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(54) Title: ALKANOIC ACIDS AND THEIR ESTERS AS ANTIDIABETIC AGENTS

(57) Abstract: The present invention relates to alkanoic acids and their derivatives, which have PPAR agonist activity, and hence can be used as antidiabetic compounds. Compounds disclosed herein can be used for the treatment of diabetes and diabetes-associated complications, for the treatment of diseases and conditions in which insulin resistance is the central pathophysiological mechanism, and for treatment of diseases or conditions such as Type II diabetes, dyslipidaemia, hypertension, coronary heart disease, cardiovascular disease, atherosclerosis, nephrosclerosis, polycystic ovarian syndrome, eating disorders, diabetes nephropathy, glomerulonephritis, glomerularsclerosis, nephrotic syndrome, psoriasis or obesity. Processes for preparation of disclosed compounds, pharmaceutical compositions containing the disclosed compounds, and methods for treating diabetes mellitus and the diseases and condition mediated through insulin resistance are provided.

ALKANOIC ACIDS AND THEIR ESTERS AS ANTIDIABETIC AGENTS

Field of the Invention

The present invention relates to alkanoic acids and their derivatives, which have PPAR agonist activity, and hence can be used as antidiabetic compounds. Compounds disclosed herein can be used for the treatment of diabetes and diabetes-associated complications, for the treatment of diseases and conditions in which insulin resistance is the central pathophysiological mechanism, and for treatment of diseases or conditions such as Type II diabetes, dyslipidaemia, hypertension, coronary heart disease, cardiovascular disease, atherosclerosis, nephrosclerosis, polycystic ovarian syndrome, eating disorders, diabetes nephropathy, glomerulonephritis, glomerularsclerosis, nephrotic syndrome, psoriasis or obesity. Processes for preparation of such compounds, pharmaceutical compositions containing such compounds, and methods for treating diabetes mellitus and the diseases and conditions mediated through insulin resistance are provided.

Background of the Invention

Type 2 insulin-resistant diabetes mellitus [also known as non-insulin dependent diabetes mellitus] afflicts an estimated 6% of the adult population in western society and is expected to continue to grow at a rate of 6% per annum worldwide. Type 2 diabetes is a complex metabolic disorder and is characterized by hyperglycemia. This results from contribution of impaired insulin secretion from pancreas and insulin resistance mainly in muscle and liver. Insulin resistant individuals in addition to being hyperglycemic, exhibit a constellation of closely related clinical indications, which include obesity, hypertension, dyslipidemia, premature atherosclerosis. In fact, 80% of diabetic mortality arises from atherosclerotic cardiovascular disease (ASCVD). Uncontrolled hyperglycemia can further lead to late stage complications such as nephropathy, neuropathy and retinopathy.

Non-pharmacological approaches to lower high blood sugar include a strict control of diet followed by vigorous exercise. Presently, several pharmacological agents are also available as hypoglycemic agents including insulin secretagogues - sulphonyl ureas

(glimeperide) and non sulphonyl ureas (repaglinide)- which increase insulin secretion from pancreatic cells; biguanides – metformin – which lower hepatic glucose production; and α-glucosidase inhibitors – acarbose – which delays intestinal absorption of carbohydrate.

PPAR (Peroxisome-Proliferator-Activated Receptor) are ligand-activated transcription factors (members of nuclear receptor family), which are offering promising therapeutic approach to type 2 diabetes mellitus. PPAR exists in three subtype forms α, γ and δ (or β). PPAR γ is abundantly expressed in adipose tissues. Direct activation of PPAR γ leads to induction of adipocyte genes such as for fatty acid transporter 1 which in turn contributes to lowering of triglycerides and free fatty acid (FFA) levels. As FFA is a potential mediator of insulin resistance, lowering of FFA levels contributes to efficacy of PPAR γ activation in increasing insulin sensitivity and consequently glucose uptake in skeletal muscle cell. Glitazones – rosiglitazone and pioglitazone – belongs to this class of drug and are now proven insulin sensitisers [Moller, D.E.; *Nature*, 2001, 414(6865), 821-827]

WO 03/018553 discloses compounds, pharmaceutical compositions containing such compound, processes for preparing such compounds, and their use as reported antidiabetic agents. WO 02/100813 discloses compounds, pharmaceutical compositions containing such compound, processes for preparing such compounds, and their use as antidiabetic agents. WO 02/16331 discloses oxazolyl-arylpropionic acid derivatives and their use as PPAR agonists. WO 01/55085 discloses propionic acid derivatives, which are described as useful in the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR). WO 00/23425 discloses compounds, pharmaceutical compositions containing such compound, processes for preparing such compounds, and their use as antidiabetic agents. WO 00/63161 discloses certain 1,4-disubstituted phenyl derivatives that are described as acting as agonists to PPAR-γ receptors. WO 99/08501 discloses β-aryl-α-oxysubstituted alkylcarboxylic acids, which are described as having antiobesity and hypocholesterolemic properties. WO 97/31907 discloses substituted 4-hydroxy-phenylalkanoic acid derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their use in the treatment and/or prophylaxis of hyperglycemia, dyslipidemia, and is of particular use in the treatment of Type

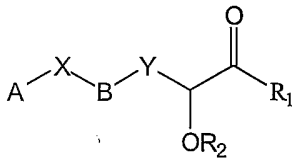
II diabetes. WO 94/01420 discloses certain heterocyclic compounds, to a process for preparing such compounds, to pharmaceutical compositions containing such compounds and to the use of such compounds and compositions in medicine.

U.S. Patent No. 6,274,608 discloses compounds, their preparation and use in the treatment of condition mediated by nuclear receptors, in particular the Retinoid X Receptor (RXR) and the Peroxisome Proliferator-Activated Receptor (PPAR) families. Such conditions include diabetes and obesity. U.S Patent No. 6,054,453 discloses β-aryl-α-oxysubstituted alkylcarboxylic acids, compositions containing them, and their use as hypolipidemic and antihyperglycemic agents. U.S. Patent No. 6,214,820 discloses compounds which are described as useful in the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR). U.S. Patent No. 6,258,850 discloses 3-aryl-2-hydroxypropionic acid derivatives, process and intermediates for their manufacture, pharmaceutical preparations containing them and the use of the compounds in clinical conditions associated with insulin resistance. U.S. Patent No. 6,297,580 discloses substituted 4-hydroxy-phenyl alkanoic acid derivatives described as having agonist activity to PPAR.

