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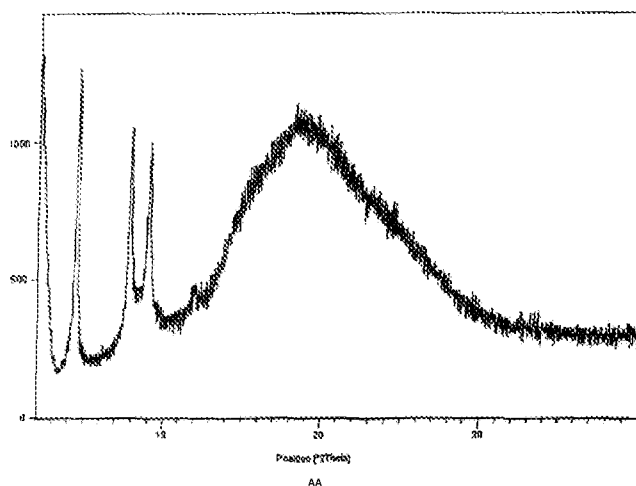
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[Continued on next page]

(54) Title: PYRROLE COMPOUND, COMPOSITIONS AND PROCESS FOR PREPARATION THEREOF



(57) Abstract: The present invention relates to compositions comprising saroglitazar magnesium wherein the saroglitazar magnesium has a purity of greater than or equal to 99% by weight, and dimer compound of Formula (IV) present in an amount relative to saroglitazar magnesium less than about 0.3% by weight by area percentage of HPLC. The present invention also related to the process for the preparation thereof and pharmaceutical compositions comprising the same.



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PYRROLE COMPOUND, COMPOSITIONS AND PROCESS FOR PREPARATION THEREOF

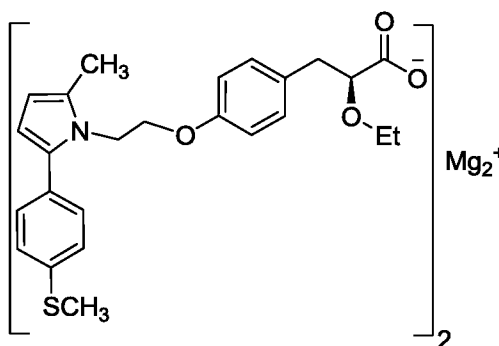
FIELD OF THE INVENTION

The present invention relates to pyrrole compound, compositions and process for the preparation thereof. In particular, the invention relates to saroglitazar magnesium, compositions and process for the preparation of saroglitazar magnesium.

BACKGROUND OF THE INVENTION

The following discussion of the prior art is intended to present the invention in an appropriate technical context and allow its significance to be properly appreciated. Unless clearly indicated to the contrary, however, reference to any prior art in this specification should be construed as an admission that such art is widely known or forms part of common general knowledge in the field.

Pyrrole derivative of present invention is chemically 2-ethoxy-3-(4-(2-(2-methyl-5-(4-(methylthio)phenyl)-1H-pyrrol-1-yl)ethoxy)phenyl)propanoate, which may be optically active or racemic and its pharmaceutically acceptable salts, hydrates, solvates, polymorphs or intermediates thereof. The INN name for pyrrole derivative is Saroglitazar® which is marketed as its magnesium salt of Formula (I), having below chemical structure.



(I)

The compound of Formula (I) lower or modulate triglyceride levels and/or cholesterol levels and/or lower density lipoproteins (LDL) and raise HDL plasma levels and hence are useful in combating different medical conditions, where such lowering (and raising) is beneficial. Thus, it could be used in the treatment and/or prophylaxis of obesity, hyperlipidemia, hypercholesteremia, hypertension, atherosclerotic disease events, vascular

restenosis, diabetes and many other related conditions. The compound of Formula (I) are useful to prevent or reduce the risk of developing atherosclerosis, which leads to diseases and conditions selected from arteriosclerotic cardiovascular diseases, stroke, coronary heart diseases, cerebrovascular diseases, peripheral vessel diseases and related disorders.

- 5 U.S. Patent No. 6,987,123 B2 discloses novel heterocyclic compounds, their preparation, pharmaceutical compositions containing them and their use in medicine. The patent discloses different pathways for the synthesis of pyrrole derivatives.

U.S. Patent Nos. 7,041,837 B2, 7,323,491 B2, 8,110,598 B2, 8,212,057 B2 disclose different pyrrole derivatives and their intermediates.

- 10 International (PCT) Publication No. WO 2012/104869 provides the use of compound of Formula (I) for the treatment of lipodystrophy.

International (PCT) Publication No. WO 2014/195967 discloses process for the preparation of saroglitazar and its pharmaceutically acceptable salts thereof.

- 15 International (PCT) Publication No. WO 2015/029066 discloses polymorphic form of saroglitazar free acid and its pharmaceutically acceptable salts thereof.

International (PCT) Publication No. WO 2015/033357 discloses an improved process for the preparation of saroglitazar magnesium.

- The different physical properties exhibited by polymorphs affect important pharmaceutical parameters selected from storage, stability, compressibility, density and dissolution rates (important in determining bioavailability). Stability differences may result from changes in chemical reactivity (e.g., differential hydrolysis or oxidation, such that a dosage form discolors more rapidly when comprised of one polymorph than when comprised of another polymorph), mechanical changes (e.g., tablets crumble on storage as a kinetically favored crystalline form converts to thermodynamically more stable crystalline form) or both (e.g., 25 tablets of one polymorph are more susceptible to breakdown at high humidity). Solubility differences between polymorphs may, in extreme situations, result in transitions to crystalline forms that lack potency or are toxic. In addition, the physical properties of the crystalline form to that of an amorphous form may be important in pharmaceutical processing. For example, an amorphous form may provide better bioavailability than the 30 crystalline form.

Therefore, it may be desirable to have an amorphous form of drugs with high purity to meet the regulatory requirements and also highly reproducible processes for their preparation.

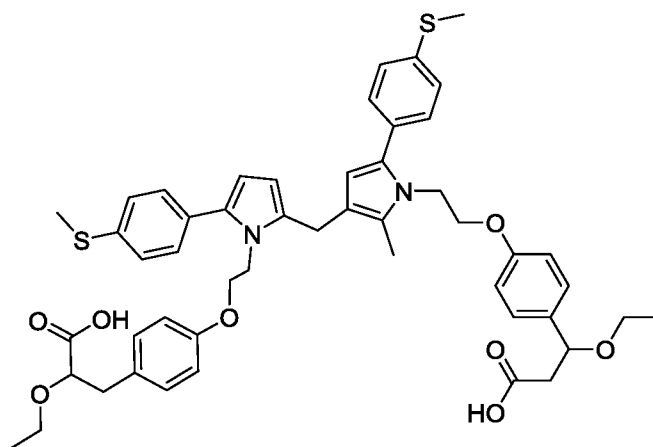
In view of the above, it is therefore, desirable to provide an efficient, more economical, less hazardous and eco-friendly process for the preparation of saroglitazar magnesium having high purity. However, the present invention provides a process for the preparation of saroglitazar magnesium and compositions thereof suitable for development of finished formulations having high purity.

