(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 June 2008 (26.06.2008)

PCT

(10) International Publication Number
WO 2008/075380 A2

(51) International Patent Classification:
C07D 417/02 (2006.01)

(21) International Application Number:
PCT/IN2007/000599

(22) International Filing Date:
20 December 2007 (20.12.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2749/DEL/2006 21 December 2006 (21.12.2006) IN
1638/DEL/2007 1 August 2007 (01.08.2007) IN

(71) Applicant *(for all designated States except US)*: **IND-SWIFT LABORATORIES LIMITED** [IN/IN]; E-5, Industrial Area, Phace-II, S.A.S. Nagar, Mohali 160 055, Punjab (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **SRINIVASAN CHIDAMBARAM, Venkateswaran** [IN/IN]; Ind-Swift Laboratories Limited, E-5, Industrial Area, Phace-II, S.A.S. Nagar, Mohali 160 055, Punjab (IN). **JOHAR, Perminder, Singh** [IN/IN]; Ind-Swift Laboratories Limited, E-5, Industrial Area, Phace-II, S.A.S. Nagar, Mohali 160 055, Punjab (IN). **WADHWA, Lalit** [IN/IN]; Ind-Swift Laboratories Limited, E-5, Industrial Area, Phace-II, S.A.S. Nagar, Mohali 160 055, Punjab (IN).

(74) Agent: **AGGARWAL, Asha**; Ind-Swift Laboratories Limited, E-5, Phase-II, Industrial Area, Phase II, S.A.S Nagar, Mohali 160 055, Punjab (IN).

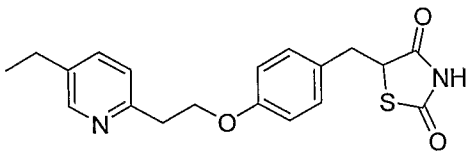
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv))*

Published:
— *without international search report and to be republished upon receipt of that report*

(54) Title: PROCESS FOR THE PREPARATION OF THIAZOLIDINE DERIVATIVES



(I)

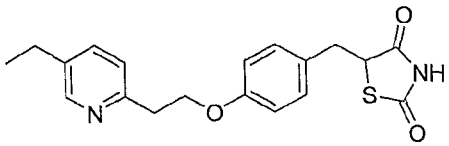
(57) Abstract: The present invention relates to an industrially advantageous process for the preparation of thiazolidine derivatives, such as pioglitazone of formula I and its pharmaceutically acceptable salts.This invention also provides novel synthetic intermediates useful in the process for the preparation of pioglitazone.

WO 2008/075380 A2

'PROCESS FOR THE PREPARATION OF THIAZOLIDINE DERIVATIVES'

FIELD OF THE INVENTION

The present invention relates to an industrially advantageous process for the preparation of thiazolidine derivatives. In particular, the present invention relates to a novel process for preparing pioglitazone of formula I and its pharmaceutically acceptable salts.

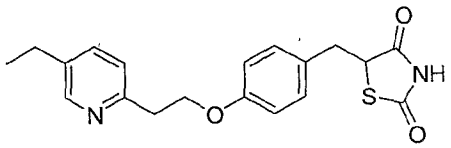


Formula I

This invention also relates to novel synthetic intermediates useful in the process for the preparation of pioglitazone.

BACKGROUND OF THE INVENTION

Pioglitazone of formula I is an oral antihyperglycemic agent that acts primarily by decreasing insulin resistance and is chemically known as (±)-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione.



Formula I

Pharmacological studies indicate that pioglitazone improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. Pioglitazone improves glucose resistance while reducing circulating insulin levels. Pioglitazone is currently marketed as its hydrochloride salt under trade name ACTOS.

Pioglitazone and its hydrochloride have been disclosed in US patent 4,687,777. This patent discloses preparation of pioglitazone by the reaction of 2-(5-ethyl-2-pyridyl)ethanol with 4-fluoronitrobenzene to give 4-[2-(5-ethyl-2-pyridyl)ethoxy] nitrobenzene, which is reduced to yield the corresponding amino compound, 4-[2-(5-ethyl-2-pyridyl)ethoxy]aminobenzene. This amino compound is then diazotized and treated with aqueous hydrobromic acid and methylacrylate to give methyl-2-bromo-3-{4-[2-(5-ethyl-2 pyridyl)ethoxy] phenyl}propionate; which in turn is treated with thiourea to yield a crucial intermediate, 5-{4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl}-2-imino-4-thiazolidinone, which is further hydrolyzed to obtain

pioglitazone of formula I. Several methods for production of various thiazolidinedione derivatives are described in Drugs of Future, 15, 1080 (1990); Chemical and Pharmaceutical Bulletin, 30, 3563 (1982); 30, 3580 (1982) and 32, 2267 (1984).

These methods invariably comprise low temperature diazotisation, condensation with lachrymetric and readily polymerizable reagent acrylic ester in the presence of a copper catalyst by Meerwein arylation reaction, to give a haloester, reacting it with thiourea to give an iminothiazolidinone and finally hydrolyzing the same to get the required thiazolidinedione derivative.

Meerwein arylation is associated with exothermicity, evolution of large amounts of nitrogen gas, tarry byproducts requiring cumbersome purification, lower yields and use of an excess of toxic and irritant acrylic ester. Moreover the bromo ester intermediate itself is lachrymatory in nature.

The above disadvantages and the problem of waste disposal coupled with effluent treatment of environmentally unfriendly substances and heavy metals make the known route technically and commercially unattractive.

US patent 4,812,570 discloses a process for the preparation of pioglitazone by reacting alkyl pyridyl ethanol with a halogenating agent or a sulfonyl halide to give a halo or alkyl- or aryl-sulfonyloxy derivatives, which when reacted with alkali metal salt of hydroxy benzaldehyde, gives alkyl pyridyl ethoxy benzaldehyde, which on further reaction with 2,4-thiazolidinedione followed by catalytic reduction gives pioglitazone. However this process leads to the formation of side products such as 2-vinyl-5-ethyl pyridine from tosylates. An alternative method for the preparation of alkyl pyridyl ethoxy benzaldehyde requires high temperature in presence of Raney nickel for the conversion of cyanide to formyl group. Additionally, the purification of the intermediates is also difficult in this process and the product is obtained in low overall yield.

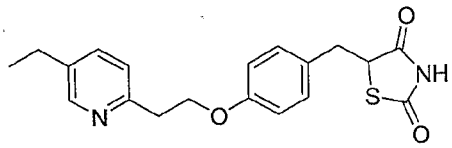
The processes of the prior art as described above, to prepare pioglitazone and its pharmaceutically acceptable salts, involve technically arduous methods like low temperature diazotization, evolution of large excess of nitrogen gas, handling of problematic reagents that are corrosive and toxic; intermediates, which are lachrymetric, not-amenable for easy scale up, formation of impurities, long reaction times, higher costs and special methods for effluent management and waste disposal etc. Therefore commercial applicability of the said processes is limited.

In view of the above mentioned drawbacks and disadvantages of the prior art procedures, it is desirable to develop an improved, efficient, cost effective, operationally facile, environmentally benign and amenable to scale up synthesis of pioglitazone.

Thus, the present invention meets the need in the art and provides an improved process for the preparation of thiazolidine derivatives particularly pioglitazone, which is unique with respect to its simplicity, cost effectiveness, and scalability by using mild reaction conditions and novel intermediates.