Summary of the Invention

Particular alkanoic acids and their derivatives, which have PPAR agonist activity, and hence can be used as antidiabetic compounds are disclosed. Processes for the synthesis of these compounds are also disclosed. Pharmaceutically acceptable salts, pharmaceutically acceptable solvates, polymorphs, N-oxides or metabolites of these compounds having the same type of activity are also provided. Pharmaceutical compositions containing the compounds, and which may also contain pharmaceutically acceptable carriers or diluents, which can be used for the treatment of diabetes mellitus and the disease or condition mediated through insulin resistance are also provided. Other aspects are set forth in accompanying description which follows and in the part will be apparent from the description or may be learnt by the practice of the invention.

In accordance with one aspect, there are provided compounds having the structure of Formula I,

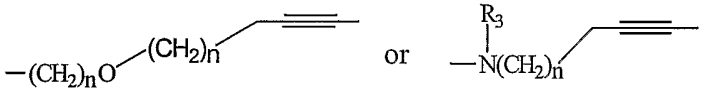


Formula I

their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, N-oxides or polymorphs wherein

A can represent alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, acyl, acyloxy, aroyl, aroyloxy, aryl or heterocycle.

X can represent no atoms, oxygen,

 or

wherein n is an integer 0 to 3, and R_3 represents hydrogen or alkyl.

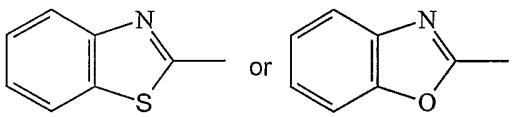
B can represent aryl or heterocycle.

Y can represent $(CH_2)_m$ wherein m represents an integer 1 to 3.

R_1 can represent $-OR_3$ or $-NR_3R_4$, wherein R_3 and R_4 can independently represent hydrogen or alkyl.

R_2 can represent alkyl, cycloalkyl, aryl or aralkyl.

In some particular embodiments, A can be, for example,



In accordance with another aspect, there are provided processes for preparing compounds disclosed herein.

Relative to the above description of the present invention, the following definitions apply. As used herein, the term "alkyl" refers to straight or branched saturated hydrocarbon having one to six carbon atom(s). One or more hydrogen atom(s) of said alkyl can optionally be replaced by halogen, hydroxy, alkoxy, cyano, nitro or $-NR_3R_4$, wherein R_3 and R_4 are selected from hydrogen and alkyl. Examples of alkyl include, but are not limited to, methyl, ethyl, propyl, isopropyl and butyl, and the like. As used herein, the terms "alkenyl" or "alkynyl" stands for unsaturated hydrocarbon having two to six carbon atoms. One or more hydrogen of said alkenyl or alkynyl can be replaced by halogen. Examples of alkenyl and alkynyl include, but are not limited to, ethylene, propylene, ethynyl and propynyl, and the like. As used herein, the term "cycloalkyl" refers to saturated carbocyclic ring having three to seven carbon atoms. Examples of cycloakyl include, but are not limited to, cyclopropyl, cyclobutyl and cyclopentyl, and the like. As used herein, the term "cycloalkenyl" refers to unsaturated carbocyclic ring having three to seven carbon atoms. Examples of cycloakenyl include, but are not limited to, cyclobutenyl and cyclopentenyl, and the like. The "cycloalkyl" or "cycloalkenyl" may optionally be substituted with halogen, hydroxy, cyano, nitro or $-NR_3R_4$, wherein R_3 and R_4 are selected from hydrogen and alkyl.

As used herein, the term "halogen" refers to fluorine, chlorine, bromine or iodine. As used herein, the terms "acyl" and "acyloxy" refers to COR_5 and $OCOR_5$ wherein R_5 represents alkyl. As used herein, the terms "aroyl" and "aroyloxy" refers to COR_6 and $OCOR_6$ wherein R_6 represents aryl. As used herein, the term "alkoxy" refers to $O\text{-}R_5$ wherein R_5 represents alkyl. As used herein, the term "thioalkyl" refers to $-S\text{-}R_5$ wherein R_5 refers to alkyl. As used herein, the term "cycloalkoxy" refers to $O\text{-}R_7$ wherein R_7 represents cycloalkyl or cycloalkenyl.

As used herein, the term "aryl" stands for an aromatic radical having 6 to 14 carbon atoms. Examples of aryl include, but are not limited to, phenyl, napthyl, anthryl and biphenyl, and the like. As used herein, the term "heterocycle" refers to non-aromatic, aromatic or aromatic fused with non-aromatic ring system having one or more heteroatom(s) in either the aromatic or the non-aromatic part wherein the hetero atom(s) is/ are selected from nitrogen, sulphur and oxygen and the ring system includes mono, bi or tricyclic. One or more carbon

atom(s) of non-aromatic ring fused with aromatic ring may be replaced by carbonyl or sulfonyl group. Examples of heterocycles include, but are not limited to, benzoxazinyl, benzthiazinyl, benzimidazolyl, benzofuranyl, carbazolyl, Indolyl, oxazolyl, phenoxazinyl, pyridyl and phenothiazinyl, and the like. The aryl and heterocycle may optionally be substituted with one or more substituent(s) independently selected from halogen, hydroxy, nitro, mercapto, cyano, alkyl, aryl, alkoxy, thioalkyl, cycloalkoxy, $-NR_8R_9$, $-CONR_8R_9$, $-COOR_9$, $-OCOR_9$, $-COR_9$, $-NHSO_2R_9$ and $-SO_2NHR_9$ wherein R_8 and R_9 are independently selected from hydrogen, alkyl, aryl and aralkyl.

As used herein, the term "polymorphs" includes all crystalline form for compounds described herein. In addition, some of the compounds described herein may form solvates with water (for example, hydrate, hemihydrate or sesquihydrate) or common organic solvents. Such solvates are also encompassed within the disclosure.

Formula I has at least one asymmetric center, therefore, compounds disclosed herein may exist as pure enantiomers or racemic mixtures. It is to be understood that all such isomers and mixtures therefore are encompassed within the scope of the disclosure.

