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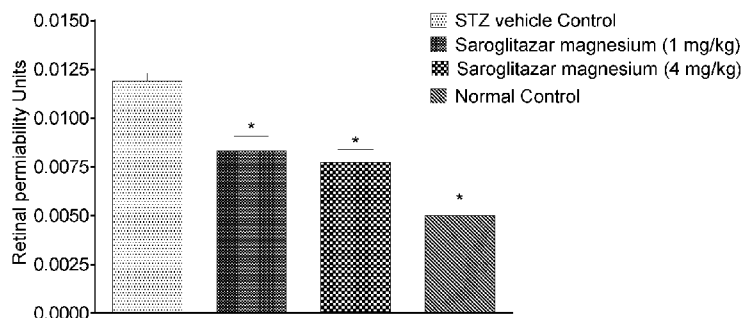
(54) Title: DUAL PPAR MODULATORS FOR THE TREATMENT OF DIABETIC RETINOPATHY AND DIABETIC EYE DIS-
EASES

Figure 1

(57) **Abstract:** The present invention relates to the use of Saroglitzazar or a pharmaceutically acceptable salt thereof, for the treatment of, or the prevention, delay of progression, or treatment of a disease or condition related with disorders of the eye. The disorders of the eye is selected from ocular inflammation, corneal inflammation, diabetic retinopathy (DR), diabetic macular edema, macular degeneration (including, but not limited to, age related macular degeneration), uveitis, retinal inflammation, retinal vascular leakage, retinal neovascularization, cancer, and other inflammatory and neovascular disorders of the eye. The present invention further relates to the use of a pharmaceutical composition comprising Saroglitzazar, or a pharmaceutically acceptable salt thereof, for the prevention, delay of progression, or treatment of a disease or condition which is selected from ocular inflammation, corneal inflammation, diabetic retinopathy (DR), diabetic macular edema, macular degeneration (including, but not limited to, age related macular degeneration), uveitis, retinal inflammation, retinal vascular leakage, retinal neovascularization, cancer, and other inflammatory and neovascular disorders of the eye.





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DUAL PPAR MODULATORS FOR THE TREATMENT OF DIABETIC RETINOPATHY AND DIABETIC EYE DISEASES

FIELD OF INVENTION

5 The present invention relates to the use of Saroglitazar or a pharmaceutically acceptable salt thereof, for the treatment of, or the prevention, delay of progression, or treatment of a disease or condition related with disorders of the eye. The disorders are selected from ocular inflammation, corneal inflammation, diabetic retinopathy (DR), diabetic macular edema, macular degeneration (including, but not limited to, age related macular degeneration), uveitis, 10 retinal inflammation, retinal vascular leakage, retinal neovascularization, cancer, and other inflammatory and neovascular disorders of the eye. The present invention further relates to the use of a pharmaceutical composition comprising Saroglitazar, or a pharmaceutically acceptable salt thereof, for the prevention, delay of progression, or treatment of a disease or condition which is selected from ocular inflammation, corneal inflammation, diabetic retinopathy (DR), 15 diabetic macular edema, macular degeneration (including, but not limited to, age related macular degeneration), uveitis, retinal inflammation, retinal vascular leakage, retinal neovascularization, cancer, and other inflammatory and neovascular disorders of the eye. The present invention is also related to the pharmaceutical topical ophthalmic composition comprising Saroglitazar, or a pharmaceutically acceptable salt thereof, for the prevention, delay 20 of progression, or treatment of a disease or condition which is selected from ocular inflammation, corneal inflammation, diabetic retinopathy (DR), diabetic macular edema, macular degeneration (including, but not limited to, age related macular degeneration), uveitis, retinal inflammation, retinal vascular leakage, retinal neovascularization, cancer, and other inflammatory and neovascular disorders of the eye.

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BACKGROUND OF INVENTION

Diabetic Retinopathy is a common and specific micro vascular complication of diabetes, and is a major cause of preventable blindness [Yau JW, Diabetes Care. 2012 Mar;35(3):556-64]. It is associated with increased risk of life-threatening systemic vascular complications, including 30 stroke, coronary heart disease, and heart failure. As of 2015, there are more than 415 million

people suffering from diabetes, and it is being projected that the number of diabetic patients will reach 642 million by 2040 (<http://www.diabetesatlas.org/>; accessed 26-Oct-2016). Diabetes can be generally divided into two types: type 1 (insulin dependent) and type 2 (insulin independent), although patients of both types will have hyperglycemia. Diabetic eye diseases are the most feared complications of diabetes, with more than 50% of people with type 2 diabetes having retinopathy after 10 years of disease. Diabetic retinopathy (DR) and other microvascular complications remain a major source of disability in patients with diabetes. Better control of glucose, blood pressure, and lipids in recent years has reduced the risk of DR, but many patients continue to experience progressive eye damage and require specialist ophthalmic care. It is estimated that about one-third of the diabetic patients have signs of DR and about one-tenth of them even have vision-threatening retinopathy (J. B. Saaddine, A. A. Honeycutt, K. M. V. Narayan, X. Zhang, R. Klein, and J. P. Boyle, *Archives of Ophthalmology*, vol. 126, no. 12, pp. 1740–1747, 2008.). It is also documented that nearly 60% and 35% of DR patients progress to proliferative DR and severe vision loss in 10 years, respectively (T. Y. Wong, M. Mwamburi, R. Klein et al., *Diabetes Care*, vol. 32, no. 12, pp. 2307–2313, 2009.). Clinically, DR can be classified into nonproliferative (NPDR) and proliferative (PDR) (N. Cheung, P. Mitchell, and T. Y. Wong, *The Lancet*, vol. 376, no. 9735, pp. 124–136, 2010.). NPDR is characterized by the presence of microaneurysms, hemorrhages, hard exudates (liquid deposits), cotton wool spots, intraretinal microvascular abnormalities, venous beading, and loop formation. NPDR, if severe, complicates into PDR, which is characterized by neovascularization of the retina and vitreous hemorrhage. If untreated, it can result into vision loss due to retinal detachment. Maculopathy, including macular edema and ischemia, can occur at any stage of DR, which accounts for the majority of the blindness due to DR. The increasing number of diabetic patients and a longer life span in the aging population imply an increase in patients suffering from DR. It severely affects the quality of life of the patients and also increases the medical and economic burden to the society. As a consequence, effective therapy is urgently needed.

