreatitis. Thus, patients With FCS typically present in childhood with massively elevated triglyceride levels (>2,000 mg/dL), and recurrent bouts of abdominal pain due to pancreatitis. Into adult hood, the triglyceride levels remain elevated, and patients typically experience multiple episodes of abdominal pain and pancreatitis, which can result in hospitalization and
25 death. Patients also experience other manifestations including eruptive xanthomas, lipemia retinalis, hepatosplenomegaly, and mild neuro-cognitive deficits. The main therapeutic goal in FCS treatment is to prevent or treat pancreatitis via the reduction of triglycerides.

Unfortunately, standard lipid-lowering therapies, such as fibrates, omega-3 fatty acids, statins,
30 and nicotinic acid derivatives (niacin), are not effective in lowering triglycerides in patients with FCS. Therefore, the standard of care therapy for FCS patients is a very low fat diet (10% by

calories), something which is very difficult to stay compliant with throughout a lifetime [The Familial Chylomicronemia Syndrome. Santamarina-Fojo S. Lipid Disorders 1998. 27(3): 551-567].

- 5 At present there is thus no effective pharmaco therapy for treating FCS and there is thus a need for new methods of treating familial chylomicronemia syndrome (FCS), also known as Type I hyperlipoproteinemia.

10 Type V hyperlipoproteinemia patients represent a second group at risk for the chylomicronemia syndrome and are usually diagnosed by severe hypertriglyceridemia as adults. This is a heterogenous group at the extreme end of a spectrum of multifactorial hypertriglyceridemia. Patients with type V hyperlipoproteinemia generally have both an underlying genetic cause and one or more acquired causes of hypertriglyceridemia. The underlying genetic causes include well characterized dyslipidemia such as familial combined hyperlipidemia (Type HA),
15 dysbetalipoproteinemia (Type III) and familial hypertriglyceridemia (Type VI), and a group of less well characterized dyslipidemias (e.g. heterozygous LPL deficiency, defects in apoA & apoC genes, defects in fatty acid binding and transport proteins). Acquired causes of hypertriglyceridemia include comorbid diseases (eg type 2 diabetes, obesity, insulin resistance, lipodystrophy, hypothyroidism), medications (e.g. beta blockers, thiazide diuretics, estrogen,
20 glucocorticoids, transplant medications), and other factors (e.g. pregnancy, alcohol intake).

The primary goal of therapy in Type V patients is to reduce the triglyceride levels, and therefore reduce the risk of pancreatitis. Most patients can be successfully treated by addressing the underlying acquired cause(s) of the elevated triglycerides, such as reducing the amount of
25 dietary fat intake, treating uncontrolled co-morbid diseases such as T2DM (Type 2 diabetes mellitus), discontinuing offending medications, and initiating lipid lowering medications such as fibrates, omega-3 fatty acids, or nicotinic acid derivatives (niacin) [Chylomicronemia Syndrome. Chait A., Brunzell J. Adv Intern Med 1992. 37:249-73.]. Despite optimal therapy, some Type V patients continue to have elevated triglyceride levels. There is thus a need for new
30 methods of treating Type V hyperlipoproteinemia, especially for those patients whose triglyceride levels remain elevated even after treatment with conventional therapies.

WO 2011123401 discloses use of certain DGAT1 inhibitors, or their pharmaceutically acceptable salts or esters, for the prevention, delay of progression or treatment of a disease or condition which is selected from chylomicronemia syndrome, familial chylomicronemia syndrome and Type V hyperlipoproteinemia. WO 2013169648 describes a pharmaceutical combination, such as a combined preparation of two pharmaceutical composition, comprising at least one DGAT1 inhibitor, or a pharmaceutically acceptable salt or ester thereof and at least one kind of triglyceride lowering drug selected from the group consisting of (a) at least one PPAR alpha agonist or a pharmaceutically acceptable salt thereof or ester thereof, and (b) at least one compound selected from the group consisting of (i) natural or synthetic omega-3 fatty acids or pharmaceutical acceptable esters, derivatives, conjugates, precursors or salts thereof or mixtures thereof, or (ii) omega-3 oils, and optionally at least one pharmaceutically acceptable carrier for simultaneous, separate or sequential use, in particular for the treatment of hypertriglyceridemia, in particular chylomicronemia (also called hyperchylomicronemia)

WO 2013163508 describes tetrahydropyran DGAT1 inhibitors for use in the prevention, delay of progression or treatment of a disease or condition which is selected from chylomicronemia syndrome, familial chylomicronemia syndrome, and Type V hyperlipoproteinemia.