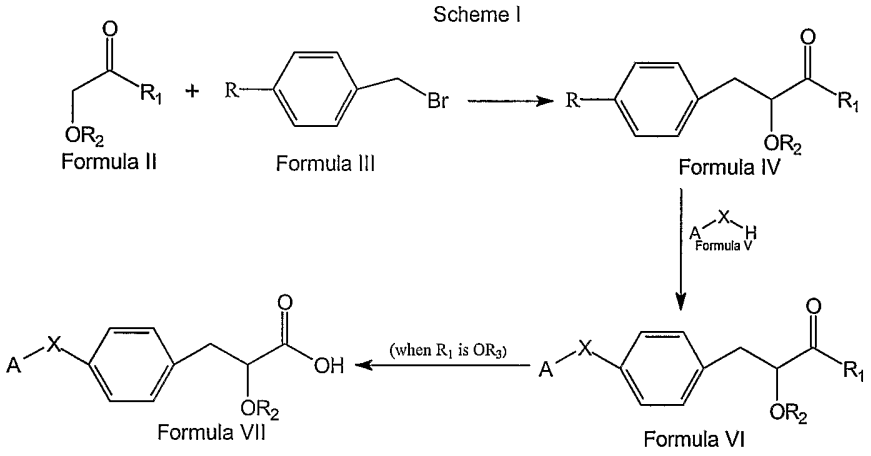
The phrase "pharmaceutically acceptable salts" denotes salts of the free acid which substantially possess the desired pharmacological activity of the free acid. Suitable inorganic base addition salts include, but are not limited to, aluminum, calcium, lithium, magnesium, potassium, sodium and zinc salts. Suitable organic base addition salts include, but are not limited to, primary, secondary and tertiary amines, cyclic amines, N, N′-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine and procaine salts. The pharmaceutically acceptable salts may be prepared by conventional methods known in the prior art. The salt forms may differ from the compound described herein in certain physical properties such as solubility.

Detailed Description of the Invention

The compounds described herein may be prepared by techniques well known in the art and familiar to the average synthetic organic chemist. In addition, the compounds of the

present invention may be prepared by the following reaction sequences as depicted in Scheme I.

Scheme I



Compounds of Formula VII can be prepared according to Scheme I, for example. Thus, a compound of Formula II (for example, these commercially available for example, from Fluka) is reacted with a compound of Formula III (for example, these commercially available from for example, Fluka) to give a compound of Formula IV (wherein R_1 and R_2 are the same as defined earlier and R represents bromine or iodine), which on reaction with a compound of Formula V gives a compound of Formula VI (wherein A and X are the same as defined earlier), which is finally hydrolyzed to give a compound of Formula VII. The compound of Formula IV (when R is OTf) can also be used in the reaction with compound of Formula V. The compounds of Formula IV (when R is OTf) can be prepared from phenolic precursor by methods well known in the literature. The phenolic intermediates can be prepared according to methods described in PCT application 03/27084 and 03/27915. The compounds of Formula IV can also be prepared following a procedure reported in PCT application WO 99/08501.

The reaction of a compound of Formula II with a compound of Formula III to give a compound of Formula IV can be carried out in a solvent such as, for example, tetrahydrofuran or ether. The reaction of a compound of Formula II with a compound of Formula III can be

carried out in the presence of an organic base such as, for example LDA, butyl lithium or the like known in the prior art.

The reaction of a compound of Formula IV with a compound of Formula V to give a compound of Formula VI can be carried out in a solvent such as, for example, dimethylformamide, chloroform, tetrahydrofuran, acetonitrile or dioxane. The reaction of a compound of Formula IV with a compound of Formula V can be carried out in the presence of an organic base such as, for example, triethylamine, diethylamine, tributylamine, 4-dimethylamino pyridine or pyridine. The reaction of a compound of Formula IV with a compound of Formula V can be carried out in the presence of copper (I) iodide, and a suitable palladium catalyst such as, for example, palladium (II) acetate, palladium (II) trifluoroacetate, palladium (II) propionate, tetrakis(triphenylphosphine) palladium (0), bis(dibezylidineacetone) palladium (0) or bis(triphenylphosphine) palladium (II) chloride. Alternatively, phosphine, for example, triphenylphosphine may be used as additive. The reaction may also be carried out in the absence of copper (I) iodide.

The hydrolysis of a compound of Formula VI to give a compound of Formula VII can be carried out in a solvent or solvent system such as, for example, tetrahydrofuran, methanol, ethanol or mixtures thereof. The hydrolysis of a compound of Formula VI to give a compound of Formula VII can be carried out in the presence of a base such as, for example, lithium hydroxide, sodium hydroxide or potassium hydroxide.

In the above scheme, where specific bases, coupling agents, solvents, etc., are mentioned it is be understood that other bases, coupling agents, solvents, etc., known to those skilled in the art may be used. Similarly the reaction temperature and duration may be adjusted according to the desired needs.

An illustrative list of compounds of the invention are listed below (also shown in Table I and 2):

2-Ethoxy-3-[4-{3-(2-[5-ethylpyridin-2-yl])ethoxy}propyn-1-yl]phenyl propanoic acid ethyl ester (Compound No. 1)

2-Ethoxy-3-[4-{3-(N-methyl-N-pyrid-2-ylamino)}prop-1-ynyl]phenyl propionic acid ethyl ester (Compound No. 2)

2-Ethoxy-3-[4-{3-(N-benzthiazol-2-yl-N-methylamino)prop-1-ynyl]phenyl propanoic acid ethyl ester (Compound No. 3)

2-Ethoxy-3-[4-{3-(N-benzoxazol-2-yl-N-methylamino)}prop-1-ynyl]phenyl propanoic acid ethyl ester (Compound No. 4)

2-Ethoxy-3-[4-{3-(2-phenyl-5-methyl-oxazol-4-yl)methoxy)prop-1-ynyl]phenyl propanoic acid ethyl ester (Compound No. 5)

2-Ethoxy-3-[4-{3-(2-[5-ethylpyridin-2-yl])ethoxy}propyn-1-yl]phenyl propanoic acid (Compound No. 6)

2-Ethoxy-3-[4-{3-(2-phenyl-5-methyloxazol-4-yl)methoxyprop-1-ynyl]phenyl propanoic acid (Compound No. 7)

2-Ethoxy-3-[4-{3-(N-benzooxazol-2-yl-N-methylamino)}prop1-ynyl}phenyl propanoic acid (Compound No. 8)