SUMMARY OF THE INVENTION

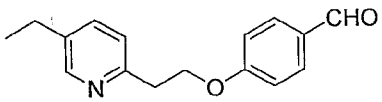
The present invention relates to a novel and efficient process for the preparation of thiazolidine derivatives such as pioglitazone of formula I,



Formula I

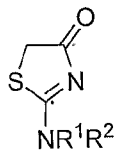
and pharmaceutically acceptable salts thereof which comprises:

reacting 4-[2-(5-ethyl-pyridin-2-yl)ethoxy]benzaldehyde of formula II,



Formula II

with a thiazolone compound of formula IIIa or salt thereof,



Formula IIIa

wherein R^1 and R^2 are same or different and R^1 and R^2 can be hydrogen or

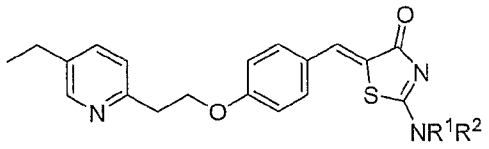
R^1 can be hydrogen and R^2 can be C_{1-6} alkyl group wherein alkyl can be linear, branched or cycloalkyl or alkenyl or alkynyl or aryl or alkaryl, or heterocyclic with one or two hetero atoms selected from nitrogen, oxygen or sulfur, or

R^1 and R^2 can be C_{1-6} alkyl group wherein alkyl can be linear, branched or cycloalkyl or alkenyl or alkynyl or aryl or alkaryl, or heterocyclic with one or two hetero atoms selected from nitrogen, oxygen or sulfur, or

R^1 and R^2 are C_{1-6} alkyl groups joined to each other at the terminal carbons forming five or six membered ring containing one or two hetero atoms selected from nitrogen, oxygen or sulfur such as piperidino, morpholino, piperizino, pyrrolidino, 4-alkyl piperizino, thiomorpholino, azetidino, aziridino, or

R^1 can be hydrogen or C_{1-6} alkyl and R^2 can be sulfonylalkyl or sulfonylalkylaryl or sulfonylaryl wherein aryl can be optionally substituted with alkyl or halo; alkanoyl or aranoyl or heteroaranoyl groups, C_{1-6} alkoxy group or dialkylamino or piperidino, morpholino, piperizino, pyrrolidino, 4-alkyl piperizino, thiomorpholino, azetidino, aziridino and the like.

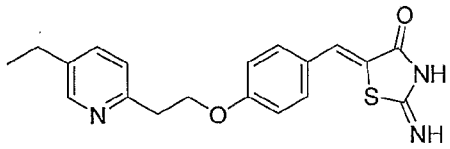
under mild reaction conditions to form a novel benzylidene derivative of formula IVa,



Formula IVa

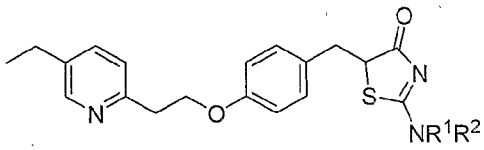
wherein R^1 and R^2 are as defined above,

or optionally with variable amounts of deprotected imine compound, 5-{4-[2-(5-ethyl-pyridin-2-yl)-ethoxy]-benzylidene}-2-imino-thiazolidin-4-one of formula V,



Formula V

reducing the resulting benzylidene deivative of formula IVa to form novel benzyl derivative of formula VIa,



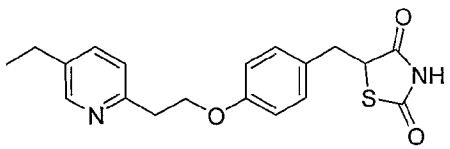
Formula VIa

wherein R^1 and R^2 are as defined above,

and converting the benzyl derivative of formula VIa to pioglitazone and pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

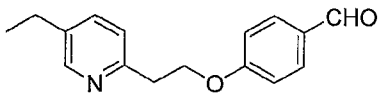
The process of this invention is a high throughput, novel and efficient process for the preparation of highly pure thiazolidine derivatives such as pioglitazone of formula I,



Formula I

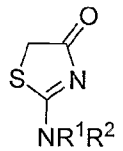
and pharmaceutically acceptable salts thereof.

One embodiment of the present invention provides an improved and efficient process for preparing pioglitazone of formula I and pharmaceutically salt thereof starting from 4-[2-(5-ethyl-pyridin-2-yl)ethoxy]benzaldehyde of formula II.



Formula II

Generally, aldehyde compound of formula II is reacted with a thiazolone compound of formula IIIa or salt thereof,



Formula IIIa

wherein R^1 and R^2 are same or different and R^1 and R^2 can be hydrogen or

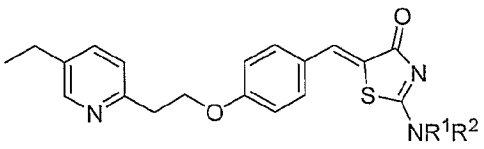
R^1 can be hydrogen and R^2 can be C_{1-6} alkyl group wherein alkyl can be linear, branched or cycloalkyl or alkenyl or alkynyl or aryl or alkaryl ,or heterocyclic with one or two hetero atoms selected from nitrogen, oxygen or sulfur, or

R^1 and R^2 can be C_{1-6} alkyl group wherein alkyl can be linear, branched or cycloalkyl or alkenyl or alkynyl or aryl or alkaryl, or heterocyclic with one or two hetero atoms selected from nitrogen, oxygen or sulfur, or

R^1 and R^2 are C_{1-6} alkyl groups joined to each other at the terminal carbons forming five or six membered ring containing one or two hetero atoms selected from nitrogen, oxygen or sulfur such as piperidino, morpholino, piperizino, pyrrolidino, 4-alkyl piperizino, thiomorpholino, azetidino, aziridino, or

R^1 can be hydrogen or C_{1-6} alkyl and R^2 can be sulfonylalkyl or sulfonylalkylaryl, or sulfonylaryl wherein aryl can be optionally substituted with alkyl or halo; alkanoyl or aranoyl or heteroaranoyl groups, C_{1-6} alkoxy group or dialkylamino or piperidino, morpholino, piperizino, pyrrolidino, 4-alkyl piperizino, thiomorpholino, azetidino, aziridino and the like,

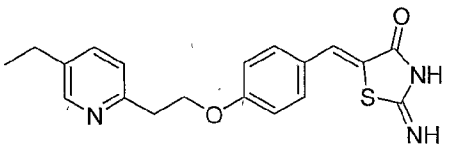
under mild reaction conditions to form a benzylidene derivative of formula IVa including isomers, tautomer, salts, solvates or mixtures thereof, that further forms the part of invention.



Formula IVa

wherein R^1 and R^2 are as defined above.

It has been observed that in some cases compound of formula IVa, *wherein atleast one of the R^1 or R^2 is hydrogen*, is found to have variable percentage of deprotected imine compound, 5-{4-[2-(5-ethyl-pyridin-2-yl)-ethoxy]-benzylidene}-2-imino-thiazolidin-4-one of formula V,



Formula V

However conditions favoring the formation of either pure compound of formula IVa or compound of formula V or mixture thereof depend upon choice and amount of solvent, base and catalyst, temperature variation, and concentration of reactants.

It has been observed that the presence of variable amount of compound of formula V in compound of formula IVa does not interfere with the further course of the reaction and its formation doesn't reduce the yield and purity of the ensuing intermediates in the preparation of pioglitazone.