SUMMARY OF THE INVENTION

The present invention features saroglitazar magnesium, compositions and process for its preparation. The compositions of saroglitazar magnesium are useful in the treatment and conditions, including but not limited to prophylaxis of obesity, hyperlipidemia, hypercholesteremia, hypertension, atherosclerotic disease events, vascular restenosis, diabetes and to prevent or reduce the risk of developing atherosclerosis, which leads to diseases and conditions selected from arteriosclerotic cardiovascular diseases, stroke, coronary heart diseases, cerebrovascular diseases, peripheral vessel diseases and related disorders.

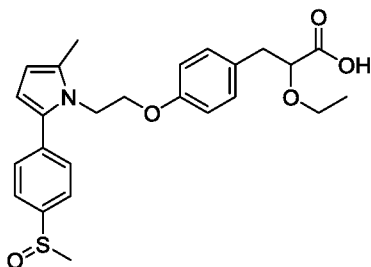
In one general aspect there is provided a composition comprising saroglitazar magnesium and a dimer compound of Formula (IV).

In one embodiment, the dimer compound comprises the structure of Formula (IV),



In another general aspect there is provided a composition comprising saroglitazar magnesium and a sulfoxide compound of Formula (V).

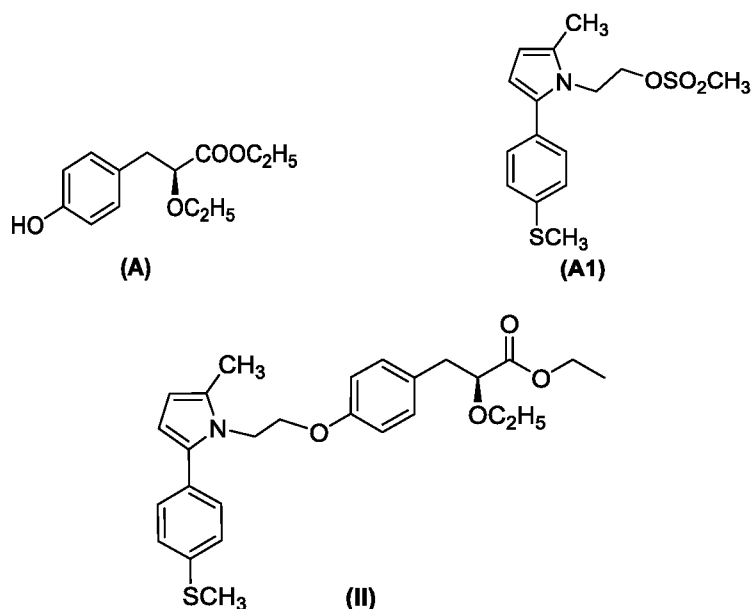
In second embodiment, the sulfoxide compound comprises the structure of Formula (V),



In another general aspect there is provided a pharmaceutical composition of saroglitzar magnesium of the present invention.

- 5 In another general aspect there is provided a process for the preparation of substantially pure saroglitzar magnesium, the process comprising:

(a) reacting a hydroxy compound (A) with a mesylate compound (A1) in one or more solvents in the presence of a base to obtain an alkoxy ester compound of Formula (II);



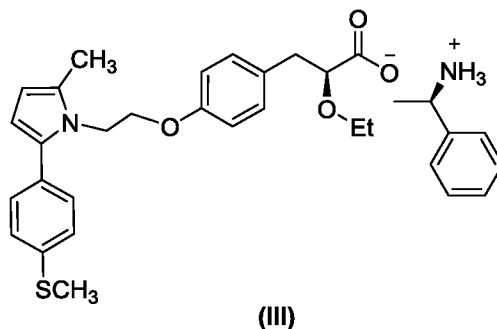
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(b) hydrolyzing the alkoxy ester compound of Formula (II) with a base in one or more solvents at a lower temperature to obtain a reaction mixture;

(c) optionally, washing the reaction mixture with one or more solvents to obtain an aqueous layer;

- 15 (d) treating the aqueous layer with one or more solvents and adjusting the pH 2.0 to 6.0;

- (e) extracting the aqueous layer with one or more solvents to obtain an organic layer;
- (f) treating the organic layer with S-(-)- α -methylbenzyl amine to obtain saroglitasar S-(-)- α -methylbenzyl amine (SMBA) salt of Formula (III);



- 5 (g) purifying the saroglitasar SMBA salt with one or more solvents to obtain pure saroglitasar SMBA salt; and
- (h) treating the pure saroglitasar SMBA salt with magnesium source to obtain the substantially pure saroglitasar magnesium.

The details of one or more embodiments of the invention are set forth in the accompanying
 10 description.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 discloses the X-ray diffractogram (XRD) of substantially pure saroglitasar magnesium as per example-1.

DETAILED DESCRIPTION OF THE INVENTION

- 15 The above and other objects of the present invention are achieved by the process of the present invention, which leads to saroglitasar magnesium and compositions thereof suitable for pharmaceutical use. The invention provides substantially pure saroglitasar magnesium suitable for development of finished formulations, which exhibit better control of impurities and stability under various stress conditions.
- 20 Optionally, the solution, prior to any solids formation, can be filtered to remove any undissolved solids, solid impurities prior to removal of the solvent. Any filtration system and filtration techniques known in the art can be used.

All ranges recited herein include the endpoints, including those that recite a range “between” two values. Terms such as “about”, “generally”, “substantially,” and the like are to be construed as modifying a term or value such that it is not an absolute. This includes, at very least, the degree of expected experimental error, technique error and instrument error for a given technique used to measure a value.

The term “substantially pure” herein means saroglitazar magnesium has a purity of greater than or equal to 99% by weight, and dimer compound of Formula (IV) present in an amount relative to saroglitazar magnesium less than about 0.3% or sulfoxide compound of Formula (V) present in an amount relative to saroglitazar magnesium less than about 0.2% by area percentage of HPLC relative to saroglitazar magnesium. In particular, the saroglitazar magnesium comprises of one or more impurities within the permissible ICH limits suitable for pharmaceutical preparations. For example, but not limited to less than 0.15%, particularly less than 0.1% or more particularly less than 0.05% when measured by area percentage of HPLC relative to saroglitazar magnesium.

As used herein, the term “solution” or “reaction mixture” does not limit to a clear solution only and includes any hazy or opaque mass obtained.

As used herein, the term “obtaining” means isolating the saroglitazar magnesium by way of filtration, filtration under vacuum, centrifugation, decantation. The product obtained may be further or additionally dried to achieve the desired moisture values. For example, the product may be dried in a tray drier, dried under vacuum and/or in a Fluid Bed Drier.

The term “composition” used herein means a physical mixture of two or more components.

As used herein, the term “mean particle size” (also used interchangeably with “VMD” for “volume mean diameter”) equal to or greater than a given diameter or being within a given particle size range means that the average of all saroglitazar magnesium particles in the sample have an estimated volume, based on an assumption of spherical shape, greater than or equal to the volume calculated for a spherical particle with a diameter equal to the given diameter as determined by laser diffraction in Malvern Master Sizer 2000 equipment or its equivalent.

