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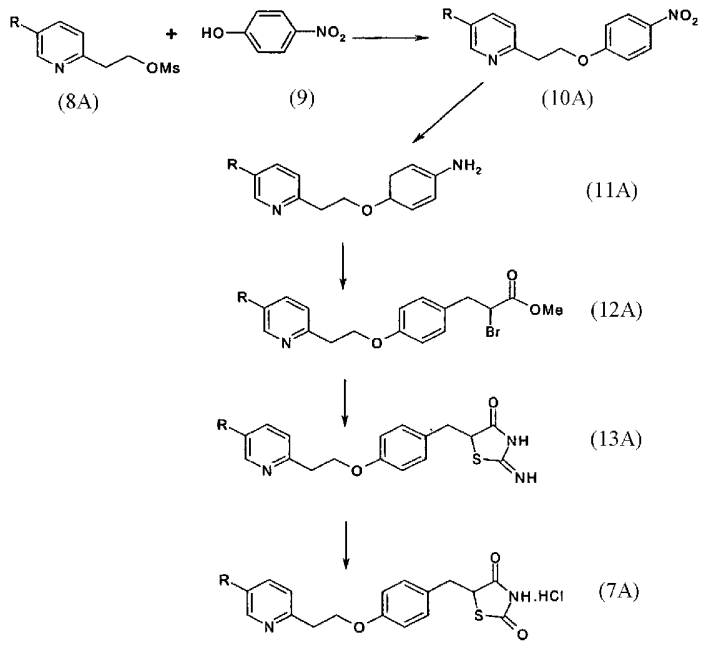
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[Continued on next page]

(54) Title: IMPROVED PROCESS FOR PREPARATION OF THIAZOLIDINEDIONE DERIVATIVES



(57) Abstract: Method of obtaining anti diabetic agent of formula (7A) where in R=alkyl, aryl, heteroaryl, or trifluoromethyl as per the reaction scheme wherein the corresponding pyridine base of general formula (8A), where in Z is a leaving group other than halogen with p-nitro phenol (9) under basic conditions, followed by (a) catalytically reducing the nitro group in compound of general formula (10A) with hydrogen (b) diazotizing the amino group present in the organic residue (11A) (c) converting the diazotized residue into a derivative of 2-halopropionate of general formula (12A) following Meerwein arylation using acrylate ester (d) cyclizing the derivative of 2-halopropionate of formula (12A), with thiouriea (e) hydrolizing the resulting imine (13A), thus giving thiazolidinedione of general formula (7A) as an antidiabetic agent, in particular pioglitazone where R=ethyl in (7A).

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— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