Diabetic eye diseases are a group of eye conditions that affect people with diabetes. These conditions include diabetic retinopathy, diabetic macular edema (DME), cataract, and glaucoma.

All these forms of diabetic eye disease have the potential to cause severe vision loss and blindness. Diabetic retinopathy involves changes to retinal blood vessels that can cause them to bleed or leak fluid, distorting vision. DME is a consequence of diabetic retinopathy that causes swelling in the area of the retina called the macula. Controlling diabetes—by taking medications
5 as prescribed, staying physically active, and maintaining a healthy diet—can prevent or delay vision loss. Because diabetic retinopathy often goes unnoticed until vision loss occurs, early detection, timely treatment, and appropriate follow-up care of diabetic eye disease can protect against vision loss.

Diabetic retinopathy is a very common complication of diabetes mellitus that is associated with
10 aberrant neovascularization DR is a chronic and progressive disorder, primarily affecting retinal capillaries. Breakdown of the blood-retinal barrier is a common pathological change in patients with diabetes and in streptozotocin (STZ)-induced diabetic animal models. In the early stages of DR, the retinal vascular permeability is increased without the appearance of clinical retinopathy. Retinal vascular leakage and thickening of the retina lead to diabetic macular edema (DME). In
15 the late stages of DR, over-proliferation of capillary endothelial cells results in retinal neovascularization (NV), the abnormal formation of new vessels from preexisting capillaries in the retina and vitreous. This, in turn, leads to proliferative diabetic retinopathy (PDR). The abnormal angiogenesis can ultimately cause severe vitreous cavity bleeding and/or retinal detachment, resulting in severe vision loss. Multiple growth factors in the eye, such as but not
20 limited to, VEGF, bFGF, IGF-1, and PEDF, are implicated in the pathogenesis of DR. Alterations of these growth factors and their receptors in diabetes have been identified in both experimental and clinical studies. Increased VEGF levels are at least partly responsible for retinal vascular leakage, retinal vascular hyper-permeability and retinal neovascularization in patients with DR. VEGF therefore plays an important role in the development and pathogenesis
25 of DR. Inhibition of VEGF and VEGF receptors has been shown to prevent retinal NV in diabetic animal models.

Retinopathy in both type 1 and type 2 diabetes develops retinal vascular leakage, inflammation, neovascularization, and fibrosis (Yam JC, Kwok AK. Hong Kong Med J. 2007). There are very few promising therapies for treatment of diabetic eye diseases. Besides systemic therapy such as
30 glycemic control, blood pressure control, lipid-lowering therapy and ocular therapy (including

but not limited to, laser photocoagulation, surgical intervention, intravitreal injection of anti-VEGF agents, etc.) are used. Even though it is well established that vascular endothelial growth factor (VEGF) mediates the pathologic processes of vascular leakage and angiogenesis in DR, anti-VEGF compounds are not always effective in all patients with DR (Gardlik R, Semin
5 Ophthalmol. 2015 Jul;30(4):252-63). This may be ascribed to the fact that DR is mediated by multiple angiogenic, inflammatory, and fibrogenic factors such as VEGF, tumor necrosis factor- α , intercellular adhesion molecule-1 (ICAM-1), and connective tissue growth factor, and thus, blockade of VEGF alone is not sufficient to ameliorate all of the perturbed signaling. In addition to the associated risks, it is also important anti-VEGF agents were used to treat DME-related
10 vision loss, and there is a need for an agent that will prevent diabetic retinopathy risk. Anti-VEGF agents have not been shown to reduce DR progression and may increase cardiovascular events if used long-term in patients with less severe DR. The long-term efficacy and safety of anti-VEGF agents have not been established.

The peroxisome proliferator-activated receptor (PPAR) family of nuclear receptors is composed
15 of three family members. The main classes of PPAR agonists are:

PPAR-alpha agonists, PPAR-gamma agonists and PPAR-beta/delta (β/δ) agonists; PPAR-alpha is the main target of fibrate drugs, such as gemfibrozil, ciprofibrate, bezafibrate, and fenofibrate; WO 2013049621 describes an ophthalmic compositions comprising the PPAR-alpha agonist fenofibrate for the treatment and prevention of inflammation, fibrosis,
20 angiogenesis and/or tumorigenesis. However, fenofibrate exhibits pleiotropic effects (Tsimihodimos V et al, Curr Pharm Des. 2009; 15(5):517-28); and high doses of fenofibrate are associated with renal toxicity.

PPAR-gamma is the main target of the drug class of thiazolidinedione's (TZDs), such as Pioglitazone and Rosiglitazone. WO2000000194 disclosed the ophthalmic use of PPAR-gamma
25 agonist.

No major therapeutic candidate has been developed for PPAR-(β/δ) agonists yet, one of the few compounds which have been identified as a PPAR-(β/δ) agonists is the is a research chemical named GW501516. WO 2016057656 disclose methods of use of GW501516 for treating

PPAR-gamma related diseases such as mitochondrial diseases, muscular diseases, vascular diseases, demyelinating diseases, and metabolic diseases.