The term “pharmaceutically acceptable” means that which is useful in preparing a pharmaceutical composition that is generally non-toxic and is not biologically undesirable, and includes that which is acceptable for veterinary use and/or human pharmaceutical use.

The term "pharmaceutical composition" is intended to encompass a drug product including the active ingredient(s), pharmaceutically acceptable excipients that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients. Accordingly, the pharmaceutical compositions encompass any composition made by admixing the active ingredient, active ingredient dispersion or composite, additional active ingredient(s), and pharmaceutically acceptable excipients.

The terms herein below are interchangeable and used in the description.

"DMF" refers to N,N-dimethylformamide.

10 "DMAC" refers to N,N-dimethylacetamide.

"DMSO" refers to N,N-dimethylsulfoxide.

"NMP" refers to N-methylpyrrolidone.

"THF" refers to tetrahydrofuran.

"MTBE" refers to methyl tert-butyl ether.

15 "TEA" refers to triethylamine.

"TBA" refers to tert-butyl amine.

"DIPA" refers to diisopropyl amine.

"DIPEA" refers to diisopropyl ethylamine.

"DBU" refers to 1,8-diazabicyclo[5.4.0]undec-7-ene.

20 "DABCO" refers to 1,4-diazabicyclo[2.2.2]octane.

"DBN" refers to 1,5-Diazabicyclo[4.3.0]non-5-ene.

"SMBA" refers to S-(-)- α -methylbenzyl amine.

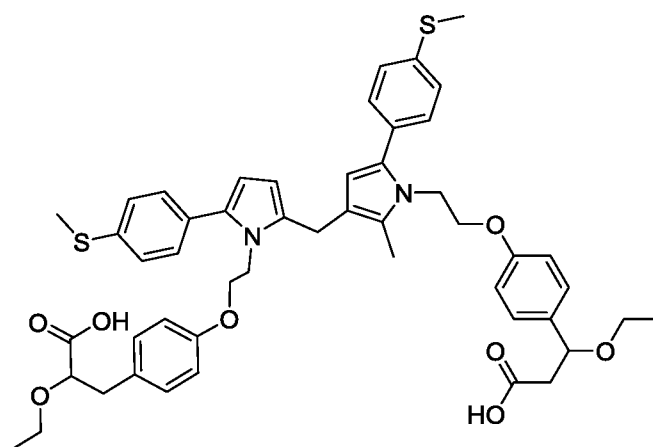
"RRT" refers to relative retention time.

"HPLC" refers to high performance liquid chromatography.

In one general aspect there is provided a composition comprising saroglitazar magnesium and a dimer compound of Formula (IV).

In general, the composition comprising saroglitazar magnesium wherein the saroglitazar magnesium has a purity of greater than or equal to 99% by weight, and dimer compound of
5 Formula (IV) present in an amount relative to saroglitazar magnesium less than about 0.3% by weight by area percentage of HPLC.

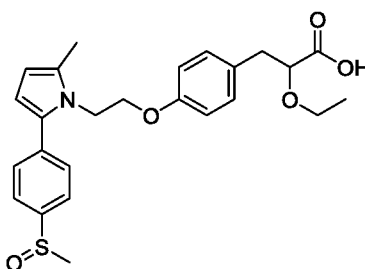
In one embodiment, the dimer compound comprises the structure of Formula (IV),



In another general aspect there is provided a composition of saroglitazar magnesium and a
10 sulfoxide compound of Formula (V).

In general, the composition comprising saroglitazar magnesium wherein the saroglitazar magnesium has a purity of greater than or equal to 99% by weight, and sulfoxide compound of Formula (V) present in an amount relative to saroglitazar magnesium less than about 0.2% by weight by area percentage of HPLC.

15 In second embodiment, the sulfoxide compound comprises the structure of Formula (V),



In another general aspect there is provided a composition comprising saroglitazar magnesium having a dimer compound (IV) present in an amount relative to saroglitazar

magnesium less than about 0.3% or sulfoxide compound (V), present in an amount relative to saroglitazar magnesium less than about 0.2% by weight by area percentage of HPLC.

In some embodiments, the saroglitazar magnesium comprises less than about 0.25% by weight, less than about 0.2% by weight, less than about 0.15% by weight or less than about 0.1% by weight of dimer compound of Formula (IV) relative to saroglitazar magnesium by area percentage of HPLC.

In some embodiments, the saroglitazar magnesium comprises less than about 0.15% by weight, less than about 0.1% by weight, less than about 0.05% by weight of sulfoxide compound of Formula (V) relative to saroglitazar magnesium by area percentage of HPLC.

In general, the composition comprising saroglitazar magnesium wherein the saroglitazar magnesium has a purity of greater than or equal to 99% by weight, and impurities at RRT 1.06, RRT 1.27, RRT 1.41 and RRT 1.52 present in an amount relative to saroglitazar magnesium less than about 0.15% by weight by area percentage of HPLC.

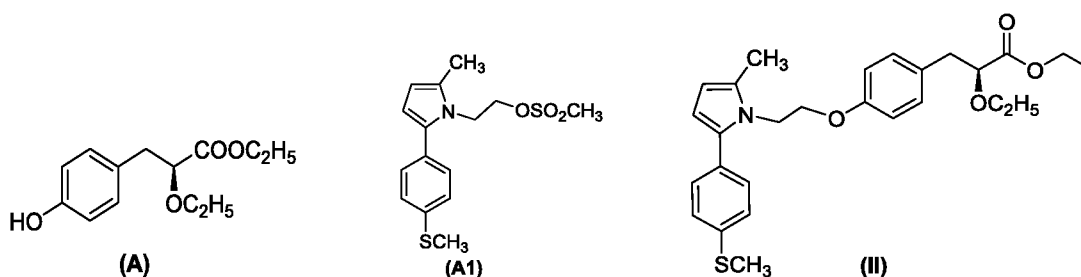
In general, the composition comprising one or more of impurities at RRT 1.06, RRT 1.27, RRT 1.41 and RRT 1.52 in an amount relative to saroglitazar magnesium less than about 0.1% by weight by area percentage of HPLC.

In another general aspect, there is provided a dimer compound of Formula (IV).

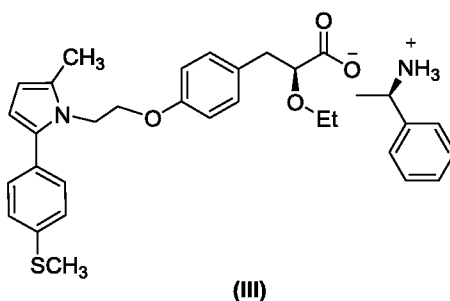
In another general aspect, there is provided a sulfoxide compound of Formula (V).

In another general aspect there is provided a process for the preparation of substantially pure saroglitazar magnesium, the process comprising:

(a) reacting a hydroxy compound (A) with a mesylate compound (A1) in one or more solvents in the presence of a base to obtain an alkoxy ester compound of Formula (II),



- (b) hydrolyzing the alkoxy ester compound of Formula (II) with a base in one or more solvents at a lower temperature to obtain a reaction mixture;
- (c) optionally, washing the reaction mixture with one or more solvents to obtain an aqueous layer;
- 5 (d) treating the aqueous layer with one or more solvents and adjusting the pH 2.0 to 6.0;
- (e) extracting the aqueous layer with one or more solvents to obtain an organic layer;
- (f) treating the organic layer with S-(-)- α -methylbenzyl amine to obtain saroglitazar S-(-)- α -Methyl benzyl amine (SMBA) salt of Formula (III);



- 10 (g) purifying the saroglitazar SMBA salt with one or more solvents to obtain pure saroglitazar SMBA salt; and
- (h) treating the pure saroglitazar SMBA salt with magnesium source to obtain substantially pure saroglitazar magnesium.