2-Ethoxy-3-[4-{3-(2-phenyl-4-methylimidazol-1-yl)}prop-1-ynyl]phenyl propanoic acid ethyl ester (Compound No. 9)

2-Ethoxy-3-[4-{3-(indolin-1-yl)}prop-1-ynyl]phenyl propanoic acid ethyl ester (Compound No. 10)

2-Ethoxy-3-[4-{3-(2-methyl-4-oxo-2,4-dihydroquinazolin-3-yl)}prop-1-ynyl]phenyl propanoic acid ethyl ester (Compound No. 11)

2-Ethoxy-3-[4-[3-{2,3-dihydro-1,4-benzthiazin-4-yl)}prop-1-ynyl]phenyl propanoic acid ethyl ester (Compound No. 12)

2-Ethoxy-3-[4-{3-(3-oxo-2H-1,4-benzoxazin-4-yl)}prop-1-ynyl]phenyl propanoic acid ethyl ester (Compound No. 13)

2-Ethoxy-3-[4-{3-(carbazol-9-yl)}prop-1-ynyl]phenyl propanoic acid ethyl ester (Compound No. 14)

2-Ethoxy-3-[4-{3-(phenoxazin-10-yl)}prop-1-ynyl]phenyl propanoic acid ethyl ester (Compound No. 15)

2-Ethoxy-3-[4-{3-(2,3-dihydro-1,4-benzoxazin-4-yl)}prop-1-ynyl]phenyl propanoic acid ethyl ester (Compound No. 16)

2-Ethoxy-3-[4-{3-(2-methyl-4-oxo-2,4-dihydroquinazolin-3-yl)}prop-1-ynyl]phenyl propanoic acid (Compound No. 17)

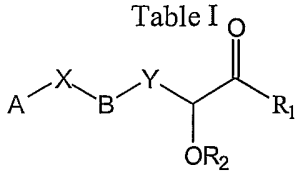
2-Ethoxy-3-[4-{3-(2,3-dihydrobenzothiazin-4-yl)}prop-1-ynyl]phenyl propanoic acid (Compound No. 18)

2-Ethoxy-3-[4-{3-(phenoxazin-10-yl)}prop-1-ynyl]phenyl]propanoic acid (Compound No. 19)

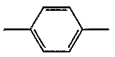
2-Ethoxy-3-[4-{3-(carbazol-9-yl)}prop-1-ynyl]phenyl propanoic acid (Compound No. 20)

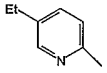
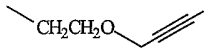
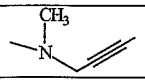
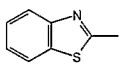
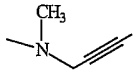
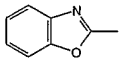
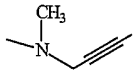
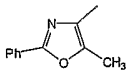
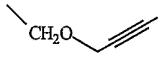
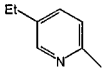
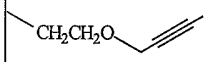
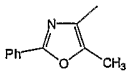
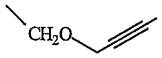
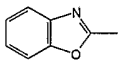
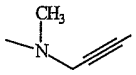
2-Ethoxy-3-[4-{3-(2,3-dihydro-1,4-benzoxazin-4-yl)}prop-1-ynyl] phenyl propanoic acid (Compound No. 21)

Table I

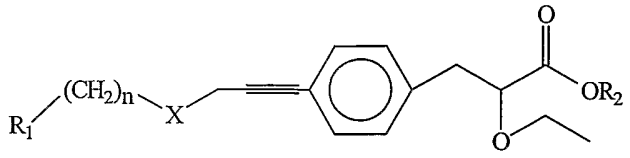


Formula I

(Wherein B =  , Y= -CH_2-, R_2=Et, R_1=OR_3)

Compound No.	A	X	R_3
1			Et
2			Et
3			Et
4			Et
5			Et
6			H
7			H
8			H

Further particular compounds according to the disclosure herein are included in Table 2.



Formula I

Table 2

Compound No.	R_1	R_2	n	X
9	2-phenyl-4-methylimidazol-1-yl	Ethyl	0	--
10	Indolin-1-yl	Ethyl	0	--
11	2-methyl-4-oxo-2,4-dihydroquinazolin-3-yl	Ethyl	0	--
12	2,3-dihydro-1,4-benzthiazin-4-yl	Ethyl	0	--
13	3-oxo-2H-1,4-benzoxazin-4-yl	Ethyl	0	--
14	Carbazol-9-yl	Ethyl	0	--
15	Phenoxazin-10-yl	Ethyl	0	--
16	2,3-dihydro-1,4-benzoxazin-4-yl	Ethyl	0	--
17	2-methyl-4-oxo-2,4-dihydroquinazolin-3-yl	Hydrogen	0	--
18	2,3-dihydro-1,4-benzthiazin-4-yl	Hydrogen	0	--
19	Phenoxazin-10-yl	Hydrogen	0	--
20	Carbazol-9-yl	Hydrogen	0	--
21	2,3-dihydro-1,4-benzoxazin-4-yl	Hydrogen	0	--

In another aspect, pharmaceutical compositions are provided comprising, as an active ingredient, at least one of the disclosed compounds or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carriers or diluents. Compounds disclosed herein may be administered to human or animals for treatment by any route, which effectively transports the active compound to the appropriate or desired site of action such as oral, nasal, pulmonary, transdermal or parenteral (rectal, subcutaneous, intravenous, intraurethral, intramascular, intranasal). A particular method of administration is oral administration. The pharmaceutical compositions can comprise a pharmaceutically effective amount of a compound of the present invention formulated together with one or more pharmaceutically

acceptable carriers. As used herein, the term "pharmaceutically acceptable carriers" is intended to include non-toxic, inert solid, semi-solid or liquid filler, diluents, encapsulating material or formulation of any type.

Solid form preparations for oral administration include capsules, tablet, pills, powders, granules, sachets and suppositories. For solid form preparations, the active compound is mixed with at least one inert, pharmaceutically acceptable excipients or carrier such as sodium citrate, dicalcium phosphate; binders such as carboxymethyl cellulose, alginates, gelatins, polyvinylpyrolidinone, acacia; disintegrating agents such as agar-agar, calcium carbonate, alginic acid, certain silicates and sodium carbonate; absorption acceptors such as quaternary ammonium compounds; wetting agents such as cetyl alcohol, glycerol monostearate; adsorbents such as kaolin; lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycol, sodium lauryl sulphate and mixture thereof. In the case of capsules, tablets, pills, the dosage form may also comprise buffering agents.