Generally, the thiazolone compound of formula IIIa or salts thereof is reacted with aldehyde compound of formula II in the presence of base in suitable solvent. Usually the reaction can be conducted at a temperature range of 20 to 120°C, preferably at a temperature range of 20 to 90°C and it takes about 1-20 hours, preferably 3-10 hours for completion of reaction. The completion of reaction can be monitored by thin layer chromatography (TLC) or high performance liquid chromatography (HPLC). When absence of starting material is observed during the course of reaction, the solvent is optionally, completely or partially distilled off and the reaction mixture is cooled to a temperature of about 0°C to room temperature and filtered. The crude product is optionally neutralized with appropriate amount of aqueous mineral acid particularly hydrochloric acid to obtain benzylidene derivative of formula IVa.

Suitable solvent can be selected from amongst C_{1-6} aliphatic alcohols such as methanol, ethanol, isopropanol, n-propanol; C_{5-8} aliphatic or aromatic hydrocarbons such as hexane, pentane, heptane, toluene, xylene; C_{3-6} esters such as ethyl acetate, butyl acetate; C_{2-5} ethers such as diethyl ether, diisopropyl ether, t-butyl methyl ether, 1,2 dimethoxy ethane, tetrahydrofuran and dioxane; C_{3-6} ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone; C_{1-3} aliphatic

halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, dichloroethane; nitriles such as acetonitrile; and amides such as *N,N*-dimethylformamide or mixtures thereof.

The base can be selected from, but not limited to ammonia, ammonium acetate, methylamine, ethylamine, butylamine, pyrrolidine, piperidine, morpholine, piperazine, diethylamine, diisopropylamine and triethylamine; or their salts with aliphatic carboxylic acids preferably acetic acid; alkali metal alkoxides such as sodium methoxide and sodium ethoxide; alkali metal carbonate such as potassium carbonate and sodium carbonate; alkali metal hydroxide such as sodium hydroxide, potassium hydroxide, alkali metal bicarbonate such as sodium bicarbonate, potassium bicarbonate, alkali metal hydride such as sodium hydride; alkali metal acetate such as sodium acetate and potassium acetate; alkaline earth metal oxides such as calcium oxide and the like.

The base can be used as pure or a mixture thereof in a given ratio with or without a phase transfer catalyst such as benzyltriethylammonium chloride, cetyltrimethyl ammonium bromide, tetrabutylammonium bromide and the like.

It has been observed that in some cases, preferably wherein *R^1 is hydrogen or C_{1-6} alkyl and R^2 is alkanoyl, aranoyl or heteroaranoyl group,* the use of base like ammonium acetate gives exclusively compound of formula IVa and use of excess of piperidine gives exclusively compound of formula V as the product.

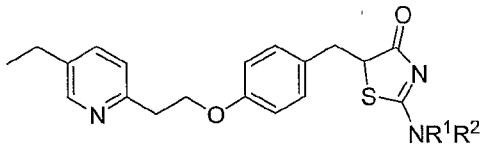
In one specific embodiment of the present invention, aldehyde compound of formula II is reacted with thiazolone compound of formula IIIa (*wherein R^1 is hydrogen and R^2 is sulfonyl-p-tolyl*), 4-methyl-N-(4-oxo-4,5-dihydrothiazol-2-yl)benzenesulfonamide in the presence of base in suitable solvent such as given above at a temperature of 20-90°C. After completion of reaction, solvent is distilled off and the reaction mixture is cooled and neutralized with dilute mineral acid such as hydrochloric acid to give *N*-(5-{4-[2-(5-ethyl-pyridin-2-yl)ethoxy]benzylidene}-4-oxo-4,5-dihydrothiazol-2-yl)-4-methyl- benzenesulfonamide.

The starting material, aldehyde compound of formula II can be prepared by conventional procedures reported in prior art in patents such as U.S. Patent Nos. 4,812,570, 4,898,947, 5,554,758, 5,952,509, 6,100,403 and EP 1 694 646 etc. Typically, aldehyde compound of formula II can be prepared by dissolving 5-ethyl-2-(2-hydroxy-ethyl)pyridine in inert solvent like toluene, tetrahydrofuran and the like; in the presence of base like triethylamine, aqueous sodium hydroxide and the like. The solution is cooled to 0°C to ambient temperature followed by the dropwise addition of methanesulfonyl chloride or p-toluenesulfonyl chloride or any other suitable protecting group. The reaction mixture is stirred for few hours at 0°C to ambient

temperature. After workup, the isolated product is treated with sodium or potassium salt of 4-hydroxy-benzaldehyde and stirred at ambient temperature under inert atmosphere for a period of about 1-4 hours. After work up, aldehyde compound of formula II is isolated.

Yet another starting material, thiazolone compound of formula IIIa can be procured from commercial source or prepared by conventional procedures reported in prior art such as EP 0126934, Organic Synthesis Collection Vol. 3, p-751 (1955) and Khimiko-Farmatsevticheskii Zhurnal, 9(6), 12-15; 1975, Farmatsevtichnii Zhurnal (kiev) (1965), 20(1), 6-9, Dyes & Pigments 57 (2), 107-114, 2003, etc.

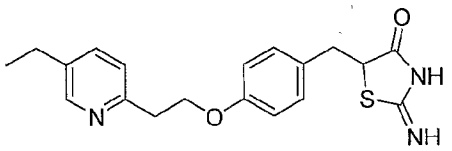
According to yet another embodiment of the present invention, benzylidine derivative of formula IVa optionally with variable amounts of 5-{4-[2-(5-ethyl-pyridin-2-yl)-ethoxy]-benzylidene}-2-imino-thiazolidin-4-one of formula V is further reduced to benzyl derivative of formula VIa, or an isomer or mixture or a tautomer form or a salt, or a solvate thereof.



Formula VIa

wherein R^1 and R^2 are as defined above. Compound of formula VIa, or an isomer or mixture or a tautomer form or a salt, or a solvate thereof, represents yet another novel and crucial intermediate in the preparation of pioglitazone, that further represents part of the invention.

The compound of formula VIa, *wherein atleast one of the R^1 or R^2 is hydrogen* is found to have variable percentage of deprotected imine compound of formula VI,



Formula VI

a known and crucial intermediate in the preparation of pioglitazone.

The reduction conditions employed for reducing compound of formula IVa may be selected from the known reduction methods and preferably can be performed by using known reducing agent selected from, but not limited to borane compounds and metal hydrides such as borane-tetrahydrofuran, borane-dimethylsulfide, borane-amine, borane-lewis acid, borane-triphenylphosphine, lithium aluminium hydride, sodium borohydride, lithium borohydride, diborane, potassium borohydride, tetraalkylammonium borohydride, zinc borohydride, and the like.

Along with reducing agent a metal ion and/or a ligand can also be used. Preferred metal ion is cobalt (II). Sources of cobalt (II) ion include cobalt chloride, cobalt diacetate, cobalt sulfate and the like. The ligand can be selected from dimethylglyoxime, 2,2'-bipyridyl, or 1,10-phenanthroline, optionally coligands like ethanolamines such as triethanolamine, diethanolamine, ethanolamine, cinchonine, cinchonidine, quinine, quinidine, and the like can be used.

Specifically, the reduction of compound of formula IVa is conducted at -20 to 45°C for a period of about 1-60 hours using an appropriate reducing agent as described above in a suitable solvent in the presence or absence of base or salt.

Base or salt can be selected from sodium hydroxide, potassium hydroxide, sodium carbonate, lithium carbonate, potassium carbonate, potassium bicarbonate, ammonium carbonate, ammonium bicarbonate, potassium bromide, potassium iodide, lithium iodide, lithium bromide, sodium halides and the like. Optionally, the base can be used in mixture with a phase transfer catalyst such as benzyltriethylammonium chloride, cetyltrimethyl ammonium bromide, tetrabutylammonium bromide.