In general, the solvent comprises one or more of alcohols selected from methanol, ethanol, isopropanol, 2-propanol, 1-butanol, and t-butyl alcohol; ketones selected from acetone, butanone, and methyl isobutyl ketone; esters selected from ethyl acetate, isopropyl acetate, t-butyl acetate, and isobutyl acetate; chlorinated hydrocarbons selected from methylene dichloride, ethylene dichloride, and chlorobenzene; hydrocarbons selected from pentane, hexane, heptane, and cyclohexane; ethers selected from tetrahydrofuran, 1,4-dioxane, diisopropyl ether, diethyl ether, and methyl tert-butyl ether; or mixture thereof. In particular, the mixture of cyclohexane and tetrahydrofuran may be used.

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In general, the base comprises one or more of sodium hydroxide, potassium hydroxide, lithium hydroxide, calcium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydride, potassium hydride, potassium tert-

butoxide, and sodium pentoxide. In particular, potassium carbonate is used. The base may be preferably anhydrous.

Optionally, the reaction may be catalyzed by a phase transfer catalyst. The phase transfer catalyst comprises one or more of tetrabutyl ammonium bromide (TBAB), tetrabutyl ammonium iodide (TBAI), benzyl triethyl ammonium chloride (TEBAC), polyethylene glycol (PEG-200, 400, 600, 800, 1000), crown ethers like 12-crown-4, 15-crown-5, 18-crown-6, dibenzo-18-crown-6, and diaza-18-crown-6. In particular, the phase transfer catalyst may be 18-crown-6.

In general, the reaction of a hydroxy compound (A) and a mesylate compound (A1) may be performed under heating at 35°C to about reflux temperature of solvents. In particular, the reaction may be heated at 75°C to 85°C till the completion of the reaction. The reaction may be heated for about 35 hours to about 50 hours. Particularly for about 48 hours.

In another general aspect the obtained alkoxy ester (II) may be preceded further without isolating. Therefore, the alkoxy ester (II) may be further hydrolyzed *in-situ*.

The base for hydrolyzing the alkoxy ester (II) comprises one or more of sodium hydroxide, potassium hydroxide, lithium hydroxide, calcium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydride, potassium hydride, potassium tert-butoxide, and sodium pentoxide. In particular, sodium hydroxide may be used.

In general, the hydrolysis of the alkoxy ester at above room temperature results in increase of dimer impurity and sulfoxide compounds. Therefore, the hydrolysis of alkoxy ester is particular performed below 25°C, more particular from 18°C to 22°C to have reduced level of dimer compound and sulfoxide compound.

In general, the reaction mixture after hydrolysis of alkoxy ester compound of Formula (II) may be washed with one or more solvents. The solvent comprises one or more of water, methanol, ethanol, isopropanol, 2-propanol, 1-butanol, t-butyl alcohol, acetone, butanone, methyl isobutyl ketone, ethyl acetate, isopropyl acetate, isobutyl acetate, methyl t-butyl ether, t-butyl acetate, n-butyl acetate, methylene dichloride, ethylene dichloride, and chlorobenzene, or mixture thereof. In particular, the mixture of water and methyl t-butyl ether may be used.

In general, the separated aqueous layer may be treated with one or more solvents and pH is adjusted 2.0 to 6.0 with hydrochloride acid solution. The pH is particular adjusted from about 5.0 to 6.0 and the organic layer is separated. In general, the solvent comprises one or more of methanol, ethanol, isopropanol, 2-propanol, 1-butanol, t-butyl alcohol, acetone, butanone, methyl isobutyl ketone, ethyl acetate, isopropyl acetate, isobutyl acetate, methyl t-butyl ether, t-butyl acetate, n-butyl acetate, methylene dichloride, ethylene dichloride, and chlorobenzene, or mixture thereof. In particular methyl t-butyl ether may be used.

The separated organic layer may be treated with S-(-)- α -methylbenzyl amine and stirred for 1-3 hours at 10° C - 35° C to obtain saroglitazar SMBA salt. Particularly for about 2 hours at 20° C. Further, the reaction mass is filtered, washed with one or more solvent and dried to obtain to obtain saroglitazar S-(-)- α -methylbenzyl amine salt. The solvent comprises one or more of ethyl acetate, isopropyl acetate, isobutyl acetate, methyl t-butyl ether, t-butyl acetate, n-butyl acetate, methylene dichloride, ethylene dichloride, and chlorobenzene, or mixture thereof. In particular, methyl t-butyl ether may be used.

The saroglitazar SMBA salt may be purified with one or more solvents at 10° C - 30° C to obtain pure saroglitazar SMBA salt. Particularly for about 2 hours at 20° C. The solvent comprises one or more of water, methanol, ethanol, isopropanol, 2-propanol, 1-butanol, t-butyl alcohol, acetone, butanone, methyl isobutyl ketone, ethyl acetate, isopropyl acetate, isobutyl acetate, methyl t-butyl ether, t-butyl acetate, n-butyl acetate, methylene dichloride, ethylene dichloride, tetrahydrofuran and chlorobenzene, or mixture thereof. In particular mixture of tetrahydrofuran and water may be used.

The purification process mentioned above may be repeated to obtain pure saroglitazar SMBA salt.

In general, the pure saroglitazar SMBA salt Formula (III) may be treated with one or more solvents. The solvent comprises one or more of water, methanol, ethanol, isopropanol, 2-propanol, 1-butanol, t-butyl alcohol, acetone, butanone, methyl isobutyl ketone, ethyl acetate, isopropyl acetate, isobutyl acetate, t-butyl acetate, n-butyl acetate, methylene dichloride, ethylene dichloride, and chlorobenzene, or mixture thereof. In particular, isopropyl acetate may be used.

The separated aqueous layer may be treated with a magnesium source to obtain saroglitazar magnesium. In general, the magnesium source comprises one or more of

magnesium hydroxide, magnesium methoxide, magnesium acetate, magnesium chloride, and magnesium metal. In particular, the magnesium source may be magnesium acetate tetrahydrate in the form of its solution in water.

5 In general, the reaction mixture thus obtained may be extracted with one or more of solvents. The solvent comprises one or more of ethyl acetate, isopropyl acetate, isobutyl acetate, t-butyl acetate, n-butyl acetate, methylene dichloride, ethylene dichloride, and chlorobenzene, or mixture thereof. In particular, methylene dichloride may be used.