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IMPROVED PROCESS FOR PREPARATION OF THIAZOLIDINEDIONE DERIVATIVES

Field of Invention

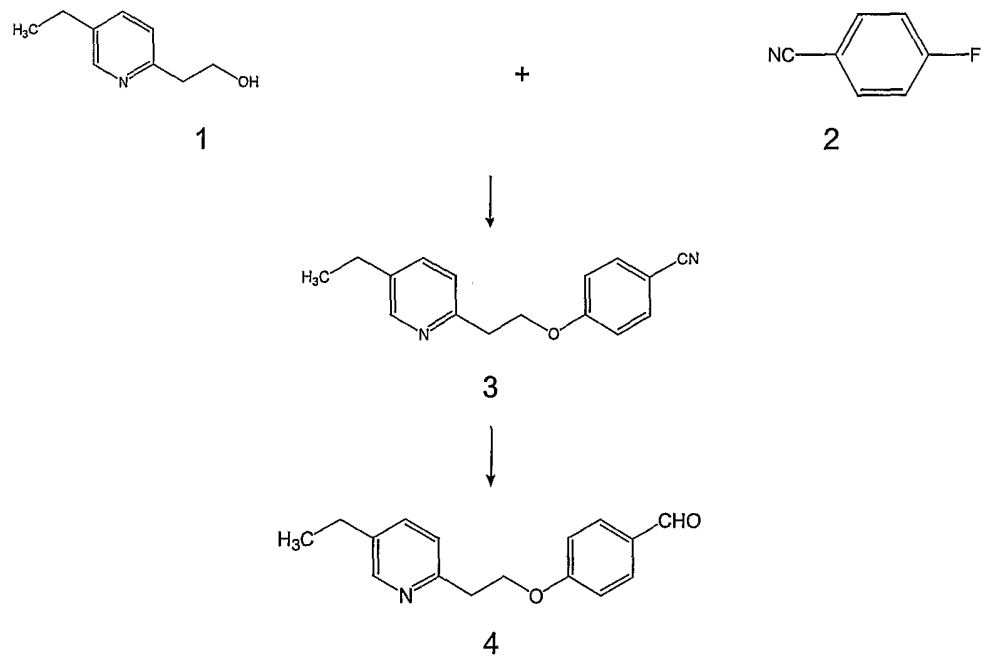
The present invention provides a novel method for preparation of Thiazolidinedione derivatives including pioglitazone, cglitazone, englitazone and rosiglitazone and their pharmaceutically acceptable salts

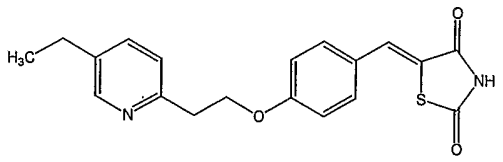
Background of the Invention

The preparation of thiazolidinedione derivative especially pioglitazone hydrochloride is described in various publications and patents. A brief discussion of the relevant prior art is given below.

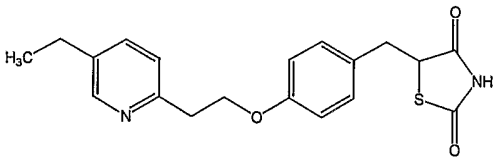
Y. Momose et al in *Chem. Pharm. Bull*; 39, 1440, (1991), K. Meguro *et al.* in the Japanese Patent No., 139182 and the article in *Chem. Abstr.* 109: 6504h, (1988) describe a process for making thiazolidinedione derivative including pioglitazone based on Scheme-1

Scheme-1

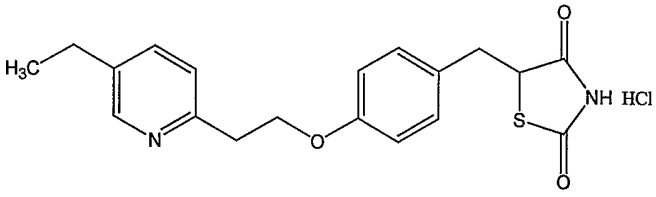




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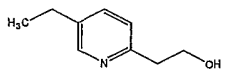
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The yields are generally <50%. The conversion of the nitrile to aldehyde involves reduction with Raney Nickel alloy in formic acid a reaction that is cumbersome and hazardous. The yield of the reduced product is as low as 30%. Further the conversion of compound 5 in Scheme-1, *i.e.* 5-[4-(2-(5-ethyl-2-pyridyl) ethoxy]benzylidene]2.4-thiazolidinedione to Pioglitazone base is effected in DMF as solvent using palladium black catalyst. The reaction requires hydrogen pressure of 50kg/cm^2 and a temperature in the range of 50-60°C. These operations are low yielding (<20%), cumbersome, hazardous using expensive raw materials such as palladium and therefore remain unattractive to the industry.

D. A. Clark *et al.*, in *J. Med Chem* 34, 319-325, (1991), describe a process for making substituted dihydropyran and dihydrobenzofuran thiazolidinedione including Englitazone. This reaction process involves reduction of double bond using palladium on carbon in acetic acid as solvent. The reaction gives low yield of pioglitazone in pure form (<10%) and the product is contaminated with material obtained from the reduction of pyridine ring that are difficult to separate.