A fourth class, which is dual PPAR agonist is represented by the so-called glitazars, which bind to both the alpha and gamma PPAR isoforms. These include the compounds
5 Aleglitazar, Muraglitazar, Tesaglitazar and Saroglitazar.

In our hand we have tried Aleglitazar for the use of diabetic retinopathy and we can found that Saroglitazar is showing good effect as compared to Aleglitazar.

Thus, new compositions for treatment of this severe disease condition are desired. Therefore, there exists a need for new and improved compositions containing dual PPAR agonists as well
10 as methods of production and use thereof. Such PPAR agonists may preferably be a dual PPAR agonist. Such compositions and methods would be useful in the treatment and prevention of neovascularization-associated and/or Wnt signaling pathway associated diseases, including but not limited to, inflammation, fibrosis, angiogenesis and/or tumorigenesis. The present disclosure is directed to compositions and methods, which overcome the disadvantages and defects of the
15 prior art.

The present invention describes the use of a PPAR modulator of formula (1) and pharmaceutically acceptable salts thereof for the prevention and treatment of eye disorders. Wherein eye disorders is ocular inflammation, corneal inflammation, diabetic retinopathy (DR), diabetic macular edema, macular degeneration (including, but not limited to, age related
20 macular degeneration), uveitis, retinal inflammation, retinal vascular leakage, retinal neovascularization, cancer, and other inflammatory and neovascular disorders of the eye.

SUMMARY OF THE INVENTION

The compound of formula (1) (Saroglitazar) is approved as its Magnesium salt for the treatment of treating Diabetic Dyslipidemia or Hypertriglyceridemia in type 2 diabetes, not controlled by
25 statins alone.

There is also provided the use of Saroglitazar, or a pharmaceutically acceptable salt thereof or solid or topical ophthalmic composition, for use in the reduction of ocular inflammation,

corneal inflammation, diabetic retinopathy (DR), diabetic macular edema, macular degeneration (including, but not limited to, age related macular degeneration), uveitis, retinal inflammation, retinal vascular leakage, retinal neovascularization, cancer, and other inflammatory and neovascular disorders of the eye.

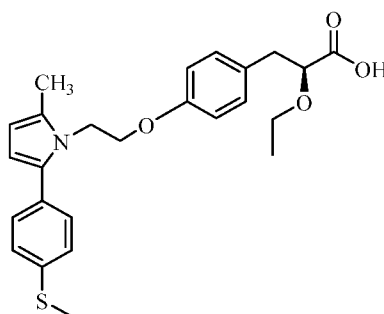
5 BRIEF DESCRIPTION OF DRAWING

Figure 1: Effect of Saroglitzazar Mg on retinal permeability in established diabetic retinopathy induced by streptozotocin after 4 weeks of treatment in male Sprague Dawley rats.

Figure 2: Prophylactic effect of Saroglitzazar Mg on retinal permeability in diabetic retinopathy induced by streptozotocin after 4 weeks of treatment in male Sprague Dawley rats.

10 DETAILED DESCRIPTION

The present invention thus provides the use of Saroglitzazar of formula (1), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the prevention, delay of progression, or treatment of a disease or condition related with disorders of the eye. The disorders are selected from ocular inflammation, corneal inflammation, diabetic retinopathy (DR), diabetic macular edema, macular degeneration (including, but not limited to, age related macular degeneration), uveitis, retinal inflammation, retinal vascular leakage, retinal neovascularization, cancer, and other inflammatory and neovascular disorders of the eye.



(1)

The pharmaceutically acceptable salt of compound of formula (1) is selected from organic or inorganic salts. Inorganic salt is selected from Calcium, Magnesium, Sodium, Potassium, Zinc, Ammonium and Lithium. Organic salt is selected from L-Arginine, Tromethamine, L-Lysine, Meglumine, Benethamine, Piperazine, Benzylamine, Dibenzylamine, Dicyclohexylamine, Diethylamine, Diphenylamine, α -naphthylamine, O-phenylenediamine, 1,3-Diaminopropane, (S)- α -naphthylethylamine, (S)-3-methoxyphenylethylamine, (S)-4-methoxyphenylethylamine, (S)-4-chlorophenylethylamine, (S)-4-methylphenylethylamine, Cinchonine, Cinchonidine, (-)-Quinine, Benzathine, Ethanolamine, Diethanol amine, Triethanolamine, imidazole, Diethylamine, Ethylenediamine, Choline, Epolamine, Morpholine 4-(2-hydroxyethyl), N-N-diethylethanolamine, Deanol, Hydrabamine, Betaine, Adamantanamine, L-Adamantanmethylethylamine and Tritylamine.

In one of the preferred embodiment the pharmaceutically acceptable salt of compound of formula (1) is Magnesium.

In one of the preferred embodiment use of the Magnesium salt of compound of formula (1) for the manufacture of a medicament for the prevention, delay of progression, or treatment of a diabetic retinopathy.

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

- the pharmaceutically active substance of formula (1) or its pharmaceutically acceptable salt;
- a suitable buffering agent;
- a suitable stabilizer;
- optionally with one or more pharmaceutically acceptable excipients.

The pharmaceutically acceptable salt of compound of formula (1) is as described earlier.

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, sulfobutyl ether 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 active substance of Formula (1) or its pharmaceutically acceptable salt is used in the range of 0.5 mg to 5 g.

Usually the compositions are adapted for oral administration. However, they may be adapted for other modes of administration, for example parenteral administration, sublingual or transdermal administration.

The compositions may be in the form of tablets, capsules, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

5 In order to obtain consistency of administration it is preferred that a composition of the invention is in the form of a unit dose.

Unit dosage presentation forms for oral administration may be in tablet or capsule form and may as necessary contain conventional excipients such as binding agents, fillers, lubricants, glidants, disintegrates and wetting agents.