WO 2011079257 describes a fully human antibody or antigen-binding fragment of a human antibody that specifically binds and inhibits human angiopoietin-like protein 4 (hANGPTL4) which are useful in treating diseases or disorders associated with ANGPTL4, such as hyperlipidemia, hyperlipoproteinemia and dyslipidemia, including hypertriglyceridemia, hypercholesterolemia, chylomicronemia.

WO 2012162129 describes some other novel DGAT1 inhibitors for use in the prevention, delay of progression or treatment of a disease or condition which is selected from chylomicronemia syndrome, familial chylomicronemia syndrome, and Type V hyperlipoproteinemia

WO 2013106358 describes novel role for microRNA (miR) regulation of lipid metabolism via the MTP pathway, leading to reductions in apoB secretion and blood lipid levels. It describes

inhibition of MTP expression and activity by miR regulation as a new therapeutic target for treatment of cardiovascular disease and conditions or diseases associated with cardiovascular disease such as hyperlipidemia, atherosclerosis, and metabolic syndrome.

- 5 EP 1725234 describes methods and compositions for treating hyperlipidemia and/or hypercholesterolemia comprising administering to the subject an effective amount of an MTP inhibitor to inhibit hyperlipidemia and/or hypercholesterolemia in said subject.

- 10 WO 2014205449 describes compounds, compositions and associated methods for reducing expression of ApoCIII mRNA and protein in a subject having, or at risk of having, diabetes.

- WO 2014019919 discloses pharmaceutical compositions comprising 15-OHEPA and, optionally, one or more cardiovascular agents, as well as therapeutic methods for treating various diseases including homozygous familial chylomicronemia, hypercholesterolemia, hyperlipidemia, hyperlipidemia in HIV positive subjects.

- The present invention describes the use of a PPAR modulator of formula (1) for the treatment of familial chylomicronemia, hypercholesterolemia, hyperlipidemia, hyperlipidemia in patients in need thereof. It has surprisingly been found that Saroglitazar Magnesium of formula (1) is useful for the treatment of the above conditions alone, unlike those reported in the prior art where the PPAR agonists had to be used in combination with a second therapeutic agent.

SUMMARY OF THE INVENTION

- 25 The compound of formula (1) is approved for the treatment of treating diabetic dyslipidemia or hypertriglyceridemia in type 2 diabetes, not controlled by statins alone.

- The present inventors have surprisingly found that Saroglitazar Magnesium of formula (1), reduces postprandial triglyceride levels in animal models. Obese Zucker (fatty) rat is one of the oldest models of NIDDM (Non-insulin dependent diabetes mellitus), resembling human type II diabetes, i.e. diabetes associated with obesity. It is characterized by hyperphagia and associated with mild hyperglycaemia, insulin resistance, mild glucose intolerance, hyperlipidaemia

5 specially hypertriglyceridemia. When the non-ionic detergent Triton WR-1339 is injected into Zucker fa/fa rats, there is a progressive accumulation of triacylglycerols in the plasma/serum (Friedman & Byers, J Exp Med. 1953 Jan;97(1):117-30; Otway & Robinson, J Physiol. 1967 May;190(2):321-32.). This effect has been interpreted as being due to the inability of lipoprotein
lipase present in the extrahepatic tissues to hydrolyse the plasma triacyl glycerols of Triton-
treated animals (Scanu & Oriente, JEM vol. 113 no. 4 735-757 1961 ; Otway & Robinson, 1967). So the nonionic detergent, Triton WR-1339 (Triton), has commonly been used to inhibit
LPL for this purpose to produce the condition of severe hypertriglyceridemia similar to familial
chylomicronemia syndrome and Type V hyperlipoproteinemia in humans. The Compound (1)
10 was also tested for hyper-chylomicronemia and chylomicron dynamics and tissue uptake, distribution and recycling of lipids *in vivo* by using ¹³C-palmitate in Zucker fa/fa rats. (ref.: PNAS, vol.112, no. 4, 1143-1148; Journal of lipid Research, vol. 38, 1997, 1888-1895). The results demonstrate metabolic defects, which although exaggerated, closely parallel the defects
in postprandial handling of plasma lipids in patients with chylomicronemia syndrome
15 (including patients with familial chylomicronemia syndrome and patients With Type V hyperlipoproteinemia).

The present invention thus provides Saroglitazar Magnesium for use in the prevention, delay of
progression, or treatment of a disease or condition which is selected from chylomicronemia
20 syndrome, familial chylomicronemia syndrome, and Type V hyperlipoproteinemia.

There is also provided Saroglitazar Magnesium for use in the reduction of postprandial triglyceride levels in patients suffering from a disease or condition which is selected from
chylomicronemia syndrome, familial chylomicronemia syndrome, and Type V
hyperlipoproteinemia.