The appropriate solvent can be mixture of water and C_{1-8} aliphatic alcohols selected from methanol, ethanol, isopropanol, n-propanol, the like or mixtures thereof. Additionally one can also add a solvent selected from ethers such as diethyl ether, diisopropyl ether, t-butyl methyl ether, 1,2-dimethoxyethane, tetrahydrofuran and dioxane; aromatic hydrocarbons such as toluene and xylene; aliphatic halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; aliphatic hydrocarbons such as pentane, hexane and heptane; esters such as ethyl acetate and butyl acetate; nitriles such as acetonitrile; *N,N*-dimethylformamide; dimethylsulfoxide; sulfolane or mixtures thereof.

In the present invention, the reaction is conducted preferably in the presence of water. In this case, the volume ratio of water to the solvent (the solvent using a lower alcohol singly, or a mixture of a lower alcohol and the organic solvent) ranges, for example, from 1 to 30 volume %, preferably from 10 to 20 volume %.

The completion of reaction is monitored by TLC and/or HPLC. After completion of reaction, the reaction mixture is quenched by the addition of a suitable quenching agent at low temperature to afford compound of formula VIa.

Suitable quenching agent can be selected from ammonium chloride, inorganic acids selected from sulfuric acid, hydrochloride acid, the like or organic acid selected from acetic acid, formic acid, benzoic acid, the like or any other reagent selected from ketones such as acetone, ethyl methyl ketone, methylisobutyl ketone.

In one specific embodiment of the present invention, compound of formula IVa *(wherein R^1 is hydrogen and R^2 is sulfonyl-p-tolyl)*, *N*-(5-{4-[2-(5-ethyl-pyridin-2-yl)ethoxy]benzylidene}-4-oxo-4,5-dihydrothiazol-2-yl)-4-methyl-benzenesulfon amide, is treated with hydrated cobaltous chloride in the presence or absence of ligand such as dimethylglyoxime in suitable solvent as defined above, followed by treatment with reducing agent like sodium borohydride at a temperature of 0-15°C for 4-9 hours. After complete reduction, the reaction mass is quenched with suitable quenching agent like ammonium chloride and N-(5-{4-[2-(5-ethyl-pyridin-2-yl)ethoxy]benzyl}-4-oxo-4,5-dihydrothiazol-2-yl)-4-methyl-benzenesulfonamide is isolated after removal of solvent and work up.

In yet another embodiment of the present invention, benzyl derivative of formula VIa can be hydrolysed and converted to pioglitazone of formula I and acid addition salts thereof by following the conventional procedures reported in the prior art. Typically compound of formula VIa is hydrolysed using stoichiometric to excess of mineral acid such as sulfuric acid, hydrochloric acid and the like, preferably hydrochloric acid.

The compound of formula I may be isolated as free base, but it is usually more convenient to isolate the compounds of the instant invention as acid addition salts. Such acid salts are exemplified by mineral salts like hydrochloride, hydrobromide, sulfate; organic acid salts like succinate, maleate, fumarate, malate, tartrate, oxalate; and sulfonates like methanesulfonate, benzenesulfonate, toluenesulfonate, etc.

These salts are prepared in the usual manner, i.e., by reaction of the free base with a suitable organic or inorganic acid, for example, one of the pharmaceutically acceptable acids as described above. Typically, the base of formula I is treated with a suitable solvent such as a ketone e.g. acetone or straight chain or branched C_{1-8} alcohol preferably methanol, ethanol; nitriles of general formula RCN wherein R is C_{2-5} alkyl; tetrahydrofuran, dioxane, dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone, sulfolane; halogenated solvents and/or mixture thereof and the like and acidified with an acid dissolved in a like solvent. Although it is advantageous to dissolve pioglitazone free base and acid in different solvents. The acid solution is added until the salt formation is complete.

According to yet another embodiment of the present invention, acid hydrolysis of benzyl derivative of formula VIa by hydrochloric acid directly yields pioglitazone hydrochloride. Generally benzyl derivative of formula VIa is treated with mineral acid such as hydrochloric acid in a suitable solvent, the reaction being performed at a temperature of from room temperature to reflux temperature of the solvent to yield pioglitazone hydrochloride. Solvent can be selected from C_{1-4} alcohols such as methanol, ethanol, isopropanol, n-propanol, n-butanol, isobutanol, the

like and mixtures thereof. The reaction can also be performed in the absence of solvents. The choice of solvent and strength of hydrochloric acid used depends upon the nature of protecting group and specific illustrations of suitable procedures can be had by reference to the examples herein below.

In one specific embodiment of the present invention, benzyl derivative of formula VIa (where R^1 is hydrogen and R^2 is sulfonyl-p-tolyl), N-(5-{4-[2-(5-ethyl-pyridin-2-yl)ethoxy]benzyl}-4-oxo-4,5-dihydrothiazol-2-yl)-4-methyl-benzenesulfonamide is hydrolysed with concentrated hydrochloric acid to obtain pioglitazone hydrochloride.

If desired, the pioglitazone hydrochloride can readily be converted to the corresponding free base by treatment with a suitable base such as potassium carbonate, sodium carbonate, ammonium hydroxide, potassium hydroxide, sodium hydroxide and the like.

In yet another embodiment of the present invention, pioglitazone hydrochloride can also be prepared from other organic carboxylic acid addition salts of pioglitazone by treating with hydrochloric acid, the said reaction being performed in the presence or absence of suitable solvents selected from C_{3-10} ketone preferably selected from acetone, ethyl methyl ketone, methyl isobutyl ketone; straight chain or branched C_{1-8} alcohol preferably methanol, ethanol; nitriles of general formula RCN wherein R is C_{2-5} alkyl; tetrahydrofuran, dioxane, dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone, sulfolane, halogenated solvents and/or mixture thereof.

Isolation and purification of the compounds and intermediates described above can be effected, if desired, by any suitable separation or purification procedure such as, for example, filtration, centrifugation, extraction, acid-base treatment, crystallization, conventional isolation and refining means such as concentration, concentration under reduced pressure, solvent-extraction, crystallization, phasic-transfer or chromatography, column chromatography, or by a combination of these procedures. Specific illustrations of suitable separation and isolation procedures can be had by reference to the examples herein below. However, other equivalent separation or isolation procedures could, of course, also be used.

According to yet another embodiment of the present invention, pioglitazone hydrochloride can further be purified by treatment with suitable organic solvents like acetonitrile, acetone, methanol, ethanol, isopropanol, n-propanol, methyl isobutyl ketone, ethyl methyl ketone, toluene, C_{1-6} ester, C_{2-5} nitriles, the like and/or mixtures thereof. Alternatively, pioglitazone hydrochloride can further be purified by treatment with hydrochloride such as ethyl acetate hydrochloride, alcoholic hydrochloride and the like, in the presence of suitable organic solvents like acetone, methanol, ethanol, isopropanol, n-propanol, methyl isobutyl ketone, ethyl methyl

ketone, toluene, C_{1-6} ester, C_{2-5} nitriles, the like and/or mixtures thereof. The reaction is preferably conducted at a temperature of room temperature to 60°C for a period of 1-10 hours.

Major advantages realized in the present invention are that process may be easily and conveniently scaled-up for industrial large-scale production and the process is simple, economical, high throughput and environment friendly.

Although, the following examples illustrate the present invention in more detail, but should not be construed as limiting the scope of the invention.