The solid preparations of tablets, capsules, pills, granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art.

Liquid form preparations for oral administration can include pharmaceutically acceptable emulsions, solution, suspensions, syrup and elixir. For liquid preparations, the active compound can be mixed with water or other solvent, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (such as cottonseed, groundnut, corn, germ, olive, custard sesame oil), glycerol, and fatty acid esters of Sorbitan and mixture thereof. Besides inert diluents, the oral composition can also include adjuvant such as wetting agents, emulsifying agents, suspending agents, sweetening agents, flavoring agents and perfuming agents.

Injectible preparations such as sterile injection or aqueous solution may be formulated according to the art using suitable dispersing or wetting and suspending agent. Among the

acceptable vehicles and solvents that may be employed are water, Ringer's solutions, and isotonic sodium chloride.

The formulations disclosed herein may be formulated to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known to the art.

Examples set forth below demonstrate general synthetic procedures for the preparation of representative compounds. The examples are provided to illustrate particular aspect of the disclosure and do not limit the scope of the present invention as defined by the claims.

EXAMPLES

Example 1: Preparation of Compound of Formula IV

To a solution of n-butyl lithium (1.6 equiv) in tetrahydrofuran was added diisopropylamine (1.842 equiv) dropwise over a period of 30 minutes at -78°C. After addition the reaction mixture was stirred at 0°C for 1 hour. The reaction mixture was cooled back to -78°C and ethyl ethoxy acetate (1 equiv) was added dropwise over a period of 30 minutes. The reaction mixture was further stirred at -78°C for 1 hour followed by addition of 4-bromobenzylbromide (0.769 equiv) at this temperature. The reaction mixture was stirred at – 60 ^{0}C till the completion of reaction and tetrahydrofuran was evaporated. The aqueous layer was extracted with dichloromethane, washed with water brine, dried over anhydrous sodium sulphate, concentrated and residue purified on column (silica gel, 100 mesh) using 10% ethyl acetate in hexane.

Example 2: Preparation of compound of Formula V

In a 3-neck round-bottomed flask fitted with nitrogen gas inlet, guard tube and septum was placed dimethylformamide and sodium hydride (1.2 equiv). The suspension was cooled to 0 ^{0}C and a solution of heterocycle in dimethylformamide was added slowly. Ice bath was removed and the stirring continued at an ambient temperature for 1 hour. The clear solution was cooled down to 0 ^{0}C again and propargyl bromide added slowly. The reaction mixture

was allowed to warm to an ambient temperature. After completion of reaction, water was added to reaction mixture and organics extracted with ethyl acetate. Organic layer was washed with water, brine, dried over anhydrous sodium sulphate and concentrated on rotary evaporator. The residue was purified on column (Silica gel, 100-200 mesh).

Example 3: Preparation of compound of Formula VI

A mixture of 2-ethoxy-3-[4-bromo]phenyl propionic acid ethyl ester (1 equiv), bis(triphenylphosphine) palladium (II) chloride (0.05 equiv), triphenylphosphine (0.1 equiv) and triethylamine (2 equiv) in dry dimethylformamide was stirred at 65-70°C for 15 minutes. The solution of compound of Formula V (1.2 equiv) in dimethylformamide (dry) was then added to the reaction mixture at this temperature over a period of 30 minutes. After completion of reaction, the reaction mixture was poured into ice cold water and organic extracted with dichloromethane, washed with water, brine, dried over anhydrous sodium sulphate, concentrated and residue purified on column (silica gel; 100-200 mesh).

The following compounds were prepared following the above procedures.

2-ethoxy-3-[4-{3-(2-[5-ethylpyridin-2-yl])ethoxy}propyn-1-yl]phenyl propanoic acid ethyl ester; MS (+ve ion mode): m/z 410 (M^++1).

2-ethoxy-3-[4-{3-(N-Methyl-N-pyrid-2-ylamino)}prop-1-ynyl]phenyl propionic acid ethyl ester; MS (+ve ion mode): m/z 367 (M^++1).

2-ethoxy-3-[4-{3-(N-benzthiazol-2-yl-N-methylamino)prop-1-ynyl]phenylpropanoic acid ethyl ester.

2-ethoxy-3-[4-{3-(N-benzoxazol-2-yl-N-methylamino)}prop-1-ynyl]phenyl propanoic acid ethyl ester; MS (+ve ion mode): m/z 407 (M^++1).

2-ethoxy-3-[4-{3-(2-phenyl-5-methyl-oxazol-4-yl)methoxy)prop-1-ynyl]phenyl propanoic acid ethyl ester; MS (+ve ion modes): m/z 448 (M^++1).

2-ethoxy-3-[4-{3-(2-phenyl-4-methylimidazol-1-yl)}prop-1-ynyl]phenyl propanoic acid ethyl ester; MS (+ve ion mode): m/z 417 (M^++1).

2-ethoxy-3-[4-{3-(indolin-1-yl)}prop-1-ynyl]phenyl propanoic acid ethyl ester; MS (+ve ion mode): m/z 378 (M^++1).

2-ethoxy-3-[4-{3-(2-methyl-4-oxo-2,4-dihydroquinazolin-3-yl)}prop-1-ynyl]phenyl propanoic acid ethyl ester; MS (+ve ion mode): m/z 418 (M^++1).

2-ethoxy-3-[4-[3-{2,3-dihydro-1,4-benzthiazin-4-yl)}prop-1-ynyl]phenyl propanoic acid ethyl ester; MS (+ve ion mode): m/z 410 (M^++1).

2-ethoxy-3-[4-{3-(3-oxo-2H-1,4-benzoxazin-4-yl)}prop-1-ynyl]phenyl propanoic acid ethyl ester; MS (+ve ion mode): m/z 408 (M^++1).

2-ethoxy-3-[4-{3-(carbazol-9-yl)}prop-1-ynyl]phenyl propanoic acid ethyl ester; MS (+ve ion mode): m/z 426 (M^++1).

2-ethoxy-3-[4-{3-(phenoxazin-10-yl)}prop-1-ynyl]phenyl propanoic acid ethyl ester; MS (+ve ion mode): m/z 442 (M^++1).