10 The solid oral compositions may be prepared by conventional methods of blending, filling or tableting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating.

15 Oral liquid preparations may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include
20 edible oils), for example almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

For parenteral administration, liquid dosage forms are prepared utilizing the compound and a sterile vehicle, and, depending on the concentration used, can be either suspended or dissolved
25 in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anesthetic, a preservative and buffering agent can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the

water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the active compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a
5 surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

Compositions may contain from 0.1% to 99% by weight, preferably from 10-60% by weight, of the active material, depending upon the method of administration.

Examples of binding agents include acacia, alginic acid, carboxymethylcellulose calcium,
10 carboxymethylcellulose sodium, dextrates, dextrin, dextrose, ethylcellulose, gelatin, liquid glucose, guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium aluminium silicate, maltodextrin, methyl cellulose, polymethacrylates, polyvinylpyrrolidone, pregelatinised starch, sodium alginate, sorbitol, starch, syrup, tragacanth.

15 Examples of fillers include calcium carbonate, calcium phosphate, calcium sulphate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, compressible sugar, confectioner's sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, dibasic calcium phosphate, fructose, glyceryl palmitostearate, glycine, hydrogenated vegetable oil-type 1, kaolin, lactose, maize starch, magnesium carbonate, magnesium oxide, maltodextrin,
20 mannitol, microcrystalline cellulose, polymethacrylates, potassium chloride, powdered cellulose, pregelatinised starch, sodium chloride, sorbitol, starch, sucrose, sugar spheres, talc, tribasic calcium phosphate, xylitol.

Examples of lubricants include calcium stearate, glyceryl monostearate, glyceryl palmitostearate, magnesium stearate, microcrystalline cellulose, sodium benzoate, sodium
25 chloride, sodium lauryl sulphate, stearic acid, sodium stearyl fumarate, talc, zinc stearate.

Examples of glidants include colloidal silicon dioxide, powdered cellulose, magnesium trisilicate, silicon dioxide, talc.

Examples of disintegrants include alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium, colloidal silicon dioxide, croscarmellose sodium, crospovidone, guar gum, magnesium aluminium silicate, microcrystalline cellulose, methyl cellulose, polyvinylpyrrolidone, polacrillin potassium, pregelatinised starch, sodium alginate,
5 sodium lauryl sulphate, sodium starch glycollate.

An example of a pharmaceutically acceptable wetting agent is sodium lauryl sulphate. The compositions are prepared and formulated according to conventional methods, such as those disclosed in standard reference texts and are well within the scope of a skilled person. For example, the solid oral compositions may be prepared by conventional methods of blending,
10 filling or tableting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Compositions may, if desired, be in the form of a pack accompanied by written or printed
15 instructions for use.

No adverse toxicological effects are expected for the compositions or methods of the invention in the above mentioned dosage ranges. Further the composition of the present invention was found suitable for the treatment of hypertension and its associated disorders.

In a preferred embodiment, provided herein a pharmaceutical topical ophthalmic composition
20 comprises: the pharmaceutically active substance of Formula (1) or pharmaceutically acceptable salts thereof. The topical ophthalmic composition for use in the prevention, delay of progression, or treatment of a disease or condition related with disorders of the eye.

The pharmaceutical topical ophthalmic composition having concentration of the active substance of Formula (1) or pharmaceutically acceptable salts thereof ranges between 1 µg/mL
25 and 40 mg/mL, and the composition is an isotonic aqueous solution, a poly(vinyl alcohol) aqueous solution, or mixtures thereof and the pH of pharmaceutical topical ophthalmic composition is between 3 and 8.

In preferred embodiments concentration ranges of the pharmaceutical composition is between 1 µg/mL and 10 mg/mL.

The pharmaceutical composition as described further comprises a preservative. The preservative is selected from the group consisting of benzalkonium chloride, benzoic acid, alkyl parabens, alkyl benzoates, chlorobutanol, chlorocresol, cetyl alcohols, fatty alcohols, hexadecyl alcohol, organometallic compounds of mercury, mercury acetate, phenylmercury nitrate or borate, diazolidinyl urea, diisopropyl adipate, dimethyl polysiloxane, salts of EDTA, vitamin E and mixtures thereof.

In an embodiment the pharmaceutical composition as described further comprises an agent that increases permeability of the active substance of Formula (I) or pharmaceutically acceptable salts thereof. The agent that increases permeability is selected from benzalkonium chloride, saponins, fatty acids, polyoxyethylene fatty ethers, alkyl esters of fatty acids, pyrrolidones, polyvinylpyrrolidone, pyruvic acids, pyroglutamic acids, and mixtures thereof.

The active substance of Formula (I) or pharmaceutically acceptable salts thereof is incorporated in liposomes, mixed liposomes, niosomes, ethosomes, nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, micelles, mixed micelles of surfactants, surfactant-phospholipid mixed micelles, nanospheres, lipospheres and/or nanocapsules.

In another embodiment, provided herein is an ophthalmic composition comprising the compound of formula (1) or its magnesium salt. In some embodiments the ophthalmic composition of the present invention is a range of from about 0.0001% to about 95%, a range of from about 0.001% to about 50%; a range of from about 0.005% to about 40%; a range of from about 0.01% to about 35%; a range of from about 0.05% to about 30%; a range of from about 0.1% to about 25%; a range of from about 0.1% to about 20%; a range of from about 0.1% to about 15%; and a range of from about 1% to about 10%. The ophthalmic composition can be formulated in any reasonable manner to allow administration to the eye. For example, the ophthalmic composition can be formulated as an eye drop. In some embodiments, the ophthalmic composition comprises an emulsion. In some embodiments, the ophthalmic composition comprises at least one lipid.