25 There is also provided Saroglitazar Magnesium for use in the prevention, delay of progression or treatment of a symptom selected from recurrent episodes of pancreatitis, deposition of triglycerides in the skin in the form of eruptive xanthomas, hepatosplenomegaly, milky white triglyceride in the blood vessels in the back of the eye (lipemia retinalis), and mild neuro-
30 cognitive deficits.

In another embodiment, there is provided Saroglitazar Magnesium for use in the prevention, delay of progression or treatment of a symptom selected from recurrent episodes of pancreatitis, deposition of triglycerides in the skin in the form of eruptive xanthomas, hepatosplenomegaly, milky white triglyceride in the blood vessels in the back of the eye (lipemia retinalis), and mild
5 neuro-cognitive deficits, in patients suffering from a disease or condition which is selected from chylomicronemia syndrome, familial chylomicronemia syndrome, and Type V hyperlipoproteinemia.

In another aspect of the invention, there is provided a pharmaceutical composition, comprising
10 Saroglitazar Magnesium along with suitable excipients for use in the prevention, delay of progression or treatment of a disease or condition which is selected from chylomicronemia syndrome, familial chylomicronemia syndrome, and Type V hyperlipoproteinemia.

There is also provided a pharmaceutical composition, comprising compound (1), for use as defined above.

15 In another aspect, there is also provided a method for the prevention, delay of progression, or treatment of a disease or condition which is selected from chylomicronemia syndrome, familial chylomicronemia syndrome, and Type V hyperlipoproteinemia, comprising administration of a therapeutically effective amount, or a prophylactically effective amount, of compound (1) to a
20 subject, e. g. a human subject, in need of such treatment.

There is also provided a method for the reduction of postprandial triglyceride levels in patients suffering from a disease or condition which is selected from chylomicronemia syndrome, familial chylomicronemia syndrome, and Type V hyperlipoproteinemia, comprising
25 administration of a therapeutically effective amount of compound (1) to a subject, e.g. a human, in need of such treatment.

There is also provided a method for the prevention, delay of progression or treatment of pancreatitis in patients suffering from a disease or condition which is selected from
30 chylomicronemia syndrome, familial chylomicronemia syndrome, and Type V

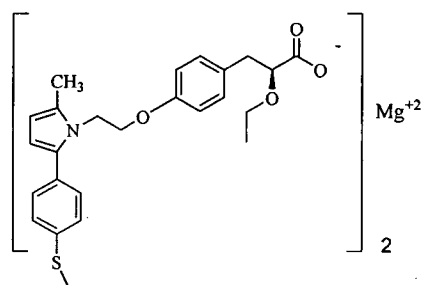
hyperlipoproteinemia, comprising administration of a therapeutically effective amount of the compound (1), to a subject, e.g. a human, in need of such treatment.

There is also provided a method for the prevention, delay of progression or treatment of a symptom selected from recurrent episodes of pancreatitis, deposition of triglycerides in the skin in the form of eruptive xanthomas, hepatosplenomegaly, milky white triglyceride in the blood vessels in the back of the eye (lipemia retinalis), and mild neuro-cognitive deficits, comprising administration of a therapeutically effective amount of compound (1), to a subject, e.g. a human, in need of such treatment.

In another embodiment, there is provided a method for the prevention, delay of progression or treatment of a symptom selected from recurrent episodes of pancreatitis, deposition of triglycerides in the skin in the form of eruptive xanthomas, hepatosplenomegaly, milky white triglyceride in the blood vessels in the back of the eye (lipemia retinalis), and mild neuro-cognitive deficits, comprising administration of a therapeutically effective amount of compound (I) to a human subject suffering from a disease or condition Which is selected from chylomicronemia syndrome, familial chylomicronemia syndrome, and Type V hyperlipoproteinemia.

DETAILED DESCRIPTION

The present invention thus provides the use of Saroglitazar Magnesium of formula (1), for the manufacture of a medicament for the prevention, delay of progression, or treatment of a disease or condition which is selected from chylomicronemia syndrome, familial chylomicronemia syndrome, and Type V hyperlipoproteinemia.