2-ethoxy-3-[4-{3-(2,3-dihydro-1,4-benzoxazin-4-yl)}prop-1-ynyl]phenyl propanoic acid ethyl ester; MS (+ve ion mode): m/z 394 (M^++1).

Example 4: Preparation of compound of Formula VII

A solution of 2-ethoxy-3-[4-{3-heterocyclyl}prop1-ynyl]phenyl propionic acid ethyl ester (1 equiv) in methanol-tetrahydrofuran (2.1) was treated with sodium hydroxide solution (10%, 2 equiv) at 0°C. The reaction mixture was neutralized with hydrochloric acid (1.0N) and extracted with dichloromethane, washed with brine, dried over anhydrous sodium sulphate, concentrated and the residue purified on column (silica gel, 100-200 mesh).

The following compounds were prepared following the above procedure

2-ethoxy-3-[4-{3-(2-phenyl-5-methyloxazol-4-yl)methoxyprop-1-ynyl]phenyl propanoic acid; MS (+ ve ion mode): m/z 420 (M^++1).

2-ethoxy-3-[4-{3-(N-benzoxazole-2yl-N-methylamino)}prop1-ynyl}phenyl propanoic acid; MS (+ ve ion mode): m/z 379 (M^++1).

2-ethoxy-3-[4-{3-(2-[5-ethylpyridin-2-yl])ethoxy}propyn-1-yl]phenyl propanoic acid; MS (+ ve ion mode): m/z 382 (M^++1).

2-ethoxy-3-[4-{3-(2-methyl-4-oxo-2,4-dihydroquinazolin-3-yl)}prop-1-ynyl]phenyl ropanoic acid; MS (+ve ion mode): m/z 391 (M^++1).

2-ethoxy-3-[4-{3-(2,3-dihydrobenzothiazin-4-yl)}prop-1-ynyl]phenyl propanoic acid; MS (+ve ion mode): m/z 382 (M^++1).

2-ethoxy-3-[4-{3-(phenoxazin-10-yl)}prop-1-ynyl]phenyl]propanoic acid; MS (+ve ion mode): m/z 414 (M^++1).

2-ethoxy-3-[4-{3-(carbazol-9-yl)}prop-1-ynyl]phenyl propanoic acid; MS (+ve ion mode): m/z 398 (M^++1).

2-ethoxy-3-[4-{3-(2,3-dihydro-1,4-benzoxazin-4-yl)}prop-1-ynyl] phenyl propanoic acid.

Example 5: Coactivator-dependent receptor ligand assays (CARLA) for PPARα/δ/γ in a homogeneous time resolved-fluorescence resonance energy transfer (TR-FRET) format

The functional and binding assays for the PPARα, PPARδ and PPARγ are a variation of the coactivator-dependent receptor ligand assay (CARLA) (Krey et al., (1997) *Mol. Endocrinol.*, 11:779-791). The present CARLA assays use a TR-FRET detection method previously reviewed (Hemmila I. LANCE, (1999) *J. Biomol. Screening*, 4:303-307; Mathis G., (1999) *J. Biomol. Screening*, 4:309-313). All assays included 3 nM of the glutathione-S-transferase (GST) fusion proteins of either the hPPARα ligand binding domain (LBD) (amino acids 167-468) (GST- hPPARα LBD), GST-hPPARδ LBD (amino acids 139-442) or GST-hPPARγ LBD (amino acids 175-476); 3 nM Eu-labelled anti-GST antibody (Wallac); 30 nM

biotinylated steroid receptor coactivator-1 (SRC-1) peptide (an N-terminal biotinylated peptide, CPSSHSSLTERHKILHRLLQEGSPS, derived from amino acids 676-700 of SRC-1); and 10 nM streptavidin-labelled allophycocyanin (APC; Prozyme).

The biotinylated SRC-1 peptide was prepared by standard solid-phase peptide synthetic methods. The GST-PPAR LBDs were expressed in pGEX vectors (Amersham Pharmacia) in the *E. coli* strain BL21(DE3) using standard expression conditions at 18 °C. In some cases, the GST-PPAR LBDs were co-expressed with groESL. The GST fusion proteins were purified on glutathione sepharose affinity columns (Amersham Pharmacia) using the method described by the manufacturer. The assay buffer contained 50 mM Tris pH 7.4, 50 mM KCl, 0.1% BSA, and 1 mM DTT. The assay was carried out in black half area 96-well plates in a final volume of 25 µl. After mixing all components, the reaction mixture sat for 3 hours at room temperature before reading the TR-FRET signal on a Wallac Victor 2 plate reader (measuring the ratio of signals at 665 nm and 620 nm). EC_{50} values were estimated with the Excel add-in program XLFit (ID Business Soltions, Guildford, Surrey, UK) utilizing a 4-parameter logistic equation. EC50 values for PPAR α, PPAR γ, and PPAR δ were determined with respect to compounds numbered 2, 5, 6, 7, 8, 10, 13, and 17-21.

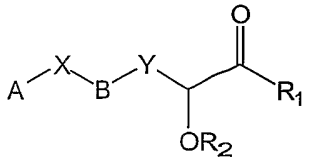
For PPAR α, the ED50 values ranged from about 30 μM to about 0.04 μM, for example from about 10 μM to about 0.04 μM, or from about 5 μM to about 0.04 μM, or from about 1.0 μM to about 0.04 μM.

For PPAR γ, the ED50 values ranged from about 30 μM to about 0.03 μM, for example from about 1.0 μM to about 0.03 μM, or from about 0.3 μM to about 0.03 μM, or from about 0.14 μM to about 0.03 μM.

For PPAR δ, the ED50 values ranged from about 30 μM to about 3 μM, for example from about 10 μM to about 3 μM, or from about 4.5 μM to about 3 μM.

We claim:

1. A compound having the structure of Formula I,

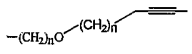
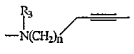


Formula I

its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, N-oxides or polymorphs wherein

A represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, acyl, acyloxy, aroyl, aroyloxy, aryl or heterocycle;

X represents no atoms, oxygen,

 or 

wherein n is an integer 0 to 3, and R_3 represents hydrogen or alkyl;

B represents aryl or heterocycle;

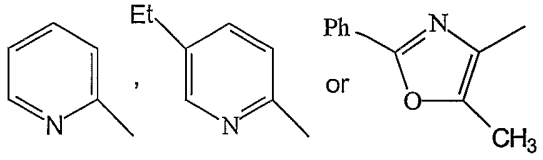
Y represents $(CH_2)_m$ wherein m represents an integer 1 to 3;

R_1 represents $-OR_3$, or $-NR_3R_4$, wherein R_3 and R_4 represent hydrogen or alkyl;

R_2 represents alkyl, cycloalkyl, aryl or aralkyl.