In some embodiments, the composition further comprises at least one delivery agent that assists in the penetration of the surface of the eye. For example, the composition can further comprise a delivery agent that assists in delivery of the composition to the cornea of the eye and/or the retina of the eye. Non-limiting examples of components of the ophthalmic composition may include: glycerin, castor oil, soybean lecithin, polyoxyethylene-polyoxypropylene block copolymer, alpha tocopherol, and carboxymethyl cellulose. In some embodiments, the ophthalmic composition includes at least one of the above; at least two of the above; at least three of the above; at least four of the above; or at least five of the above. In some embodiments, the ophthalmic composition comprises glycerin, castor oil, soybean lecithin, polyoxyethylene-polyoxypropylene block copolymer, alpha tocopherol, and carboxymethyl cellulose. Also provided herein is a kit comprising the ophthalmic composition of the invention as provided herein. This disclosure also provides a pharmaceutical composition comprising an ophthalmic composition as provided herein and a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical composition further comprises a second therapeutic agent. For example, the pharmaceutical composition can include at least one of an anti-angiogenic agent or an anti-VEGF reagent. In some embodiments, the pharmaceutical composition includes a second therapeutic agent selected from the group consisting of: bevacizumab, ranibizumab, triamcinolone acetonide, ganciclovir, foscarnet, vancomycin, ceftazidime, amikacin, amphotericin B, dexamethasone, ketorolac tromethamine, naphazoline, lidocaine hydrochloride, pemirolast potassium, brimonidine, loteprednol etabonate, azelastine hydrochloride, azithromycin, bepotastine besilate, besifloxacin, levobetaxolol hydrochloride, dorzolamide hydrochloride - timolol maleate, difluprednate, aflibercept, loteprednol etabonate, bimatoprost, pegaptanib, ofloxacin, naphazoline alone and with pheniramine, dexamethazone, levofloxacin, unoprostone isopropyl, cyclosporinepilocarpine hydrochloride, travoprost, valganciclovir HCl, trifluridine, cidofovir, verteporfm, fomivirsen, ketotifen, tafluprost, ganciclovir, gatifloxacin and suitable combinations thereof.

Further provided herein is a method of inhibiting enzyme activity and/or enzyme production of at least one angiogenic, inflammatory, or fibrogenic factor of diabetic retinopathy (DR). The method comprises administering to at least one eye of a patient suffering from or predisposed to DR at least one of the ophthalmic compositions or pharmaceutical compositions as provided

herein. In some embodiments, the factor of DR is selected from the group consisting of VEGF, ICAM-1, TNF-a, and CTGF.

This disclosure also provides a method of treating at least one retinal condition selected from the group consisting of retinal leukostasis, inflammation, vascular leakage, fibrosis, abnormal
5 neovascularization and carcinogenesis in the retina. The method comprising administering to at least one eye of a patient suffering from or predisposed to the at least one retinal condition at least one of the ophthalmic compositions or pharmaceutical compositions as provided herein.

Provided herein is a method of inhibiting and/or decreasing the occurrence and/or severity of at least one condition/disorder selected from the group consisting of ocular inflammation, corneal
10 inflammation, diabetic retinopathy, diabetic macular edema, macular degeneration, uveitis, retinal inflammation, retinal vascular leakage, and retinal neovascularization. The method comprises administering to at least one eye of a patient suffering from or predisposed to the at least one condition at least one of the ophthalmic compositions or pharmaceutical compositions as provided herein.

15 This disclosure also provides a method of inhibiting activation of Wnt signaling pathway in an eye of a patient, comprising administering to at least one eye of a patient at least one of the ophthalmic compositions or pharmaceutical compositions as provided herein.

Further provided herein is a method of inhibiting phosphorylation of low-density lipoprotein receptor-related protein 6 (LRP6) or LRP6, comprising administering to at least one eye of a
20 patient at least one of the ophthalmic compositions or pharmaceutical compositions as provided herein.

In some embodiments of the methods described above, the method can further include administration of a second therapeutic agent as provided hereinabove to the patient. Administration as described herein can include injecting the composition into the vitreous of the
25 eye of the patient. In some embodiments, administration includes topically applying the composition to a surface of the eye of the patient.

The Saroglitazar of formula (1), or a pharmaceutically acceptable salt thereof can be prepared by the general processes and examples disclosed in WO2003009841 and its Mg salt can be prepared by the process and example disclosed in WO2012104869.

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

5 Streptozotocin induced diabetic retinopathy in Sprague Dawley rats

In the rat model of diabetic retinopathy induced by administration of streptozotocin (50 mg/kg, intraperitoneal, in citrate buffer pH 4.5), Saroglitazar Mg was administered before (prophylactic) and after (curative) the development of diabetic vascular complications, in two separate experiments. Saroglitazar Mg was administered at 1 and 4 mg/kg/day per oral route for four weeks. In prophylactic treatment group, Saroglitazar Mg was administered one week after the administration of streptozotocin, while in therapeutic or curative treatment groups; treatment was initiated four weeks after streptozotocin administration. Animals were selected with random glucose higher than 350 mg/dL. In both the experiments, streptozotocin administration increased the retinal permeability.

Table 1: Effect of Saroglitazar Mg on retinal permeability in established diabetic retinopathy induced by streptozotocin after 4 weeks of treatment in male Sprague Dawley rats.

Treatment group	Retinal permeability	% change in retinal permeability against vehicle control
Vehicle control	0.012 ± 0.001	
Saroglitazar Mg (1 mg/kg)	0.008 ± 0.001	-32.7 ± 6.3*
Saroglitazar Mg (4 mg/kg)	0.008 ± 0.001	-37.3 ± 5.1*
Normal control	0.005 ± 0.001	-59.5 ± 4.7*

Note- Each data represent Mean ± SEM, n=6.* indicate p<0.05 against vehicle control.