(1)

There is also provided the use of the Compound (1) for the manufacture of a medicament for one or more of the following purposes: (a) the reduction of postprandial triglyceride levels in patients suffering from a disease or condition which is selected from chylomicronemia syndrome, familial chylomicronemia syndrome, and Type V hyperlipoproteinemia; (b) the prevention, delay of progression or treatment of pancreatitis in patients suffering from a disease or condition which is selected from chylomicronemia syndrome, familial chylomicronemia syndrome, and Type V hyperlipoproteinemia; (c) the prevention, delay of progression or treatment of a symptom selected from recurrent episodes of pancreatitis, deposition of triglycerides in the skin in the form of eruptive xanthomas, hepatosplenomegaly, milky white triglyceride in the blood vessels in the back of the eye (lipemia retinalis), and mild neuro-cognitive deficits; (d) the prevention, delay of progression or treatment of a symptom selected from recurrent episodes of pancreatitis, deposition of triglycerides in the skin in the form of eruptive xanthomas, hepatosplenomegaly, milky white triglyceride in the blood vessels in the back of the eye (lipemia retinalis), and mild neuro-cognitive deficits, in patients suffering from a disease or condition Which is selected from chylomicronemia syndrome, familial chylomicronemia syndrome, and Type V hyperlipoproteinemia.

The present invention also provides the suitable pharmaceutical composition of compounds of formula (1) or their derivative. The pharmaceutical composition of the present invention essentially comprises of:

- the pharmaceutically active substance;
- a suitable buffering agent;
- a suitable stabilizer;
- optionally with one or more pharmaceutically acceptable excipients.

The suitable stabilizers used in pharmaceutical composition are selected from Polacrillin potassium, Potassium chloride, Sodium stearyl fumarate and preferably selected from Sodium stearyl fumarate. The suitable buffering agent are selected from sodium acetate, ammonia

solution, ammonium carbonate, sodium borate, adipic Acid, glycine, monosodium glutamate and preferably selected from ammonia solution.

The pharmaceutically acceptable excipients are selected at least one from carriers, binders, antioxidant agents, disintegrating agents, wetting agents, lubricating agents, chelating agents, surface active agents, and the like.

Diluents include, but are not limited to lactose monohydrate, lactose, polymethacrylates selected from Eudragit, potassium chloride, sulfobutylether b-cyclodextrin, sodium chloride, spray dried lactose, and preferably sulfobutyl ether b-cyclodextrin. Carriers include, but are not limited to lactose, white sugar, sodium chloride, glucose, urea, starch, calcium carbonate and kaolin, crystalline cellulose, and silicic acid. Binders include, but are not limited to carbomers selected from carbopol, gellan, gum Arabic, hydrogenated vegetable oil, polymethacrylates selected from Eudragit, xanthan, lactose and Zein. Antioxidant agents include, but are not limited to, Hypophosphorous acid, Sodium formaldehyde, sodium formaldehyde sulfoxylate, sulfur dioxide, tartaric acid, thymol and methionine. Disintegrating agents include, but are not limited to, bicarbonate salt, chitin, gellan gum, polacrillin potassium and Docusate Sodium. Wetting agents include, but are not limited to, Glycerin, lactose, Docusate Sodium and Glycine, Lubricating agents used include, but are not limited to, Glycerin behenate, hydrogenated vegetable oil, sodium stearyl fumarate and Myristic Acid. Chelating agents include, but are not limited to, Maltol and Pentetic Acid. Surface active agents include but are not limited to, Nonionic surfactant selected from alkyl polyglucosides, cocamide DEA, cocamide MBA, cocamide TEA, decyl maltoside and octyl glucoside; Anionic surfactant selected from arachidic acid and arachidonic acid; Cationic surfactant selected from cetyl trimethylammonium bromide and cetylpyridinium chloride.

The following studies were conducted in suitable animal models as described hereinafter.

Experiment 1

Effect of Compound (1) on Plasma Triglycerides in a Model of Severe Hypertriglyceridemia induced by Triton WR-1339 (by inhibition of LPL) in Zucker fa/fa rats.

The obese Zucker (fatty) rat is one of the oldest models of NIDDM, resembling human type II diabetes, i.e. diabetes associated with obesity. It is characterized by hyperphagia and associated with mild hyperglycaemia, insulin resistance, mild glucose intolerance, hyperlipidaemia specially hypertriglyceridemia. When the non-ionic detergent Triton WR-1339 is injected into
 5 Zucker fa/fa rats, there is a progressive accumulation of triacylglycerols in the plasma/serum (Friedman & Byers, 1953; Otway & Robinson, 1967). This effect has been interpreted as being due to the inability of lipoprotein lipase present in the extrahepatic tissues to hydrolyse the plasma triacylglycerols of Triton-treated animals (Scanu & Oriente, 1961 ; Scanu et al., 1961 ; Otway & Robinson, 1967). So the nonionic detergent, Triton WR-1339 (Triton), has commonly
 10 been used to inhibit LPL for this purpose to produce the condition of severe hypertriglyceridemia similar to familial chylomicronemia syndrome and Type V hyperlipoproteinemia.