EXAMPLES

Example 1: Preparation of N-(5-{4-[2-(5-ethyl-pyridin-2-yl)ethoxy] benzylidene}-4-oxo-4,5-dihydrothiazol-2-yl)-4-methylbenzenesulfonamide

4-Methyl-N-(4-oxo-4,5-dihydrothiazol-2-yl)benzenesulfonamide (200g) was added to a solution of sodium hydroxide (62.2g) in methanol (1.5 lt) at 40°C followed by the addition of 4-[2-(5-ethyl-pyridin-2-yl)ethoxy]benzaldehyde (185g) and the mixture was refluxed for 7 hours. After completion of reaction, a part of methanol (1 lt) was distilled off under reduced pressure. The resulting slurry was cooled to 0-5°C and filtered. The residue was dried and slurried in a dilute hydrochloric acid. The resulting mixture was filtered, washed with water, and dried to obtain 351g of the title compound.

DSC (240.32°C peak)

IR (KBr, cm^{-1}): 3434, 1683, 1595, 1440, 1248, 1178, 1149, 1086, 1020, 900, 580

^{1}HNMR ($CDCl_3$ -DMSO-d_6) (δ ppm, 300 MHz): 8.35 (1H, bs), 7.84 (2H, d), 7.48 (1H, dd), 7.44 (1H, s), 7.43 (2H, d), 7.23 (2H, d), 7.20 (1H, d), 6.94 (2H, d), 4.37 (2H, t), 3.53 (1H, bs), 3.20 (2H, t), 2.61 (2H, q), 2.36 (3H, s), 1.22 (3H, t)

^{13}CNMR ($CDCl_3$ -DMSO-d_6) (δ ppm, 300 MHz): 182.03,176.31,158.93, 154.81, 148.34, 141.34, 140.19, 136.48, 135.34, 130.87, 128.51, 127.52, 127.47, 127, 126.22, 122.78, 114.57, 66.82, 36.74, 25.06, 20.90, and 14.99

MS m/z: 507.90 (M+1)

Example 2: Preparation of N-(5-{4-[2-(5-ethyl-pyridin-2-yl)ethoxy]benzyl}-4-oxo-4,5-dihydrothiazol-2-yl)-4-methyl-benzenesulfonamide

N-(5-{4-[2-(5-Ethyl-pyridin-2-yl)ethoxy]benzylidene}-4-oxo-4,5-dihydrothiazol-2-yl)-4-methyl-benzenesulfonamide (150g) was added to a solution of cobaltous chloride hexahydrate (2.1g) and dimethylglyoxime (2.1g) in a mixture of methanol, water and tetrahydrofuran (2.7lt, 4:1:1). The resulting suspension was cooled to 0-5°C followed by addition of sodium borohydride (29.1g).

The reaction mixture was further stirred at 0-5°C for 9 hours. Thereafter, the reaction was quenched by addition of ammonium chloride and further stirred for 2 hours. The organic solvents were distilled off under vacuum. The resulting product was filtered and dried to obtain 148g of the title compound.

DSC (180.14°C peak)

IR (KBr, cm^{-1}): 3446, 1736, 1568, 1509, 1325, 1086, 830, 660, 570

^{1}HNMR ($CDCl_3$-DMSO-d_6) (δ ppm, 300 MHz): 8.37 (1H, bs), 7.67 (2H, d), 7.54 (1H, dd), 7.35 (2H, d), 7.26 (1H, d), 7.11 (2H, d), 6.81 (2H, d), 4.67 (1H, dd), 4.28 (2H, m), 3.27 (1H, dd), 3.15 (2H, t), 3.05 (1H, dd) 2.59 (2H, q), 2.37 (3H, s), 1.19 (3H, t)

^{13}CNMR ($CDCl_3$-DMSO-d_6) (δ ppm, 300 MHz): 175.22, 170.49, 157.48, 155.19, 148.3, 143.36, 137.57, 136.58, 135.61, 130.28, 129.42, 127.74, 126.33, 122.95, 114.16, 66.62, 51.07, 36.73, 35.84, 24.96, 20.94, 15.22

MS m/z: 509.92 (M+1)

Example 3: Preparation of pioglitazone hydrochloride

N-(5-{4-[2-(5-Ethylpyridin-2-yl)ethoxy]benzyl}-4-oxo-4,5-dihydrothiazol-2-yl)-4-methylbenzenesulfonamide (110g) was refluxed in concentrated hydrochloric acid (770 ml) for 8 hours. The resulting solid was filtered and dried to obtain crude product which was then stirred in ethyl acetate hydrochloride (455 ml, 1%) for 2 hours, filtered and dried to obtain 69g of crude pioglitazone hydrochloride having purity of 98.56% by HPLC.

Pioglitazone hydrochloride, obtained above was taken in acetone (260 ml) and treated with methanolic hydrochloride (86 ml, 10%) at 45-50°C and stirred for 2 hours. Thereafter, the reaction mixture was cooled to 25-30°C, filtered and dried to obtain 61g of pure title compound having purity of 99.71% by HPLC.

Example 4: Preparation of 5-{4-[2-(5-ethyl-pyridin-2-yl)ethoxy]benzylidene}-2-morpholin-4-yl-thiazol-4-one

4-[2-(5-Ethyl-pyridin-2-yl)ethoxy]benzaldehyde (15g) was added to a solution of sodium hydroxide (2.47g), methanol (150 ml) and 2-morpholin-4-yl-thiazol-4-one (10.93g) at 25-30°C and the reaction mixture was stirred for 4 hours. Then reaction mixture was filtered, washed with isopropanol and dried to obtain 18.7g of the title compound.

IR (KBr, cm^{-1}): 3435, 1692, 1602, 1573, 1512, 1392, 1280, 1255, 1238, 1228, 1109, 1030, 888, 572

^{1}HNMR ($CDCl_3$-DMSO-d_6) (δ ppm, 300 MHz): 8.40 (1H, bs), 7.45 (3H, m), 7.26 (1H, s), 7.18 (1H, d), 6.96 (2H, d), 4.4 (2H, t), 4.08 (2H, m), 3.8 (4H, m), 3.63 (2H, m), 3.24 (2H, t), 2.63 (2H, q), 1.24 (3H, t)

Example 5: Preparation of 5-{4-[2-(5-ethyl-pyridin-2-yl)ethoxy]benzylidene}-2-morpholin-4-yl-thiazol-4-one

4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-benzaldehyde (100g) was added to a solution of sodium hydroxide (47g), methanol (1.0 lt) and 2-morpholin-4-ylthiazol-4-one hydrochloride (82.9g) at 25-30°C and the reaction mixture was stirred for 4 hours. Then reaction mixture was filtered, washed with isopropanol and dried to obtain 130g of the title compound.

Example 6: Preparation of 5-{4-[2-(5-ethyl-pyridin-2-yl)-ethoxy]-benzyl}-2-morpholin-4-yl-thiazol-4-one

5-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-benzylidene}-2-morpholin-4-yl-thiazol-4-one (110g) was added to a solution of cobaltous chloride hexahydrate (3.71g) and dimethylglyoxime (3.62g) in a mixture of methanol, water and tetrahydrofuran (1.98lt, 4:1:1). The resulting suspension was cooled to 0-5°C followed by addition of sodium borohydride (9.83g) at a temperature of 0-5°C. The reaction mixture was further stirred for 30 minutes. Thereafter, the reaction mixture was quenched by addition of ammonium chloride and stirred for 2 hours. The organic solvents were distilled off under vacuum and the resulting solid was extracted with ethyl acetate. Ethyl acetate was then distilled off under vacuum to obtain 94g of the title compound.