As shown in Figure 1, chronic administration of Saroglitazar Mg showed 32.7 and 37.3 % reduction in retinal permeability against vehicle control in curative experiment.

Table 2: Prophylactic effect of Saroglitazar Mg on retinal permeability in diabetic retinopathy induced by streptozotocin after 4 weeks of treatment in male Sprague Dawley rats.

Treatment group	Retinal permeability	% change in retinal permeability against vehicle control
Vehicle control	0.012 $\pm$ 0.001	
Saroglitazar Mg (1 mg/kg)	0.01 $\pm$ 0.001	-12.5 $\pm$ 6.6*
Saroglitazar Mg (4 mg/kg)	0.008 $\pm$ 0.001	-30.2 $\pm$ 12.8*
Normal control	0.005 $\pm$ 0.001	-56.8 $\pm$ 5.0*

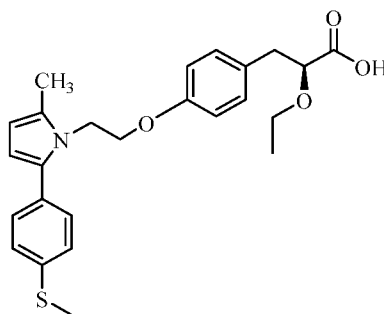
From the data disclosed in Table 2, in prophylactic experiment, Saroglitazar Mg at 1 and 4 mg/kg/day showed 12.5 and 30.2 % reduction in retinal permeability respectively than vehicle control, indicating potential for prevention of diabetes associated retinopathy.

From the above study it can be concluded that:

A chronic administration of Saroglitazar Mg produced significant reduction in retinal permeability a remarkable hallmark of diabetic retinopathy in preventive and therapeutic experiment. The findings in these studies indicate that Saroglitazar Mg can be used as an effective approach to prevent and treat diabetic retinopathy.

Claim:

1. A compound of formula (1) or pharmaceutically acceptable salt thereof,



Formula (1)

- 5 for use in the prevention, delay of progression, or treatment of a disease or condition related with disorders of the eye.
2. The disorders of the eye according to claim 1 is selected from ocular inflammation, corneal inflammation, diabetic retinopathy (DR), diabetic macular edema, macular degeneration, uveitis, retinal inflammation, retinal vascular leakage, retinal
- 10 neovascularization, cancer, and other inflammatory and neovascular disease.
3. The macular degeneration according to claim 2 is selected from age related macular degeneration.
4. The disorders of the eye according to claim 1 is diabetic retinopathy (DR).
5. The pharmaceutically acceptable salt as claimed in claim 1 which are selected from
- 15 organic or inorganic salts wherein the inorganic salt is selected from Calcium, Magnesium, Sodium, Potassium, Zinc, Ammonium and Lithium And the organic salt is selected from L-Arginine, Tromethamine, L-Lysine, Meglumine, Benethamine, Piperazine, Benzylamine, Dibenzylamine, Dicyclohexylamine, Diethylamine, Diphenylamine, α -naphthylamine, O-phenylenediamine, 1,3-Diaminopropane, (S)- α -
- 20 naphthylethylamine, (S)-3-methoxyphenylethylamine, (S)-4-methoxyphenylethylamine, (S)-4-chlorophenylethylamine, (S)-4-methylphenylethylamine, Cinchonine,

Cinchonidine, (-)-Quinine, Benzathine, Ethanolamine, Diethanol amine, Triethanolamine, imidazole, Diethylamine, Ethylenediamine, Choline, Epolamine, Morpholine 4-(2-hydroxyethyl), N-N-diethylethanolamine, Deanol, Hydrabamine, Betaine, Adamantanamine, L-Adamantanmethylaniline and Tritylamine.

- 5 6. The pharmaceutically acceptable salt as claimed in claim 5 which is the magnesium salt.
7. A pharmaceutical composition comprising:
- a. the pharmaceutically active substance of Formula (1) or pharmaceutically acceptable salt thereof;
 - b. suitable additives
 - 10 c. a suitable stabilizer;
 - d. optionally with one or more pharmaceutically acceptable excipients for use in the prevention, delay of progression, or treatment of a disease or condition related with disorders of the eye.
- 15 8. The pharmaceutical composition as claimed in claim 7, used for the ocular inflammation, corneal inflammation, diabetic retinopathy (DR), diabetic macular edema, macular degeneration, uveitis, retinal inflammation, retinal vascular leakage, retinal neovascularization, cancer, and other inflammatory and neovascular disease.
9. The pharmaceutical composition of claim 7 wherein the disease condition is diabetic retinopathy (DR)
- 20 10. The pharmaceutical composition as claimed in claim 7 wherein the suitable stabilizer is selected from antioxidants or chelating agents.
- 25 11. The pharmaceutical composition as claimed in claim 7 wherein the suitable antioxidants are selected from citric acid, alpha tocopherol, sodium sulphite, sodium metabisulphite, butylated hydroxy anisole (BHA), BHT (2,6-di-tert-butyl-4-methylphenol), monothioglycerol, Vitamin C (ascorbic acid).