In this study 20 male and 14 female Zucker fa/fa rats of 6-10 weeks of age were selected for the
 15 and on day-0, body weight of animals recorded and blood samples (approximately 80µl to 90µl) was collected via retro orbital route using isoflurane as inhalation anaesthesia, serum separated and serum triglyceride estimated and 24 animals were selected and grouped on the basis of serum triglyceride level as primary parameter as below

20 **Table no.1**

Sr.no	Treatment Group	Dosage Level	Sex	Number of Animals
1	Vehicle Control [5%PEG400 + 5% tween 80 + 90%Na-MC(0.5%)],p.o.	0 mg/kg	3F+3M	6
2	Compound (1)-1 mg/kg, p.o.	1 mg/kg	3F+3M	6
3	Compound (1)-10 mg/kg, p.o.	10 mg/kg	2F+4M	6
4	Fenofibrate 65 mg/kg, p.o.	65 mg/kg	3F+3M	6

From day-1 to Day-14, compounds were formulated in 5%PEG+ 5%Tween 80+ 90% (0.5%) Na-CMC in such a way that the final volume of administration was 2 ml/kg of body wt, and animals were dosed orally once daily as per grouping details.

- 5 On day-14 blood samples were collected after 1 hour of dosing, serum separated and serum triglycerides (TG) was estimated. Animals were being kept on 24 hours fasting after completion of day-14 activities. On day-15, after 24 hours of fasting, body wt. of all animals was recorded. Then formulations of treatment items were prepared in vehicle and Triton WR- 1339 prepared in 0.9% saline for intraperitoneal injection at dose of 250 mg/kg per 5 ml. Basal blood samples
10 collected and animals were administered orally with respective treatment and immediately injected intraperitoneally with Triton WR-1339. Blood samples (approx. 1ml per sample) were also collected at 6hr, 24 hours and 48 hours after triton administration and serum triglycerides levels were estimated using Cobas C 311 clinical chemistry autoanalyser from Roche Diagnostics using commercial diagnostic kits.

15

Calculation: % change at 6-hr, 24-hr and 48-hr for TG vs Vehicle Control was calculated using MS using MS Excel. The area under curve for TG, AUC-TG (0-48), was calculated using GraphPad® software.

20 *Results*

The serum triglycerides levels in different treatment groups (Table no. 2) and % change Vs Vehicle Control (Table no. 3) after Triton WR-1339 administration is depicted in below tables-

Table no.2

Treatment Groups	Serum Triglycerides (mg/dl) at various time point after Triton WR-1339 administration												AUC-TG (0-48 hr.) mg/dl.hr		
	0 hr			6 hr			24 hr			48 hr					
Vehicle Control	519.2	±	72.2	777.2	±	53.6	3250.6	±	485.6	2172.7	±	555.9	105218.0	±	16523.9
Compound (1)-1 mg/kg, p.o.	188.3	±	15.6	438.5	±	52.7	1797.2	±	331.3	889.5	±	353.9	54241.5	±	11182.3
Compound (1)-10 mg/kg, p.o.	93.2	±	7.9	328.9	±	111.9	1463.8	±	265.3	340.4	±	151.7	39050.3	±	6922.7
Fenofibrate 65 mg/kg, p.o.	324.9	±	45.3	1048.1	±	147.4	2871.5	±	357.4	1630.0	±	329.8	93412.8	±	12023.5

25

Table no.3

Treatment Groups	% Change in TG Vs Vehicle Control												% Change in AUC-TG vs Vehicle Control		
	0 hr			6 hr			24 hr			48 hr					
Vehicle Control															
Compound (1)-1 mg/kg, p.o.	-63.7	±	3.0	-43.6	±	6.8	-44.7	±	10.2	-59.1	±	16.3	-48.4	±	10.6
Compound (1)-10 mg/kg, p.o.	-82.0	±	1.5	-57.7	±	14.4	-55.0	±	8.2	-84.3	±	7.0	-62.9	±	6.6
Fenofibrate 65 mg/kg, p.o.	-37.4	±	8.7	34.9	±	19.0	-11.7	±	11.0	-25.0	±	15.2	-11.2	±	11.4

Compound (1) at 1 and 10 mg/kg showed significant 64% and 82% reduction in serum triglycerides (TG) at 0-hr time points revealed its triglyceride lowering potential after 15 days repeat dose treatment. Triton WR- 1339 administration produced significantly increased TG levels at 6 hours onwards, which peaked at 24 hour time point upto 3250 mg/dl. Compound (1) showed dose dependent lowering of TG levels at all-time points. Compound (1) at 1 and 10 mg/kg showed 48 and 63 % reduction in AUC-TG respectively, whereas fenofibrate at 65 mg/kg showed only 11 % reduction in AUC-TG Vs Vehicle control group. Therefore Compound (I) was shown to be significantly effective in blunting an increase in serum triglycerides in a model of severe hypertriglyceridemia induced by Triton WR-1339 (by inhibition of LPL) in Zucker fa/fa rats when compared to fenofibrate, a pure PPAR alpha.