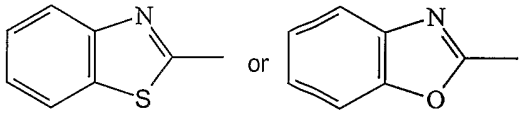
2. The compound according to claim 1, wherein A is an optionally substituted monocyclic heterocycle with the optional substituent (s) selected from alkyl, aryl and halogen.

3. The compound according to claim 1, wherein A is:

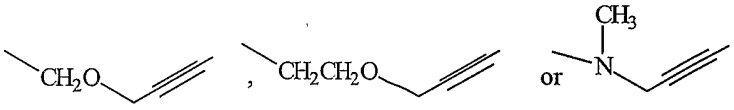


4. The compound according to claim 1, wherein A is optionally substituted bicyclic heterocycle, with the optional substituent (s) selected from alkyl, aryl and halogen.

5. The compound according to claim 1, wherein A is:



6. The compound according to claim 1, wherein X is:



7. The compound according to claim 1, wherein B is:

8. The compound according to claim 1, wherein Y is methylene.

9. The compound according to claim 1, wherein R_1 is hydrogen.

10. The compound according to claim 1, wherein R_1 is alkyl.

11. The compound according to claim 9, wherein R_1 is ethyl.

12. The compound according to claim 1, wherein R_2 is alkyl.

13. The compound according to claim 11, wherein R_2 is ethyl.

14. A compound which is:

2-Ethoxy-3-[4-{3-(2-[5-ethylpyridin-2-yl])ethoxy}propyn-1-yl]phenyl propanoic acid ethyl ester,

2-Ethoxy-3-[4-{3-(N-methyl-N-pyrid-2-ylamino)}prop-1-ynyl]phenyl propionic acid ethyl ester,

2-Ethoxy-3-[4-{3-(N-benzthiazol-2-yl-N-methylamino)prop-1-ynyl]phenyl propanoic acid ethyl ester,

2-Ethoxy-3-[4-{3-(N-benzoxazol-2-yl-N-methylamino)}prop-1-ynyl]phenyl propanoic acid ethyl ester,

2-Ethoxy-3-[4-{3-(2-phenyl-5-methyl-oxazol-4-yl)methoxy)prop-1-ynyl]phenyl propanoic acid ethyl ester,

2-Ethoxy-3-[4-{3-(2-[5-ethylpyridin-2-yl])ethoxy}propyn-1-yl]phenyl propanoic acid,

2-Ethoxy-3-[4-{3-(2-phenyl-5-methyloxazol-4-yl)methoxyprop-1-ynyl]phenyl propanoic acid,

2-Ethoxy-3-[4-{3-(N-benzooxazol-2-yl-N-methylamino)}prop1-ynyl}phenyl propanoic acid,

2-Ethoxy-3-[4-{3-(2-phenyl-4-methylimidazol-1-yl)}prop-1-ynyl]phenyl propanoic acid ethyl ester,

2-Ethoxy-3-[4-{3-(indolin-1-yl)}prop-1-ynyl]phenyl propanoic acid ethyl ester,

2-Ethoxy-3-[4-{3-(2-methyl-4-oxo-2,4-dihydroquinazolin-3-yl)}prop-1-ynyl]phenyl propanoic acid ethyl ester,

2-Ethoxy-3-[4-[3-{2,3-dihydro-1,4-benzthiazin-4-yl)}prop-1-ynyl]phenyl propanoic acid ethyl ester,

2-Ethoxy-3-[4-{3-(3-oxo-2H-1,4-benzoxazin-4-yl)}prop-1-ynyl]phenyl propanoic acid ethyl ester,

2-Ethoxy-3-[4-{3-(carbazol-9-yl)}prop-1-ynyl]phenyl propanoic acid ethyl ester,

2-Ethoxy-3-[4-{3-(phenoxazin-10-yl)}prop-1-ynyl]phenyl propanoic acid ethyl ester,

2-Ethoxy-3-[4-{3-(2,3-dihydro-1,4-benzoxazin-4-yl)}prop-1-ynyl]phenyl propanoic acid ethyl ester,

2-Ethoxy-3-[4-{3-(2-methyl-4-oxo-2,4-dihydroquinazolin-3-yl)}prop-1-ynyl]phenyl propanoic acid,

2-Ethoxy-3-[4-{3-(2,3-dihydrobenzothiazin-4-yl)}prop-1-ynyl]phenyl propanoic acid,

2-Ethoxy-3-[4-{3-(phenoxazin-10-yl)}prop-1-ynyl]phenyl]propanoic acid,

2-Ethoxy-3-[4-{3-(carbazol-9-yl)}prop-1-ynyl]phenyl propanoic acid,

2-Ethoxy-3-[4-{3-(2,3-dihydro-1,4-benzoxazin-4-yl)}prop-1-ynyl] phenyl propanoic acid, or

their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, N-oxides or polymorphs.

15. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 1 together with pharmaceutically acceptable carriers, excipients or diluents.

16. A Peroxisome Proliferator Activated Receptor (PPAR) agonist comprising a compound of claim 1.

17. A PPAR agonist composition comprising the pharmaceutical composition of claim 15.

18. A method of treating a mammal suffering from diabetes or diabetes-associated complications, comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.

19. A method of treating a mammal suffering from diseases or conditions mediated through insulin resistance and impaired insulin secretion, comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.

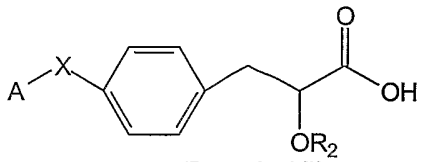
20. A method of treating a mammal suffering from the diseases or conditions selected from Type II diabetes, dyslipidaemia, hypertension, coronary heart disease, cardiovascular disease, atherosclerosis, diabetes nephropathy, glomerulonephritis, glomerularsclerosis, nephrotic syndorme, polycystic ovarian syndrome, eating disorders, psoriasis and obesity, comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.