12. The pharmaceutical composition as claimed in claim 7 wherein the suitable chelating agents are selected from Disodium EDTA, citric acid and or its salts, maleic acid, chlorambutol, chlorhexidine.
13. The pharmaceutical composition as claimed in claims 7 to 12 wherein pharmaceutically
5 active substance of Formula (I) is used in the range of 0.5 mg to 5 g.
14. The pharmaceutical composition as claimed in claim 7, wherein the suitable excipients are selected from solubilizers, diluents, fillers, disintegrants, binder, lubricants, glidants, wetting agents and solvents.
15. The pharmaceutical composition as claimed in claim 7, wherein the suitable additives
10 are selected from sodium benzoate, sodium hydroxide, sodium sulfite and sodium carbonate.
16. The pharmaceutical composition as claimed in claim 14, wherein the suitable binders are selected from acacia alginic acid, tragacanth, carboxymethylcellulose sodium, poly (vinylpyrrolidone), compressible sugar (e.g., NuTab), ethylcellulose, gelatin, liquid
15 glucose, methyl cellulose, povidone and pregelatinized starch, combinations thereof; poly(ethylene glycol), guar gum, polysaccharide, bentonites, sugars, invert sugars, poloxamers (PLURONIC F68, PLURONIC F127), collagen, albumin, celluloses in nonaqueous solvents, and the like or their suitable combinations; poly(propylene glycol), polyoxyethylene-polypropylene copolymer, polyethylene ester, polyethylene sorbitan
20 ester, poly(ethylene oxide), microcrystalline cellulose, poly(vinylpyrrolidone).
17. The pharmaceutical composition as claimed in claim 14, wherein the suitable glidants selected from glicoloidal silica, calcium silicate, magnesium silicate, silicon hydrogel, corn starch and talc.
18. The pharmaceutical composition as claimed in any claim 17 wherein the suitable
25 glidants selected from calcium stearate, magnesium stearate, mineral oil, stearic acid, zinc stearate.

19. The pharmaceutical composition as claimed in claim 17, wherein the suitable lubricants are selected from calcium stearate, magnesium stearate, mineral oil, stearic acid and zinc stearate.
20. The pharmaceutical composition as claimed in claim 17, wherein the suitable
5 disintegrant are selected from starches such as corn starch, potato starch, pre-gelatinized and modified starches, sweeteners, clays, microcrystalline cellulose, carboxymethylcellulose, alginates, sodium starch glycolate, gums, guar, locust bean, karaya, pectin, tragacanth.
21. The pharmaceutical composition as claimed in claim 17, wherein the suitable wetting
10 agent are selected from poloxamers, gelatin, casein, Glycerol mono-oleate, lecithin (phosphatides), gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, sodium lauryl sulphate, sodium dodecyl sulfate, salts of bile acids, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives,
15 polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxy methylcellulose, sodium methyl cellulose, hydroxyethyl cellulose, hydroxylpropyl cellulose, hydroxy propyl methyl cellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, and poly vinyl pyrrolidone.
22. The composition as claimed in any claim 7-21 which is formulated in tablet or capsule
20 forms.
23. The composition as claimed in any claim 7-22, wherein the pH is maintained in the range of 6 to 10.
24. A pharmaceutical topical ophthalmic composition comprising: the pharmaceutically
25 active substance of Formula (I); for use in the prevention, delay of progression, or treatment of a disease or condition related with disorders of the eye.

25. The pharmaceutical composition as claimed in claim 24, wherein the concentration of the active substance of Formula (I) ranges between 1 µg/mL and 40 mg/mL, and wherein the composition is an isotonic aqueous solution, a poly(vinyl alcohol) aqueous solution, or mixtures thereof of pH between 3 and 8.
- 5 26. The pharmaceutical composition as claimed in claim 25, wherein the concentration ranges between 1 µg/mL and 10 mg/mL.
27. The pharmaceutical composition as claimed in claim 24, wherein the ophthalmic composition further comprises a preservative.
- 10 28. The pharmaceutical composition as claimed in claim 27, wherein the preservative is selected from the group consisting of benzalkonium chloride, benzoic acid, alkyl parabens, alkyl benzoates, chlorobutanol, chlorocresol, cetyl alcohols, fatty alcohols, hexadecyl alcohol, organometallic compounds of mercury, mercury acetate, phenylmercury nitrate or borate, diazolidinyl urea, diisopropyl adipate, dimethyl polysiloxane, salts of EDTA, vitamin E and mixtures thereof.
- 15 29. The pharmaceutical composition as claimed in claim 24, wherein the ophthalmic composition further comprises an agent that increases permeability of the active substance of Formula (I).
- 20 30. The pharmaceutical composition as claimed in claim 29, wherein the agent that increases permeability is selected from the group consisting of benzalkonium chloride, saponins, fatty acids, polyoxyethylene fatty ethers, alkyl esters of fatty acids, pyrrolidones, polyvinylpyrrolidone, pyruvic acids, pyroglutamic acids, and mixtures thereof.
- 25 31. The pharmaceutical composition as claimed in claim 24, wherein the active substance of Formula (I) is incorporated in liposomes, mixed liposomes, niosomes, ethosomes, nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, micelles, mixed micelles of surfactants, surfactant-phospholipid mixed micelles, nanospheres, lipospheres and/or nanocapsules.

32. A method for the prevention, delay of progression or treatment of a disease or condition which is related with disorders of the eye comprising administration of a therapeutically effective amount of compound of formula (1) or its pharmaceutical composition to a subject in need of such treatment.

5 33. A method for the prevention, delay of progression or treatment of a disease or which is related with disorders of the eye which is selected from ocular inflammation, corneal inflammation, diabetic retinopathy (DR), diabetic macular edema, macular degeneration, uveitis, retinal inflammation, retinal vascular leakage, retinal neovascularization, cancer, and other inflammatory and neovascular, comprising administration of a therapeutically
10 effective amount of compound of formula (1) as claimed in claim 32 to a subject in need of such treatment.