10 In general, the methylene dichloride may be removed by distillation under vacuum to obtain reaction mass, which is further treated with one or more solvents to obtain substantially pure saroglitazar magnesium. The solvent comprises one or more of water, methanol, ethanol, isopropanol, 2-propanol, 1-butanol, t-butyl alcohol, acetone, butanone, methyl isobutyl ketone, ethyl acetate, isopropyl acetate, isobutyl acetate, t-butyl acetate, n-butyl acetate, methylene dichloride, ethylene dichloride, n-heptane and chlorobenzene, or mixture thereof. In particular, n-butyl acetate and n-heptane may be used.

15 In general, the substantially pure saroglitazar magnesium is amorphous characterized by x-ray powder diffraction pattern substantially as depicted in FIG.1.

The product thus obtained may be dried under vacuum tray drier, sieved and milled to obtain suitable particle size range. The milled product may be further dried till constant weight is obtained to obtain the substantially pure saroglitazar magnesium.

20 In general, the product may be sieved through a 0.5 mm sieve followed by milling. Examples of such milling include various makes of ball mills, roller mills, gyratory mills, multi-mills, and Jet-mills. Particularly mill such as Micros Super Fine Mill (available from Nara Machinery Co. Ltd or Tokyo, Japan), Multi-Mill Sr. No. G. 1.132 (available from Grooves International Pharmaceutical & Chemical Machinery), Jet-Mill from Midas
25 Micronizer M-100 Aerosol (No. 154/07-08 (available from microtech Engineering Company) or a common mixer grinder can be used. Alternatively, other commercially available milling machine can be used.

In another general aspect there is provided substantially pure saroglitazar magnesium having a purity of at least about 99% by area percentage of HPLC. In particular,
30 saroglitazar magnesium has a purity of at least about 99.5% by area percentage of HPLC.

In another general aspect there is provided substantially pure saroglitazar magnesium having a chiral purity of at least about 99% by area percentage of HPLC. In particular, saroglitazar magnesium having a chiral purity of at least about 99.5%, more particularly, a purity of at least about 99.9%, further more particularly, a purity of at least about 99.9% by area percentage of HPLC.

In another general aspect there is provided saroglitazar SMBA salt having a purity of at least about 99% by area percentage of HPLC. In particular, saroglitazar SMBA salt having a purity of at least about 99%, more particularly, a purity of at least about 99.5%, further more particularly, a purity of at least about 99.7%, by area percentage of HPLC.

10 In another general aspect there is provided a composition comprising saroglitazar SMBA salt wherein the saroglitazar SMBA salt has a purity of greater than or equal to 99% by weight, and dimer compound of Formula (IV) present in an amount relative to saroglitazar magnesium less than about 0.3% by weight by area percentage of HPLC.

15 In another general aspect there is provided a composition comprising saroglitazar SMBA salt wherein the saroglitazar SMBA salt has a purity of greater than or equal to 99% by weight, and sulfoxide compound of Formula (V) present in an amount relative to saroglitazar magnesium less than about 0.2% by weight by area percentage of HPLC.

In general, the composition comprising saroglitazar SMBA salt wherein the saroglitazar SMBA has a purity of greater than or equal to 99% by weight, and impurities at RRT 1.06, RRT 1.27, RRT 1.41 and RRT 1.52 present in an amount relative to saroglitazar SMBA less than about 0.1% by weight by area percentage of HPLC.

25 In general, the composition comprising saroglitazar SMBA salt wherein the saroglitazar SMBA has a purity of greater than or equal to 99% by weight, and impurities at RRT 1.06, RRT 1.27, RRT 1.41 and RRT 1.52 present in an amount relative to saroglitazar SMBA less than about 0.05% by weight by area percentage of HPLC.

Table-1: Summary of HPLC analysis of Saroglitazar SMBA salt

	Related substances by HPLC (%)						
Sample	HPLC Purity	Sulfoxide impurity	Dimer impurity	RRT 1.06	RRT 1.27	RRT 1.41	RRT 1.52
	NLT 98.0%	NMT 0.5%	NMT 0.5%	NMT 0.10%	NMT 0.10%	NMT 0.10%	NMT 0.10%
Saroglitazar SMBA salt before purification	99.43	0.03	0.13	0.07	0.07	0.13	0.10
	99.46	0.03	0.13	0.07	0.07	0.13	0.10
	99.50	0.03	0.13	0.06	0.06	0.13	0.08
Saroglitazar SMBA salt after first purification	99.63	0.01	0.12	0.02	0.03	0.06	0.06
	99.67	0.01	0.12	0.03	0.04	0.07	0.06
	99.68	0.01	0.12	0.03	0.03	0.06	0.05
Saroglitazar SMBA salt pure	99.72	ND	0.11	ND	0.02	0.03	0.02
	99.74	ND	0.12	ND	0.02	0.03	0.02
	99.75	ND	0.11	ND	0.02	0.03	0.02

Table-2: Summary of HPLC analysis of Saroglitazar magnesium

	Related substances by HPLC (%)						
Sample	HPLC Purity	Sulfoxide impurity	Dimer impurity	RRT 1.06	RRT 1.27	RRT 1.41	RRT 1.52
	NLT 98.0%	NMT 0.5%	NMT 0.5%	NMT 0.10%	NMT 0.10%	NMT 0.10%	NMT 0.10%
Saroglitazar magnesium	99.65	0.01	0.15	0.01	0.01	0.04	0.03

In another general aspect the unknown impurities at specific RRT are characterized by their m/z values. In particular the impurity at RRT 1.04 has m/z value of 875.3, RRT 1.25 has m/z value of 530.0, RRT 1.41 has m/z value of 640.2 and RRT 1.52 has m/z value of 438.2.

Powder X-ray Diffraction: X-ray powder diffraction spectrum was observed on a X-ray Powder diffractometer of make Rigaku or PANalytical or equivalent make having a Copper K α -radiation at a voltage of 40kV and 30mA. Approximately 150 mg sample was gently flattened on a quartz plate without further processing (e.g. Grinding and sieving) and scanned from 4° to 40° at 0.010° sampling width and 4.000° per minute.