15 Experiment-2

Effect of Compound (1) on Plasma Triglycerides Hyper-chylomicronemia and Chylomicron dynamics in Zucker fa/fa rats after 14 days repeated dose administration.

In this study, the effect of Compound (1) on hyper-chylomicronemia and chylomicron dynamics in Zucker fa/fa rats after 14 days repeated dose administration was evaluated.

Zucker (fa/fa) fatty rat of 7-8 weeks of age were purchased from Charles River Laboratory and single-housed under a pathogen free environment with constant room temperature (20-22 °C) and relative humidity (40-50%) and a 6:00pm-6:00am dark-light cycle. Rats were provided with free access to food (Lab Diet 5L0D, an irradiated regular rodent diet containing 23% of protein and 4.5% of fat) and water. Initial body weight and body composition (using a NMR analyzer) were measured 6 days post-arrival. The rats were then randomly divided into four dosing groups based BW and fat mass as below-

Table no.4

Sr.no	Treatment Group	Dosage Level	Number of Animals
1	Vehicle Control [1 % Tween 20],p.o.	0 mg/kg	9
2	Compound (1)-0.4 mg/kg, p.o.	0.4 mg/kg	9
3	Compound (1)- 4 mg/kg, p.o.	4 mg/kg	9
4	Fenofibrate 150 mg/kg, p.o.	150 mg/kg	9

Dosing was begun at 9-10 weeks of age, once daily (8-10am) by oral gavage for 14 days. On the day-14 of dosing, a final body composition (after dosing) was measured. On day-15, all animals were given a fatty tolerance test (FTT) after being fasted overnight (15-16 hours), followed by blood and tissue collection.

Fatty Tolerance Test Procedure (FTT):

1. Following an overnight fast, rats were orally gavaged with a mixture of ^{13}C -Palmitic Acid (1 and corn oil (1g of ^{13}C -P dissolved in 5ml of corn oil) at 5ml/kg.bw.
2. Blood samples were collected via tail vein bleeding using 3 x 300 ul EDTA tubes at the following time points:

0 hour (initial), 1 hour, 2 hour, 3 hour, 4 hour, 5 hour, 6 hour, 8 hour

After the 8 hour bleeding, rats were knocked down in a drop jar using isoflurane. Once sedated, the rats were hooked up to a Midmark Matrix Anesthesia isoflurane machine that dispensed isoflurane vapor at 3.5-4.5 mL/min with an oxygen flow rate of 1 L/min. Organs and tissues were dissected and frozen immediately in liquid nitrogen and stored at -80°C. LCMS and GCMS were used to assess the incorporation of ^{13}C lipids into plasma and tissue lipids (n=5 for tissue metabolomics studies).

Results

The serum triglycerides levels in different treatment groups after fatty tolerance test is given in table no.5 and ^{13}C palmitate uptake in adipose tissue is given in table no.6

Table no.5

Treatment Groups	Plasma TG (mg/dl) in FTT					
	0 min			120 min		
Vehicle Control	394.4	±	11.9	411.2	±	41.1
Compound (1)-0.4 mg/kg, p.o.	330.5	±	39.2	389.2	±	21.8
Compound (1)-4 mg/kg, p.o.	84.7	±	9.3	171.3	±	28.2
Fenofibrate 150 mg/kg, p.o.	444.7	±	16.9	502.2	±	8.1

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Table no.6

Treatment Groups	Palmitate total (micromole/mg protein)			^{13}C Palmitate (Nanomole/mg protein)			% Change in ^{13}C Palmitate uptake in adipose tissue Vs Vehicle Control
Vehicle Control	6.63	±	0.13	3.34	±	0.31	
Compound (1)-0.4 mg/kg, p.o.	7.14	±	0.30	6.20	±	0.89	86
Compound (1)-4 mg/kg, p.o.	6.60	±	0.29	11.57	±	0.73	247
Fenofibrate 150 mg/kg, p.o.	6.90	±	0.24	2.88	±	0.57	-14

From the above study it can be concluded that:

1. Compound (1) significantly reduced plasma triglyceride (TG) at 0 and 2 hour post corn oil treatment.
2. The major M+16 isotopomers of the major TG species, TG (52:3) and TG (52:4), rose in the first two hour following gavage (reflecting chylomicron production) and declined over the next 4 hours with a secondary rise at 6-8 hour. In contrast, fenofibrate treatment caused a greater increase in M+16 TG species; both low (0.4 mg/kg) and high (4 mg/kg) dose of Compound (1) significantly attenuated the appearance of M+16 TG.