IR (KBr, cm^{-1}): 3440, 1693, 1611, 1555, 1511, 1490, 1390, 1280, 1239, 1109, 1028, 887, 830

^{1}HNMR ($CDCl_3$) (δ ppm, 300 MHz): 8.30 (1H, bs), 7.37 (1H, d), 7.11 (1H, d), 7.04 (2H, d), 6.74 (2H, d), 4.36 (1H, dd), 4.23 (2H, t), 3.85 (2H, m), 3.48 (7H, m), 3.14 (2H, t), 2.84 (1H, dd), 2.53 (2H, q), 1.15 (3H, t)

Example 7:Preparation of Pioglitazone hydrochloride

5-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-benzyl}-2-morpholin-4-yl-thiazol-4-one (35g) was taken in a solution of 4N hydrochloric acid (175 ml) and isopropanol (175 ml) and was refluxed for 8 hours. The solvent was distilled off under vacuum and cold water was added. The reaction mixture was filtered and dried to obtain 31 g of crude title compound which was recrystallized from acetonitrile.

Example 8: Preparation of 5-{4-[2-(5-ethyl-pyridin-2-yl)-ethoxy]-benzylidene}-2-imino-thiazolidin-4-one

4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-benzaldehyde (88.8g) and piperidine (8.3g) were added to a stirred suspension of *N*-(4-oxo-4,5-dihydro-thiazol-2-yl)-acetamide (55g) in ethanol (500 ml).

The reaction mixture was refluxed for 5 hours. Progress of the reaction was monitored with TLC for the absence of starting material. After the completion of the reaction, the reaction mixture was cooled to room temperature, filtered and dried to obtain 98g of the title compound.

^{1}**HNMR** (DMSO-d_6) (δ ppm, 300 MHz): 8.37 (1H, bs), 7.58 (1H, dd), 7.55 (1H, s), 7.51 (2H, d), 7.29 (1H, d), 7.08 (2H, d), 4.4 (2H, t), 3.17 (2H, t), 2.58 (2H, q), 1.18 (3H, t)

Example 9: Preparation of 5-{4-[2-(5-ethyl-pyridin-2-yl)-ethoxy]-benzyl}-2-imino-thiazolidin-4-one

Method A:

5-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-benzylidene}-2-imino-thiazolidin-4-one (2.0g) was added to a solution of cobaltous chloride hexahydrate (0.04g) and dimethylglyoxime (0.04g) in a mixture of methanol, water and tetrahydrofuran (36ml, 4:1:1). The resulting suspension was stirred for 10 minutes followed by addition of sodium borohydride (0.56g) at 15-20°C. The reaction mixture was further stirred at 15-20°C for 10 hours. Progress of the reaction was monitored with TLC and HPLC. After completion of the reaction, the reaction mixture was cooled to 0°C. Then reaction mixture was quenched by the addition of ammonium chloride solution and stirred for 30 minutes at 0°C. The resulting product was filtered and dried to give 1.8 g of the title compound.

^{1}**HNMR** (DMSO-d_6) (δ ppm, 300 MHz): 8.38 (1H, bs), 7.57 (1H, dd), 7.28 (1H, d), 7.12 (2H, d), 6.81 (2H, d), 4.36 (1H, dd), 4.31 (2H, t), 3.42 (1H, dd), 3.23 (2H, t), 2.9 (1H, dd), 2.66 (2H, q), 1.23 (3H, t).

Method B:

5-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-benzylidene}-2-imino-thiazolidin-4-one (5g) and benzyl triethyl ammonium chloride (0.32g) were added to a solution of cobaltous chloride hexahydrate (0.1g) and dimethylglyoxime (0.1g) in a mixture of methanol, water and tetrahydrofuran (172ml, 4.5:1:1.5). The resulting suspension was stirred for 10 minutes followed by addition of sodium borohydride (1.4g) at a temperature of 15-20°C. The reaction mixture was further stirred at 15-20°C for 10 hours. Thereafter, the reaction mixture was quenched by addition of ammonium chloride and stirred for 30 minutes. The resulting product was filtered and dried to give 4.2 g of the title compound.

Example 10: Preparation of *N*-(5-{4-[2-(5-ethyl-pyridin-2-yl)-ethoxy]-benzylidene}-4-oxo-4,5-dihydro-thiazol-2-yl)acetamide

4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-benzaldehyde (88.8g) and ammonium acetate (2.7g) were added to a stirred suspension of N-(4-oxo-4,5-dihydro-thiazol-2-yl)-acetamide (55g) in ethanol

(500 ml). The reaction mixture was refluxed for 5 hours. Progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was cooled to room temperature, filtered and dried to obtain 125g of title compound.

^{1}**HNMR** (DMSO-d_6) (δ ppm, 300 MHz): 8.33 (1H, bs), 7.55 (4H, m), 7.25 (1H, d), 7.08 (2H, d), 4.38 (2H, t), 3.13 (2H, t), 2.53 (2H, q), 2.03 (3H, s), 1.13 (3H, t).

Example 11: Preparation of 5-{4-[2-(5-ethyl-pyridin-2-yl)-ethoxy]-benzyl}-2-imino-thiazolidin-4-one

Method A:

N-(5-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-benzylidene}-4-oxo-4,5-dihydro-thiazol-2-yl)acetamide (2.0g) was added to a solution of cobaltous chloride hexahydrate (0.4g) and dimethylglyoxime (0.4g) in a mixture of methanol, water and tetrahydrofuran (35ml, 4:1:1). The resulting suspension was stirred for 10 minutes followed by the addition of sodium borohydride (0.5g) to the reaction mass at a temperature of 15-20°C. The reaction mixture was further stirred at 15-20°C for 10 hours, cooled to 0°C. Thereafter, the reaction was quenched by the addition of ammonium chloride solution (10 ml) and then stirred for 30 minutes at 0°C. The resulting product was filtered and dried to obtain1.7 g of the title compound.

Method B:

N-(5-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-benzylidene}-4-oxo-4,5-dihydro-thiazol-2-yl)-acetamide (5g) and benzyltriethylammonium chloride (0.32g) were added to a solution of cobaltous chloride hexahydrate (0.1g) and dimethylglyoxime (0.1g) in a mixture of methanol, water and tetrahydrofuran (172ml, 4.5:1:1.5). The resulting suspension was stirred for 10 minutes followed by the addition of sodium borohydride (1.39 g) at a temperature of 15-20°C. The reaction mixture was further stirred at 15-20°C for 10 hours. Thereafter, the reaction mixture was quenched by the addition of ammonium chloride and stirred for 30 minutes. The resulting product was filtered and dried to obtain 3.6 g of the title compound.

Example 12: Preparation of pioglitazone hydrochloride

Method A

5-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-benzyl}-2-imino-thiazolidin-4-one (2g) was taken in 2N hydrochloric acid (22 ml) and refluxed for 15 hours. The reaction mixture was cooled to 25°C. Charcoal powder (0.1g) was added to reaction mixture and refluxed for 20 minutes. The reaction mixture was filtered hot to remove charcoal. The filtrate was concentrated to remove water and excess of hydrochloric acid and kept at 25°C for 10 hours. Chilled water was added to the

resulting solid, filtered, washed with water followed by n-heptane and dried to obtain 0.7g of the title compound.

Method B

A solution of oxalic acid dihydrate (0.355g) in methanol (5ml) were added to stirred solution of 5-{4-[2-(5-ethyl-pyridin-2-yl)-ethoxy]-benzyl}-2-imino-thiazolidin-4-one (1 g) in mixture of methanol and dichloromethane (10ml, 1:1). The reaction mixture was stirred at room temperature for 30 minutes and filtered, followed by distillation. To the resulting residue, 2N hydrochloric acid (10ml) was added and refluxed for 12 hours. The reaction mixture was cooled to 25°C, filtered and washed with chilled water and n-heptane and dried to obtain 0.75 g of the title compound.