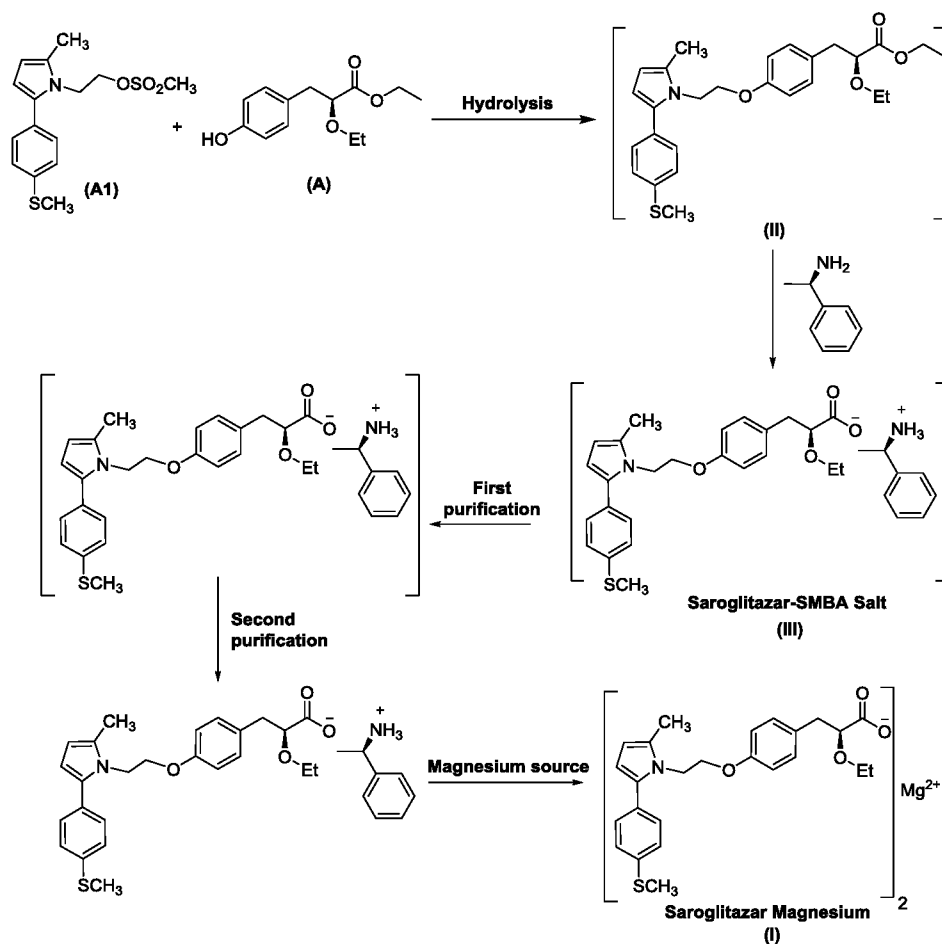
In another general aspect there is provided a pharmaceutical composition comprising saroglitazar magnesium and dimer compound of Formula (IV) together with one or more pharmaceutically acceptable excipients, diluents and carriers.

In another general aspect there is provided a pharmaceutical composition comprising saroglitazar magnesium and sulfoxide compound of Formula (V) together with one or more pharmaceutically acceptable excipients, diluents and carriers.

In another general aspect, there is provided a pharmaceutical composition comprising substantially pure saroglitazar magnesium having a mean particle size equal to or less than 100 μ m and one or more pharmaceutically acceptable excipients, diluents and carriers.

In general, the pharmaceutical compositions comprising saroglitazar magnesium of the invention may be prepared by using diluents or excipients such as fillers, bulking agents, binders, wetting agents, disintegrating agents, surface active agents, and lubricants. Various modes of administration of the pharmaceutical compositions of the invention can be selected depending on the therapeutic purpose, for example tablets, pills, powders, liquids, suspensions, emulsions, granules, capsules, suppositories, or injection preparations.

In another general aspect substantially pure saroglitazar magnesium may be prepared by reaction scheme-1, which is also within the scope of the present invention.



Scheme-1

Dosage

The effective amount of dose range of saroglitazar magnesium of Formula (I) of the present invention may be generally from 1 mg to 500 mg/day. The compound of Formula (I) may be administrated orally, intravenously, parentally or other forms of administration in the subject who is in need of treatment. Tablets, capsules, or other forms of presentation provided in discrete units may conveniently contain an amount of compound described herein which is effective at such dosage or as a multiple of the same, for instance, units containing 1 mg to 500 mg, in particular, 1 mg to 250 mg and more particularly 4 mg to 50 mg. The precise amount of compound prescribed to a patient will be the responsibility of the attendant physician. However, the dose employed will depend on a number of factors, including the age and sex of the patient, the precise disorder being treated, and its severity.

In another general aspect the saroglitazar magnesium and compositions described herein are useful for treatment of patient with a condition comprises one or more of prophylaxis of obesity, hyperlipidemia, hypercholesteremia, hypertension, atherosclerotic disease events, vascular restenosis, diabetes and to prevent or reduce the risk of developing

atherosclerosis, which leads to diseases and conditions selected from arteriosclerotic cardiovascular diseases, stroke, coronary heart diseases, cerebrovascular diseases, peripheral vessel diseases and related disorders comprising administering the pharmaceutical compositions of the present invention.

- 5 The present invention is further illustrated by the following examples which are provided merely to be exemplary of the invention and do not limit the scope of the invention. Certain modification and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Examples

10 **Example-1:**

Preparation of alkoxy ester compound

- In a 5 Liter three necked round bottom flask equipped with nitrogen atmosphere facility, mechanical stirrer, thermometer and an addition funnel, 2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (A) (100.0 g) and cyclohexane (1730.0 ml) were charged and reaction mixture was heated to 45° to 55°C. Potassium carbonate (58.0 g) was added and stirred for 30 min. methanesulfonic acid 2-[2-methyl-5-(4-methylsulfanyl-phenyl)-pyrrol-1-yl]-ethyl ester (A1) (150 g) and THF (265.0 ml) were added and heated to 75°C to 85°C for 48 hours. The reaction mixture was cooled to 25° to 35°C and water (1000.0 ml) was added and stirred for 15 min. The separated aqueous layer was treated with cyclohexane (200.0 ml) and stirred for 15 min. The organic layers were combined and washed with caustic solution (600.0 ml). The separated organic layer was washed with water (600.0 ml) and characoalized with (5.0 g) charcoal and stirred for 30 min and filtered. The filtrate was distilled to remove cyclohexane and the residue was collected (residue-A).

Example-2:

25 Preparation of saroglitazar SMBA salt:

- In a 250 mL three necked round bottom flask equipped with nitrogen atmosphere facility, mechanical stirrer, thermometer and an addition funnel, residue-A obtained in example-1 and ethanol (400 mL) were stirred for 15 min. Sodium hydroxide 20.14 g solution in water (200.0 ml) was added and the reaction mixture was stirred for 3 hours at 18-22°C. MTBE (500 mL) was added into reaction mixture and stirred for 20 minutes. The reaction mixture

was diluted with water (1800.0 ml) and stirred for 15 min. The separated aqueous layer was washed with MTBE (500 mL). The separated aqueous layer was diluted with MTBE (500 mL) and acidified with conc. HCl at adjust the pH 5-6. The separated aqueous layer was washed with MTBE. The combined organic layer was treated with (S)-(-)-methyl benzyl amine (61 g) and stirred for 1 hour at 25°C and another one hour at 10-15°C. The reaction mixture was filtered and washed with MTBE. The wet-cake was dried to obtain crude saroglitazar SMBA salt.

Purification of saroglitazar SMBA salt

In a 1 Liter three mL three necked round bottom flask equipped with nitrogen atmosphere facility, mechanical stirrer, thermometer and an addition funnel, THF (125 mL) and saroglitazar SMBA salt (100 g) obtained in example-2 were added at 25°C and stirred for 15 minutes. The reaction mixture was diluted with water (375 mL) stirred for 1 hour at 25°C and another 1 hour at 10-15°C. The reaction mixture was filtered and washed with water. The wet-cake was dried to obtain pure saroglitazar SMBA salt. Repeat the second purification of saroglitazar SMBA salt using the same process mention above.