34. Synergistic composition comprising compound of formula (I) or pharmaceutically acceptable salt thereof and second therapeutic agent selected from the group consisting of: bevacizumab, ranibizumab, triamcinolone acetonide, ganciclovir, foscarnet,
15 vancomycin, ceftazidime, amikacin, amphotericin B, dexamethasone, ketorolac tromethamine, ketorolac tromethamine, naphazoline, lidocaine hydrochloride, pemirolast potassium, brimonidine, loteprednol etabonate, azelastine hydrochloride, azithromycin, bepotastine besilate, besifloxacin, levobetaxolol hydrochloride, dorzolamide hydrochloride - timolol maleate, difluprednate, aflibercept, loteprednol
20 etabonate, bimatoprost, pegaptanib, ofloxacin, naphazoline alone and with pheniramine, dexamethazone, levofloxacin, unoprostone isopropyl, cyclosporine pilocarpine hydrochloride, travoprost, valganciclovir HCl, trifluridine, cidofovir, verteporfm, fomivirsen, ketotifen, tafluprost, ganciclovir, gatifloxacin and suitable combinations thereof.

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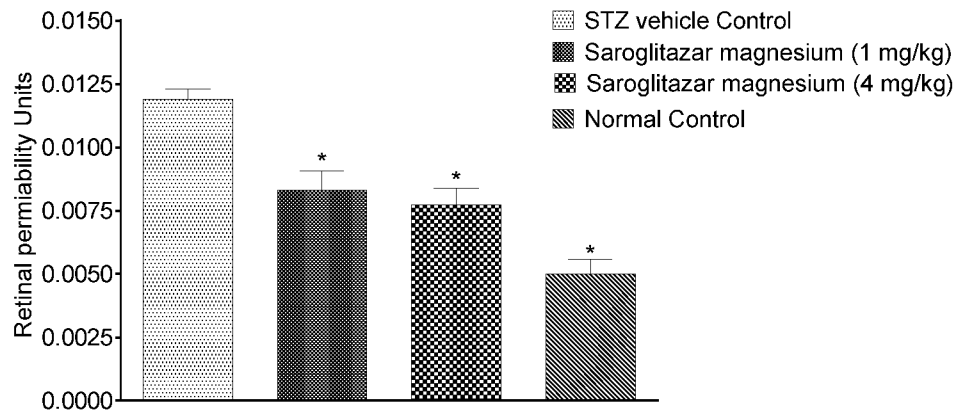


Figure 1

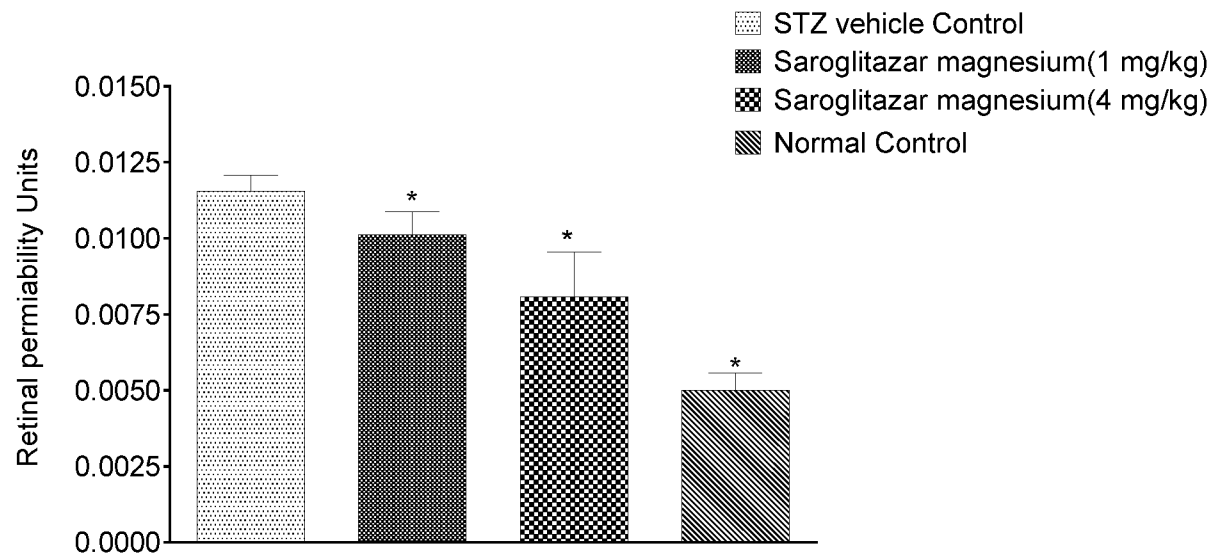


Figure 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2016/057091

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/40 A61K45/06 A61P3/10
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 A61P

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, CHEM ABS Data, EMBASE, 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	RAJENDRAKUMAR H. JANI ET AL: "A Multicenter, Prospective, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Saroglitazar 2 and 4mg 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 the whole document ----- -/--	1,2,4-33



Further documents are listed in the continuation of Box C.



See patent family annex.

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

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"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

27 February 2017

Date of mailing of the international search report

03/03/2017

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2016/057091

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ARUN SHARMA ET AL: "Saroglitazar, a novel cardiometabolic agent for diabetic dyslipidemia - A Review", JOURNAL OF YOUNG PHARMACISTS, vol. 7, no. 1, 23 December 2014 (2014-12-23), pages 2-6, XP055345058, India ISSN: 0975-1483, DOI: 10.5530/jyp.2015.1.2 page 4, left-hand column, paragraph 3 - last paragraph -----	1,2,4-33
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 page 191, right-hand column, paragraph 2 - page 195, left-hand column, last paragraph -----	1,2,4-33
X	WO 2013/049621 A1 (UNIV OKLAHOMA [US]) 4 April 2013 (2013-04-04) cited in the application abstract page 45, paragraph 2 - page 47, paragraph 1; claims 1,3,8,10-24 -----	7-34
X	EP 0 979 652 A1 (R TECH UENO LTD [JP]) 16 February 2000 (2000-02-16) the whole document -----	34
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2016/057091

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