Example 13: Preparation of N-(5-{4-[2-(5-ethyl-pyridin-2-yl)-ethoxy]-benzylidene}-4-oxo-4,5-dihydro-thiazol-2-yl)-methanesulfonamide

N-(4-Oxo-4,5-dihydro-thiazol-2-yl)-methanesulfonamide (18.4g) was added to a solution of sodium hydroxide (8.23g) in methanol (250 ml) at 40°C followed by the addition of 4-[2-(5-ethyl-pyridin-2-yl)-ethoxy]-benzaldehyde (25g) and mixture was refluxed for 4 hours. A part of methanol was distilled off under reduced pressure, cooled to 0-5°C. The resulting residue was slurried in a solution of water (100 ml) and 2N hydrochloric acid (50 ml). The resulting slurry was filtered, washed with water and dried to obtain 40.23g of the title compound.

IR (KBr, cm^{-1}): 3516, 1718, 1594, 1510, 1252, 1179, 1133, 1027, 965, 847, 692, 548

^{1}HNMR ($CDCl_3$ -DMSO-d_6) (δ ppm, 300 MHz): 8.37 (1H, bs), 7.68 (1H, s), 7.53 (3H, m), 7.26 (1H, d), 7.05 (2H, d), 4.43 (2H, t), 3.22 (2H, t), 3.10 (3H, s), 2.63 (2H, q), 1.23 (3H, t)

Example 14: Preparation of N-(5-{4-[2-(5-ethyl-pyridin-2-yl)-ethoxy]-benzyl}-4-oxo-4,5-dihydro-thiazol-2-yl)- methanesulfonamide

N-(5-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-benzylidene}-4-oxo-4,5-dihydro-thiazol-2-yl)-methanesulfonamide (25g) was added to a solution of cobaltous chloride hexahydrate (0.41g) and dimethylglyoxime (0.4g) in a mixture of methanol, water and tetrahydrofuran (450ml, 4:1:1). The resulting suspension was cooled to 0-5°C followed by the addition of sodium borohydride (5.7g) at a temperature of 0-5°C. The reaction mixture was further stirred at 0-5°C for about 7 hours. Thereafter, the reaction mixture was quenched by addition of formic acid and stirred for 2 hours. The organic solvents were distilled off under vacuum. Water (150 ml) was added to the resulting reaction product and extracted with dichloromethane, distilled completely to obtain 16g of the title compound.

IR (KBr, cm^{-1}): 3429, 1738, 1580, 1511, 1324, 1300, 1261, 1133, 1024, 968, 802, 538

^{1}HNMR ($CDCl_3$) (δ ppm, 300 MHz): 8.44 (1H, bs), 7.51 (1H, dd), 7.23 (1H, d), 7.12 (2H, d), 6.82 (2H, d), 4.33 (1H, dd), 4.27 (2H, t), 3.38 (1H, dd), 3.27 (2H, t), 3.08 (1H, dd), 2.97 (3H, s), 2.64 (2H, q), 1.24 (3H, t)

Example 15: Preparation of Pioglitazone hydrochloride

N-(5-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-benzyl}-4-oxo-4,5-dihydro-thiazol-2-yl)-methanesulfonamide (8g) was refluxed in concentrated hydrochloric acid (56ml) for 3 hours. The resulting solid was filtered and dried to obtain 4.5g of title compound.

Example 16: Preparation of N-(5-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-benzylidene}-4-oxo-4,5-dihydro-thiazol-2-yl)-4-methyl-benzenesulfonamide

4-Methyl-*N*-(4-oxo-4,5-dihydro-thiazol-2-yl)-benzenesulfonamide (380g) was added to a solution of sodium hydroxide (123.7g) in methanol (4.18 lt) at 40°C followed by the addition of 4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-benzaldehyde (352g) and reaction mixture was refluxed for 7 hours. A part of methanol was distilled off under reduced pressure, and the resulting slurry was cooled to 0-5°C and filtered. The crude compound was dried and slurried in a solution of water (2 lt) and 1N hydrochloric acid. The resulting slurry was filtered, washed with water and dried to obtain 654g of the title compound.

Example 17: Preparation of N-(5-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-benzyl}-4-oxo-4,5-dihydro-thiazol-2-yl)-4-methyl-benzenesulfonamide

N-(5-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-benzylidene}-4-oxo-4,5-dihydro-thiazol-2-yl)-4-methyl-benzenesulfonamide (500g) was added to a solution of cobaltous chloride hexahydrate (7g) and dimethylglyoxime (6.9g) in a mixture of methanol, water and tetrahydrofuran (9lt, 4:1:1). The resulting suspension was cooled to 0-5°C followed by addition of sodium borohydride (97g) at a temperature of 0-5°C. The reaction mixture was further stirred at 0-5°C for about 9 hours. Thereafter, the reaction was quenched by the addition of formic acid and stirred for 2 hours. The organic solvents were distilled off under vacuum followed by the addition of water (2.5 lt). Above solution was filtered and dried to obtain 480g of the title compound.

Example 18: Preparation of Pioglitazone hydrochloride

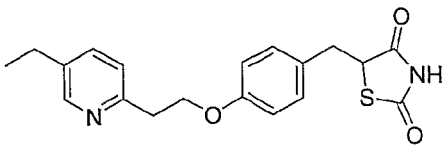
N-(5-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-benzyl}-4-oxo-4,5-dihydro-thiazol-2-yl)-4-methyl-benzenesulfonamide (450g) was refluxed in concentrated hydrochloric acid (3.15 lt) for 8 hours. The reaction mixture was filtered and the resulting residue was dried to obtain crude product. The crude product was taken in methanol (1.25 lt) followed by distillation. Ethyl acetate

hydrochloride (250 ml, 1%) was added to above product at 25-30°C, stirred for 2 hours, filtered and dried to obtain 248 g of pioglitazone hydrochloride having purity 97.21% by HPLC.

Pioglitazone hydrochloride (248g), obtained above was taken in acetone (927ml) and treated with methanolic hydrochloride (308ml, 10%) at 45-50°C and further stirred for 2 hours. The reaction mixture was cooled to 25-30°C, filtered and dried to obtain 204 g of pure title compound having purity 99.71% by HPLC.

WE CLAIM

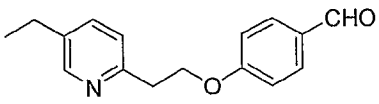
1. A process for the preparation of thiazolidine derivative, namely pioglitazone of formula I,



Formula I

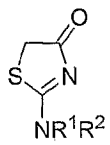
or pharmaceutical acceptable salt thereof which comprises:

(a) reacting 4-[2-(5-ethyl-pyridin-2-yl)ethoxy]benzaldehyde of formula II,



Formula II

with a thiazolone compound of formula IIIa,



Formula IIIa

wherein R^1 and R^2 are same or different and R^1 and R^2 can be hydrogen, or

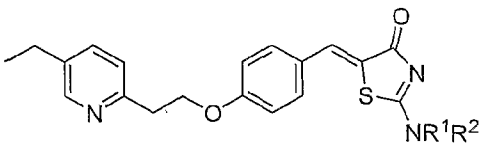
R^1 can be hydrogen and R^2 can be C_{1-6} alkyl group wherein alkyl can be linear, branched or cycloalkyl or alkenyl or alkynyl or aryl or alkaryl ,or heterocyclic with one or two hetero atoms selected from nitrogen, oxygen or sulfur, or