21. A method of treating a mammal suffering from diabetes or diabetes-associated complications, comprising administering to the mammal a therapeutically effective amount of a pharmaceutical composition according to claim 15.

22. A method of treating a mammal suffering from diseases or conditions mediated through insulin resistance or impaired insulin secretion, comprising administering to the mammal a therapeutically effective amount of a pharmaceutical composition according to claim 15.

23. A method of treating a mammal suffering from disease or condition selected from Type II diabetes, dyslipidaemia, hypertension, coronary heart disease, cardiovascular disease, atherosclerosis, diabetes nephropathy, glomerulonephritis, glomerularsclerosis, nephrotic syndorme, polycystic ovarian syndrome, eating disorders, psoriasis and obesity, comprising administering to the mammal a therapeutically effective amount of a pharmaceutical composition according to claim 15.

24. A methodof preparing a compound of Formula VII,

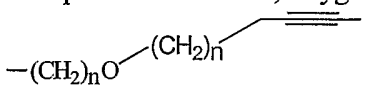


Formula VII

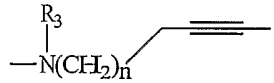
its pharmaceutically acceptable salts, solvates, enantiomers, N-oxides, polymorphs, metabolites, wherein

A represents alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, acyl, acyloxy, aroyl, aroyloxy, aryl, or heterocycle;

X represents no atom, oxygen,



or



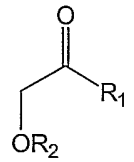
wherein n is an integer 0 to 3, and R_3 represents hydrogen or alkyl;

B represents aryl or heterocycle; and

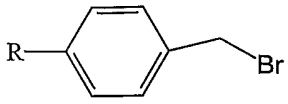
R_2 represents alkyl, cycloalkyl, aryl, or aralkyl,

the method comprising:

a) reacting a compound of Formula II with a compound of Formula III

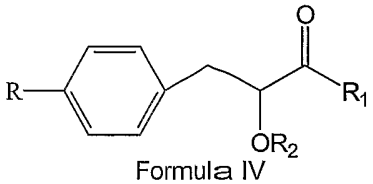


Formula II



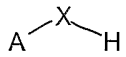
Formula III

to give a compound of Formula IV (wherein R_1 and R_2 are the same as defined earlier and R is bromine or iodine);



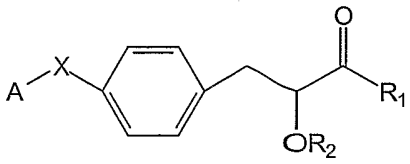
Formula IV

reacting the compound of Formula IV with a compound of Formula V



Formula V

to give a compound of Formula VI (wherein A and X are the same as defined earlier); and



Formula VI

hydrolyzing to the compound of Formula VI to give a compound of Formula VII.

25. The process according to claim 24, wherein the reaction of a compound of Formula II with a compound of Formula III to give a compound of Formula IV is carried out in a solvent selected from tetrahydrofuran and ether.

26. The process according to claim 25, wherein the reaction is carried out in tetrahydrofuran.

27. The process according to claim 24, wherein the reaction of a compound of Formula II with a compound of Formula III is carried out in the presence of a base selected from diisopropylamine, LDA and butyl lithiumpyridine.

28. The process according to claim 26, wherein the reaction is carried out in the presence of diisopropylamine.

29. The process according to claim 24, wherein the reaction of a compound of Formula IV with a compound of Formula V to give a compound of Formula VI is carried out in a solvent selected from dimethylformamide, chloroform, tetrahydrofuran, acetonitrile and dioxane.

30. The process according to claim 29, wherein the reaction is carried out in dimethylformamide.

31. The process according to claim 24, wherein the reaction of a compound of Formula IV with a compound of Formula V is carried out in the presence of an organic base selected from triethylamine, diethylamine, tributylamine, 4-dimethylamino pyridine and pyridine.

32. The process according to claim 31, wherein the reaction is carried out in the presence of triethylamine.

33. The process according to claim 24, wherein the reaction of a compound of Formula IV with a compound of Formula V is carried out in the presence of copper (I) iodide, triphenylphosphine, and a palladium catalyst selected from palladium (II) acetate, palladium (II) trifluoroacetate, palladium (II) propionate, tetrakis(triphenylphosphine) palladium (0), bis(dibezylidineacetone) palladium (0) or bis(triphenylphosphine) palladium (II) chloride.

34. The process according to claim 33, wherein the reaction is carried out in the presence of bis(triphenylphosphine) palladium (II) chloride.

35. The process according to claim 24, wherein the hydrolysis of a compound of Formula VI to give a compound of Formula VII is carried out in a solvent or solvent system selected from tetrahydrofuran, methanol, ethanol and mixture thereof.

36. The process according to claim 35, wherein the reaction is carried out in a mixture of methanol and tetrahydrofuran.

37. The process according to claim 24, wherein the hydrolysis of a compound of Formula VI to give a compound of Formula VII is carried out in the presence of a base selected from lithium hydroxide, sodium hydroxide or potassium hydroxide.

38. The process according to claim 37, wherein the reaction is carried out in the presence of sodium hydroxide.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2005/001002

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D209/68 A61K31/5415 A61P9/10

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D 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 practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/08501 A (DR. REDDY'S RESEARCH FOUNDATION; REDDY-CHEMINOR, INC) 25 February 1999 (1999-02-25) cited in the application	1,4, 7-13, 15-23
A	examples	24
X	WO 02/16331 A (ELI LILLY AND COMPANY; BROOKS, DAWN, ALISA; GODFREY, ALEXANDER, GLENN;) 28 February 2002 (2002-02-28) cited in the application example 1	1-3, 7-11, 15-23
P,X	WO 2004/113331 A (GALDERMA RESEARCH & DEVELOPMENT, S.N.C; CLARY, LAURENCE; THOREAU, ETIE) 29 December 2004 (2004-12-29) example 9	1-3,7-9, 12,13, 15-23

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

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 July 2005	22/07/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Diederen, J

INTERNATIONAL SEARCH REPORT

national application No.
PCT/IB2005/001002

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 18-24 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] *The additional search fees were accompanied by the applicant's protest.*

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2005/001002

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