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3. In all animals, Major M+16 phosphatidyl choline PC(34:1), carried primarily in HDL and VLDL, rose at similar rates, however the % labeling in the fenofibrate treated animals was significantly lower, suggesting a reduction in liver derived lipids by fenofibrate.

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4. Low and high dose of compound (1) significantly increased the accumulation of M+16 palmitate in adipose tissue (by 86% and 247%, respectively).

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5. Both Fenofibrate and compound (1) (low and high dose) decreased gastrocnemius M+16 palmitate labeling, which could be due to induction of lipid oxidation by fenofibrate and potentially compound (1) induced reduced plasma levels of TG in compound (1) treated groups.

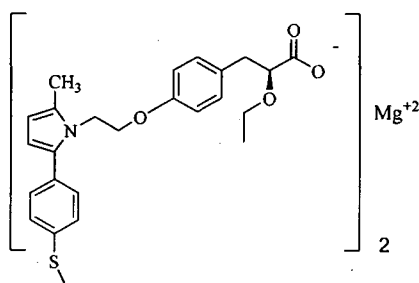
15

In conclusion, compound (1) significantly reduces fasting and postprandial TG levels through enhanced clearance of TG into adipose tissue and works by a mechanism distinct from that of fenofibrate, a 'pure' PPAR α activator.

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We claim:

1. A compound of formula (I),

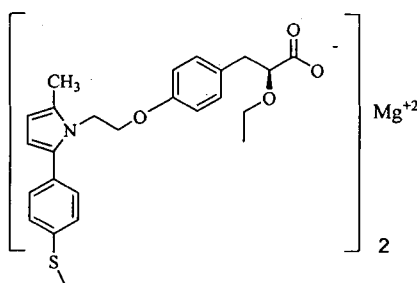


Formula (1)

for use in the prevention, delay of progression, or treatment of a disease or condition which is selected from chylomicronemia syndrome, familial chylomicronemia syndrome, and Type V hyperlipoproteinemia.

2. The compound according to claim 1 for use in the reduction of postprandial triglyceride levels in patients suffering from a disease or condition which is selected from chylomicronemia syndrome, familial chylomicronemia syndrome, and Type V hyperlipoproteinemia.
3. The compound according to claim 1 for use in the prevention, delay of progression or treatment of pancreatitis in patients suffering from a disease or condition which is selected from chylomicronemia syndrome, familial chylomicronemia syndrome, and Type V hyperlipoproteinemia.
4. The compound according to claim 1 for use in the prevention, delay of progression or treatment of a symptom selected from recurrent episodes of pancreatitis, deposition of triglycerides in the skin in the form of eruptive xanthomas, hepatosplenomegaly, milky white triglyceride in the blood vessels in the back of the eye (lipemia retinalis), and mild neuro-cognitive deficits.

5. A pharmaceutical composition comprising a compound of formula (1)



Formula (1)

and one or more excipients selected from from solubilizers, diluents, fillers, disintegrants, binder, lubricants, glidants, wetting agents and solvents for use in the prevention, delay of progression, or treatment of a disease or condition which is selected from chylomicronemia syndrome, familial chylomicronemia syndrome, and Type V hyperlipoproteinemia.

6. A pharmaceutical composition comprising a compound of formula (1) according to claim 5 for use in the reduction of postprandial triglyceride levels in patients suffering from a disease or condition which is selected from chylomicronemia syndrome, familial chylomicronemia syndrome, and Type V hyperlipoproteinemia.

7. A pharmaceutical composition comprising a compound of formula (1) according to claim 5 for use in the prevention, delay of progression or treatment of pancreatitis in patients suffering from a disease or condition which is selected from chylomicronemia syndrome, familial chylomicronemia syndrome, and Type V hyperlipoproteinemia.

8. A pharmaceutical composition comprising a compound of formula (1) according to claim 5 for use in the prevention, delay of progression or treatment of a symptom selected from recurrent episodes of pancreatitis, deposition of triglycerides in the skin in the form of eruptive xanthomas, hepatosplenomegaly, milky white triglyceride in the blood vessels in the back of the eye (lipemia retinalis), and mild neuro-cognitive deficits.

9. A method for the prevention, delay of progression or treatment of a disease or condition which is selected from chylomicronemia syndrome, familial chylomicronemia syndrome and type V hyperlipoproteinemia comprising administration of a therapeutically effective amount of compound of formula (1) or its pharmaceutical composition to a subject in need of such treatment.