Example-3:

Preparation of saroglitazar magnesium from saroglitazar SMBA salt:

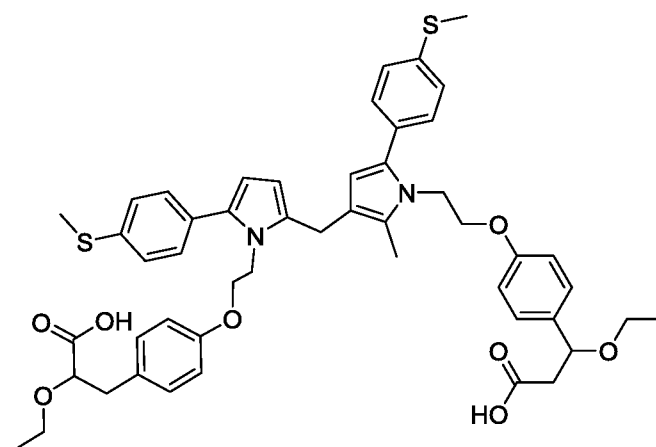
In a 250 mL three necked round bottom flask equipped with nitrogen atmosphere facility, mechanical stirrer, thermometer and an addition funnel, saroglitazar SMBA obtained in example-2 (100 g) and isopropyl acetate (400 mL) were added at 25°C. The reaction mixture was diluted with water (250 ml) and acidified with conc. HCl at adjust the pH 2-3 and stirred for 15 minutes at 25°C. The organic layer was washed with brine solution and stirred for 15 min. The separated organic layer was treated with water and NaOH solution and stirred for 15 minutes at 25°C. The separated aqueous layer was treated with magnesium acetate tetrahydrate (38.3 g) in water (100 mL) solution and stirred for 60 min. The reaction mixture was extracted with methylene dichloride (400 mL). The separated organic layer was washed with brine solution and stirred for 15 minutes at 25°C. The separated lower organic layer was treated with magnesium sulfate. The mixture was filtered and washed with MDC. N-butyl acetate was added to filtrate then MDC was distilled out under vacuum below 40 °C. The reaction mass was diluted with n-butyl acetate (30 ml). To the reaction mixture, n-heptane (900 mL) was added and stirred for 1

hour. The product was filtered and washed with n-heptane and dried in vacuum tray dryer at 25°C to 35°C for 3 hours. The product was sieved through 0.5 mm sieve and milled through jet-milled. The product was further dried in vacuum tray drier at 35°C to 45°C for 3 hours followed by drying at 55°C to 65°C at 12 hours to obtain amorphous saroglitazar magnesium (I). The compound is characterized by x-ray power diffraction (FIG.1).

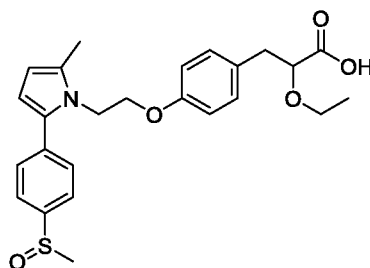
While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

We claim:

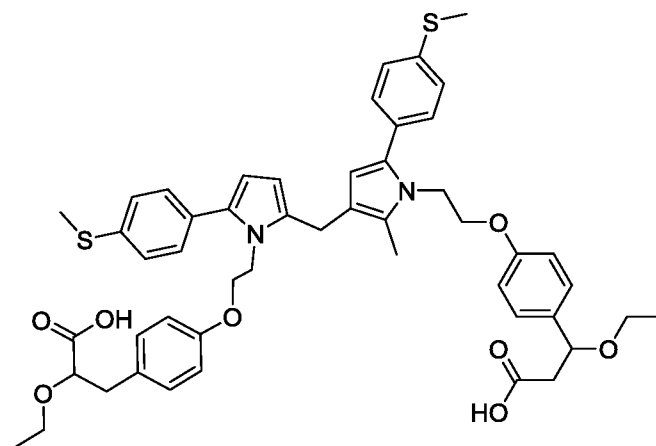
1. A composition comprising saroglitazar magnesium wherein the saroglitazar magnesium has a purity of greater than or equal to 99% by weight, and dimer compound of Formula (IV) present in an amount relative to saroglitazar magnesium less than about 0.3% by weight by area percentage of HPLC.
2. The composition according to claim 1, wherein the dimer compound comprises the structure of Formula (IV),



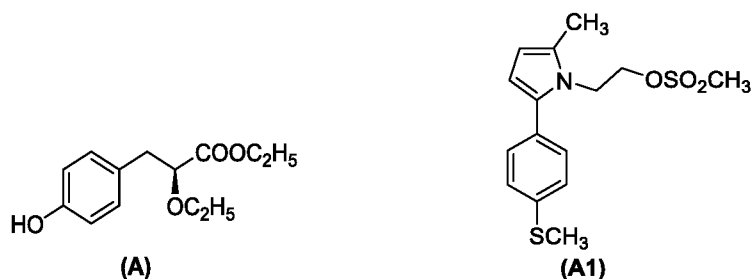
3. A composition comprising saroglitazar magnesium wherein the saroglitazar magnesium has a purity of greater than or equal to 99% by weight, and sulfoxide compound of Formula (V) present in an amount relative to saroglitazar magnesium less than about 0.2% by weight by area percentage of HPLC.
4. The composition according to claim 3, wherein the sulfoxide comprises the structure of Formula (V),

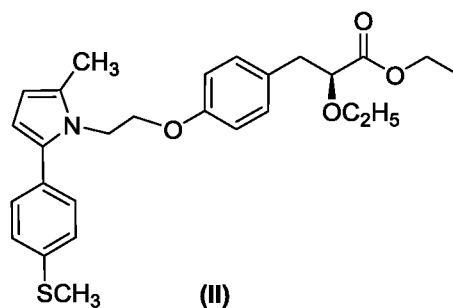


5. A dimer compound of Formula (IV),

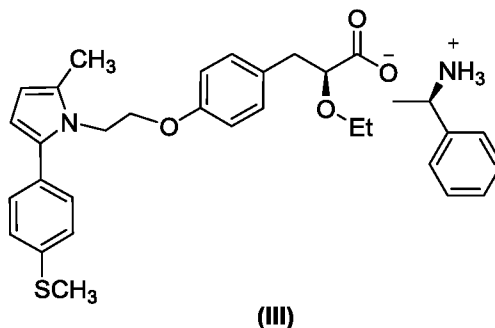


6. The composition according to claim 1 comprising sulfoxide compound of Formula (V) present in an amount relative to saroglitazar magnesium less than about 0.2% by weight by area percentage of HPLC.
7. The composition according to claim 6 further comprises one or more of impurities at RRT 1.06, RRT 1.27, RRT 1.41 and RRT 1.52 in an amount relative to saroglitazar magnesium less than about 0.15% by weight by area percentage of HPLC.
8. A pharmaceutical composition comprising saroglitazar magnesium according to claim 6.
9. A process for the preparation of substantially pure saroglitazar magnesium, the process comprising:
- (a) reacting a hydroxy compound (A) with a mesylate compound (A1) in one or more solvents in the presence of a base to obtain an alkoxy ester compound of Formula (II),





- (b) hydrolyzing the alkoxy ester compound of Formula (II) with a base in one or more solvents at a lower temperature to obtain a reaction mixture;
- (c) optionally, washing the reaction mixture with one or more solvents to obtain an aqueous layer;
- (d) treating the aqueous layer with one or more solvents and adjusting the pH 2.0 to 6.0;
- (e) extracting the aqueous layer with one or more solvents to obtain an organic layer;
- (f) treating the organic layer with S-(-)- α -methylbenzyl amine to obtain saroglitzazar S-(-)- α -methylbenzyl amine (SMBA) salt SMBA salt of Formula (III);



- (g) purifying the saroglitzazar SMBA salt with one or more solvents to obtain pure saroglitzazar SMBA salt; and
- (h) treating the pure saroglitzazar SMBA salt with magnesium source to obtain substantially pure saroglitzazar magnesium.