R^1 and R^2 can be C_{1-6} alkyl group wherein alkyl can be linear, branched or cycloalkyl or alkenyl or alkynyl or aryl or alkaryl, or heterocyclic with one or two hetero atoms selected from nitrogen, oxygen or sulfur, or

R^1 and R^2 are C_{1-6} alkyl groups joined to each other at the terminal carbons forming five or six membered ring containing one or two hetero atoms selected from nitrogen, oxygen or sulfur such as piperidino, morpholino, piperizino, pyrrolidino, 4-alkyl piperizino, thiomorpholino, azetidino, aziridino, or

R^1 can be hydrogen or C_{1-6} alkyl and R^2 can be sulfonylalkyl or sulfonylalkylaryl, or sulfonylaryl wherein aryl can be optionally substituted with alkyl or halo; alkanoyl or aranoyl or heteroaranoyl groups, C_{1-6} alkoxy group or dialkylamino or piperidino, morpholino, piperizino, pyrrolidino, 4-alkyl piperizino, thiomorpholino, azetidino, aziridino and the like

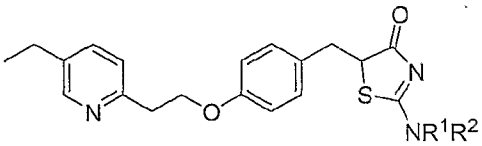
or salt thereof in the presence of base in suitable solvent to form a benzylidene derivative of formula IVa,



Formula IVa

wherein R^1 and R^2 are as defined above,

(b) reducing the resulting benzylidene derivative of formula IVa to form a benzyl derivative of formula VIa,



Formula VIa

wherein R^1 and R^2 are as defined above,

(c) hydrolysing the benzyl derivative of formula VIa to form pioglitazone or pharmaceutically acceptable salt thereof,

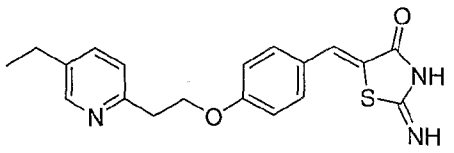
(d) isolating pioglitazone pharmaceutically acceptable salt thereof.

2. The process according to claim 1 step a), wherein base is selected from ammonia, ammonium acetate, methylamine, ethylamine, butylamine, pyrrolidine, piperidine, morpholine, piperazine, diethylamine, diisopropylamine, triethylamine, or its salt with aliphatic carboxylic acid and preferably acetic acid; alkali metal alkoxides; alkali metal carbonate; alkali metal hydroxide; alkali metal bicarbonate; alkali metal hydride; alkali metal acetate.

3. The process according to claim 1 step a), wherein solvent is selected from C_{1-6} alcohols, C_{5-8} aliphatic or aromatic hydrocarbons, C_{3-6} esters, C_{2-5} ethers, C_{3-6} ketones, C_{1-3} aliphatic halogenated hydrocarbons, acetonitrile, *N,N*-dimethylformamide, tetrahydrofuran, dioxane.

4. The process according to claim 1 step a), wherein the reaction is conducted at a temperature range of about 20 to 120°C.

5. The process according to claim 1 step a), wherein benzylidene derivative of formula IVa may have variable percentage of deprotected imine compound, 5-{4-[2-(5-ethyl-pyridin-2-yl)-ethoxy]-benzylidene}-2-imino-thiazolidin-4-one of formula V.



Formula V

6. The process according to claim 1 step b), wherein benzylidene derivative of formula IVa is reduced with a complex hydride reducing agent or a source thereof selected from borane compounds and metal hydrides, in the presence of suitable metal ion, ligand, optionally a coligand, base or a salt.

7. The process according to claim 1 step b), wherein reduction is performed using reducing agent selected from diborane, borane-tetrahydrofuran, borane-dimethylsulfide, borane-amine, borane-lewis acid, borane-triphenylphosphine, lithium aluminium hydride, sodium borohydride, lithium borohydride, potassium borohydride, tetraalkylammonium borohydride, zinc borohydride, and the like.

8. The process according to claim 1 step b), wherein preferably the reduction is performed using sodium borohydride.

9. The process according to claim 1 step b), wherein reduction is performed in the presence of suitable metal ion like cobalt (II) or source thereof selected from cobalt chloride, cobalt diacetate, cobalt sulfate and the like.

10. The process according to claim 1 step b), wherein reduction is performed in the presence of ligand selected from dimethylglyoxime, 2,2'-bipyridyl, 1,10-phenanthroline.

11. The process according to claim 1 step b), wherein reduction is optionally performed in the presence of base or salt selected from sodium hydroxide, potassium hydroxide, sodium carbonate, lithium carbonate, potassium carbonate, potassium bicarbonate, ammonium carbonate, ammonium bicarbonate, potassium bromide, potassium iodide, lithium iodide, lithium bromide, sodium halides and the like.

12. The process according to claim 1 step b), wherein reduction is optionally performed in the presence of phase transfer catalyst such as benzyltriethylammonium chloride, cetyltrimethyl ammonium bromide, tetrabutylammonium bromide.

13. The process according to claim 1 step b), wherein reduction is optionally performed in the presence of coligand selected from ethanolamines such as triethanolamine, diethanolamine, ethanolamine, cinchonine, cinchonidine, quinine, quinidine.

14. The process according to claim 1 step b), wherein the reaction is performed at a temperature range of about -20 to 45°C.

15. The process according to claim 1 step c), wherein hydrolysis is performed in the presence of mineral acid like sulfuric acid, hydrochloric acid and the like.

16. The process according to claim 1 step c), wherein hydrolysis is optionally performed in the presence of solvent selected from C_{1-4} alcohols.

17. The process according to claim 1 step c), wherein hydrolysis is performed at a temperature of from room temperature to reflux temperature of the solvent.

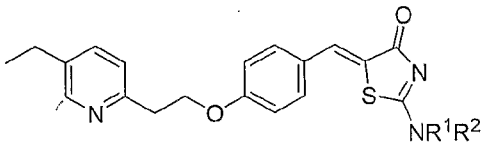
18. The process according to claim 1, wherein pioglitazone is isolated as hydrochloride.

19. The process according to claim 1, wherein preferably R^1 is hydrogen and R^2 is selected from amongst C_{1-6} alkyl group, morpholino, alkanoyl, aranoyl, sulfonylalkyl and sulfonylalkylaryl.

20. The process according to claim 1, further comprises purifying pioglitazone hydrochloride in suitable solvent such as acetonitrile, acetone, methanol, ethanol, isopropanol, n-propanol, methyl isobutyl ketone, ethyl methyl ketone, toluene, C_{1-6} ester, C_{2-5} nitriles, the like and/or mixtures thereof.

21. The process according to claim 1, further comprises purifying pioglitazone hydrochloride by treating with hydrochloride such as ethyl acetate hydrochloride, alcoholic hydrochloride and the like in the presence of suitable organic solvents like acetonitrile, acetone, methanol, ethanol, isopropanol, n-propanol, methyl isobutyl ketone, ethyl methyl ketone, toluene, C_{1-6} ester, C_{2-5} nitriles, the like and/or mixtures thereof.

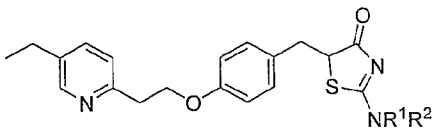
22. A benzylidene derivative of formula IVa, including isomers, tautomers, salts, solvates or mixtures thereof,



Formula IVa

wherein R^1 and R^2 are as defined above.

23. A benzyl derivative of formula VIa, including isomers, tautomers, salts, solvates or mixtures thereof,



Formula VIa

wherein R^1 and R^2 are as defined above, provided together R^1 and R^2 are not hydrogen.