10. A method for the reduction of postprandial triglyceride levels in patients suffering from a disease or condition which is selected from chylomicronemia syndrome, familial chylomicronemia syndrome, and Type V hyperlipoproteinemia, comprising administration of a therapeutically effective amount of compound of formula (1) as claimed in claim 9 to a subject in need of such treatment.

11. A method for the prevention, delay of progression or treatment of pancreatitis in patients suffering from a disease or condition which is selected from chylomicronemia syndrome, familial chylomicronemia syndrome, and Type V hyperlipoproteinemia, comprising administration of a therapeutically effective amount of compound of formula (1) as claimed in claim 9 to a subject in need of such treatment.

12. A method for the prevention, delay of progression or treatment of a symptom selected from recurrent episodes of pancreatitis, deposition of triglycerides in the skin in the form of eruptive xanthomas, hepatosplenomegaly, milky white triglyceride in the blood vessels in the back of the eye (lipemia retinalis), and mild neuro-cognitive deficits, comprising administration of a therapeutically effective amount of compound of formula (1) as claimed in claim 9 to a subject in need of such treatment.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2016/000121

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/40 A61K9/00 A61P3/06
ADD.

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)
A61K

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)

EPO-Internal, BIOSIS, EMBASE, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SOSALE ARAVIND SOSALE ET AL: "Saroglitazar for the treatment of hypertriglyceridemia in patients with type 2 diabetes: current evidence", DIABETES, METABOLIC SYNDROME AND OBESITY: TARGETS AND THERAPY, vol. 8, 1 January 2015 (2015-01-01), pages 189-196, XP055293364, DOI: 10.2147/DMSO.S49592 abstract page 191, column 1, paragraph 4 - column 2, paragraph 2 ----- -/--	1-3,5-7, 9-11



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

1 September 2016

Date of mailing of the international search report

03/11/2016

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2016/000121

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	RAJENDRAKUMAR H. JANI ET AL: "A Multicenter, Prospective, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Saroglitazar 2 and 4?mg Compared with Placebo in Type 2 Diabetes Mellitus Patients Having Hypertriglyceridemia Not Controlled with Atorvastatin Therapy (PRESS VI)", DIABETES TECHNOLOGY & THERAPEUTICS, vol. 16, no. 2, 1 February 2014 (2014-02-01), pages 63-71, XP055155508, ISSN: 1520-9156, DOI: 10.1089/dia.2013.0253 abstract	1
A	----- WO 2015/029066 A1 (CADILA HEALTHCARE LTD [IN]) 5 March 2015 (2015-03-05) page 1, paragraph 1 - page 2, paragraph 1 -----	1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2016/000121

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.:
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:

see additional sheet

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 an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-3, 5-7, 9-11

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-3, 5-7, 9-11

A compound of formula (I), for use in the prevention, delay of progression, or treatment of a disease or condition which is selected from chylomicronemia syndrome, familial chylomicronemia syndrome, and Type V hyperlipoproteinemia; the compound according to claim 1 for use in the reduction of postprandial triglyceride levels in patients suffering from a disease or condition which is selected from chylomicronemia syndrome, familial chylomicronemia syndrome, and Type V hyperlipoproteinemia; the compound according to claim 1 for use in the prevention, delay of progression or treatment of pancreatitis in patients suffering from a disease or condition which is selected from chylomicronemia syndrome, familial chylomicronemia syndrome, and Type V hyperlipoproteinemia; a pharmaceutical composition comprising a compound of formula (I) for said uses

2. claims: 4, 8, 12(all partially)

The compound according to claim 1 for use in the prevention, delay of progression or treatment of a symptom which is recurrent episodes of pancreatitis

3. claims: 4, 8, 12(all partially)

The compound according to claim 1 for use in the prevention, delay of progression or treatment of a symptom which is deposition of triglycerides in the skin in the form of eruptive xanthomas

4. claims: 4, 8, 12(all partially)

The compound according to claim 1 for use in the prevention, delay of progression or treatment of a symptom which is hepatosplenomegaly

5. claims: 4, 8, 12(all partially)

The compound according to claim 1 for use in the prevention, delay of progression or treatment of a symptom which is milky white triglyceride in the blood vessels in the back of the eye (lipemia retinalis)

6. claims: 4, 8, 12(all partially)

The compound according to claim 1 for use in the prevention,

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

delay of progression or treatment of a symptom which is
recurrent episodes of mild neuro-cognitive deficits

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IN2016/000121

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2015029066 A1	05-03-2015	EP 3039011 A1	06-07-2016
		US 2016207884 A1	21-07-2016
		WO 2015029066 A1	05-03-2015