- 10 **10.** The process according to claim 9, wherein the solvent comprises one or more of alcohols selected from methanol, ethanol, isopropanol, 2-propanol, 1-butanol, and t-butyl alcohol; ketones selected from acetone, butanone, and methyl isobutyl ketone; esters selected from ethyl acetate, isopropyl acetate, t-butyl acetate, and isobutyl acetate; chlorinated hydrocarbons selected from methylene dichloride, ethylene

dichloride, and chlorobenzene; hydrocarbons selected from pentane, hexane, heptane, and cyclohexane; ethers selected from tetrahydrofuran, 1,4-dioxane, diisopropyl ether, diethyl ether, and methyl tert-butyl ether; or mixture thereof.

- 5 **11.** The process according to claim 9, wherein the base comprises one or more of sodium hydroxide, potassium hydroxide, lithium hydroxide, calcium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydride, potassium hydride, potassium tert-butoxide, and sodium pentoxide.
- 10 **12.** The process according to claim 9, wherein the solvent in step (c) comprises one or more of water, methanol, ethanol, isopropanol, 2-propanol, 1-butanol, t-butyl alcohol, acetone, butanone, methyl isobutyl ketone, ethyl acetate, isopropyl acetate, isobutyl acetate, methyl t-butyl ether, t-butyl acetate, n-butyl acetate, methylene dichloride, ethylene dichloride, and chlorobenzene, or mixture thereof.
- 15 **13.** The process according to claim 9, wherein the solvent in step (g) comprises one or more of water, methanol, ethanol, isopropanol, 2-propanol, 1-butanol, t-butyl alcohol, acetone, butanone, methyl isobutyl ketone, ethyl acetate, isopropyl acetate, isobutyl acetate, methyl t-butyl ether, t-butyl acetate, n-butyl acetate, methylene dichloride, ethylene dichloride, tetrahydrofuran and chlorobenzene, or mixture thereof.
- 20 **14.** The process according to claim 9, wherein the magnesium source in step (f) comprises one or more of magnesium hydroxide, magnesium methoxide, magnesium acetate, magnesium chloride, and magnesium metal.
- 15.** The process according to claim 9, wherein the substantially pure saroglitazar magnesium is amorphous form characterized by x-ray powder diffraction pattern substantially as depicted in FIG.1.
- 25 **16.** The process according to claim 9, wherein the saroglitazar SMBA salt has a purity of greater than or equal to 99% by weight, and dimer compound of Formula (IV) present in an amount relative to saroglitazar magnesium less than about 0.3% or sulfoxide compound of Formula (V) present in an amount relative to saroglitazar magnesium less than about 0.2% by weight by area percentage of HPLC.
- 30 **17.** The process according to claim 16, wherein the saroglitazar SMBA salt a purity of greater than or equal to 99% by weight, and impurities at RRT 1.06, RRT 1.27, RRT

1.41 and RRT 1.52 present in an amount relative to saroglitazar SMBA less than about 0.1% by weight by area percentage of HPLC.

5 **18.** A pharmaceutical composition comprising saroglitazar magnesium and dimer compound of Formula (IV) together with one or more pharmaceutically acceptable excipients, diluents and carriers.

19. A pharmaceutical composition comprising saroglitazar magnesium and sulfoxide compound of Formula (V) together with one or more pharmaceutically acceptable excipients, diluents and carriers.

10 **20.** A method for treating a condition comprising administering the pharmaceutical composition according to claim 8, wherein the condition comprises one or more of prophylaxis of obesity, hyperlipidemia, hypercholesteremia, hypertension, atherosclerotic disease events, vascular restenosis, diabetes and to prevent or reduce the risk of developing atherosclerosis, which leads to diseases and conditions selected from arteriosclerotic cardiovascular diseases, stroke, coronary heart diseases,
15 cerebrovascular diseases, peripheral vessel diseases and related disorders.

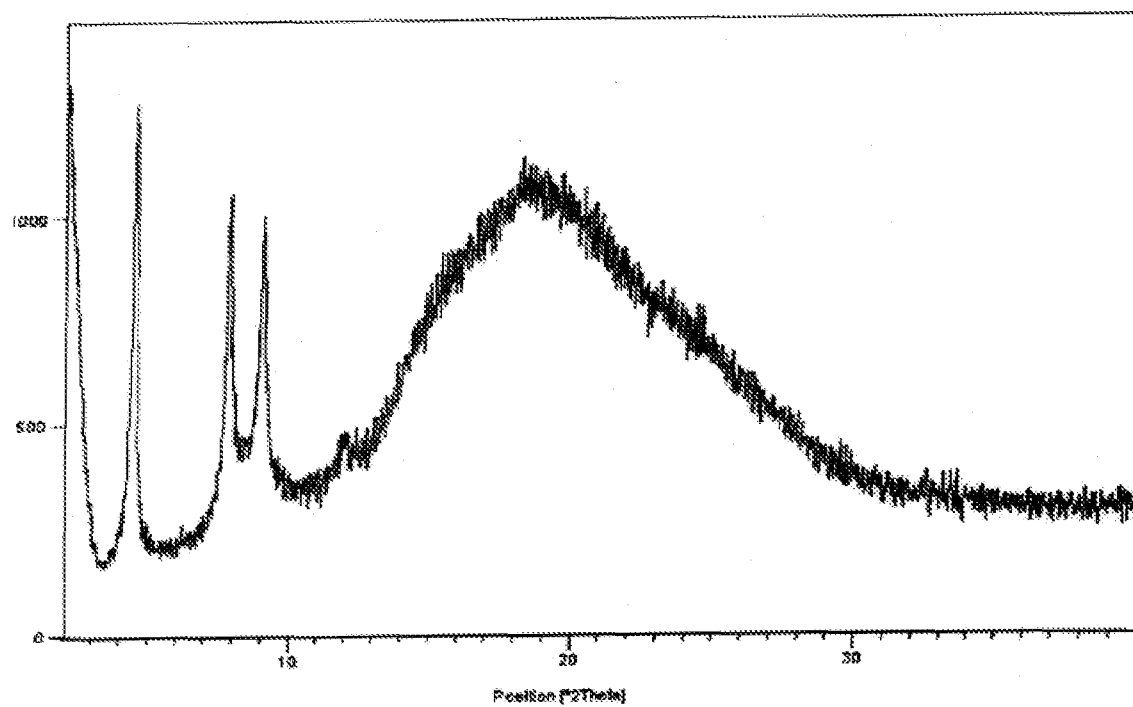


FIG. 1