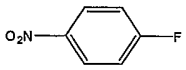
K. Meguro *et al., in U. S. Pat. No.* 4, 687, 777, Sohda. T. *et al.,* in 'Arznecna-Forsch (ARZANAD), 40(1), 37-42 (19910), and the patent EP 193256 describe the synthesis of Pioglitazone as per Scheme-2.

SCHEME – 2

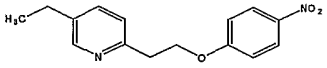


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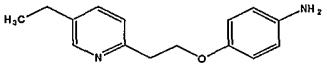
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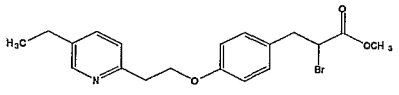
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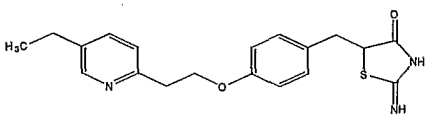
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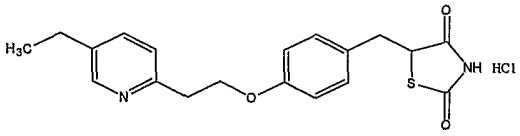
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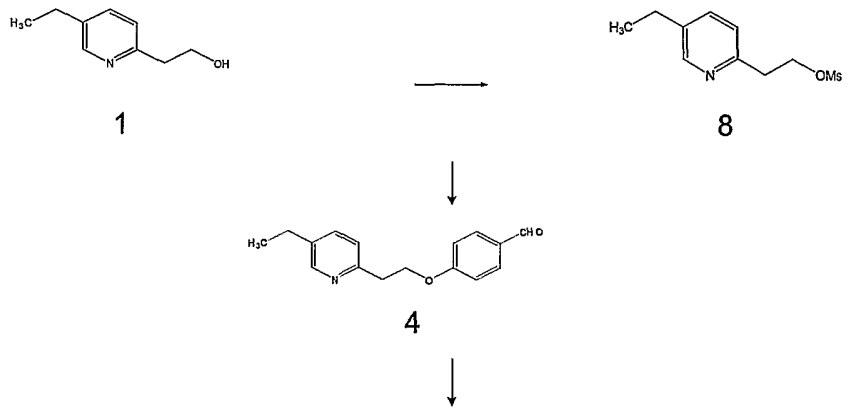
Following Scheme-2, compound represented by formula –7, is prepared by subjecting compound represented by formula-13, to hydrolysis. This reaction is carried out in a

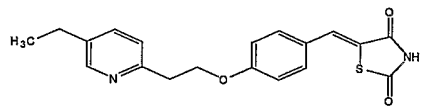
solvent using mineral acid. The solvents of choice are alcohols e.g. methanol, ethanol, propanol, butanol, isobutanol, 2-methoxy ethanol etc, dimethyl sulfoxide, sulfolane, dioxane and tetrahydrofuran, dimethoxy ethane etc., and the mineral acid used are hydrochloric acid, sulfuric acid, hydrobromic acid, etc. The reaction temperature ranges from 20-150°C with the process taking up to 20 hours. The reaction for producing compound of formula 10 from compound of formula 1 is carried out with sodium hydride and in solvent like dimethyl formamide or tetrahydrofuran at temperatures ranging from –10 to 30°C. The reduction of nitro group is done using palladium on carbon as catalyst. Compound of formula 12 is produced by subjecting compound of formula 11 to diazotization in aqueous solution of hydrobromic acid, then allowing the resultant reaction mixture to react with methyl acrylate to form the α -bromo ester of formula 12 in presence of copper catalysts. Compound of formula 12 needs to be purified by chromatography before subjecting to further reaction. Compound of formula 12 is then allowed to react with thiourea to give compound of formula -13. The reaction is carried out in methanol or isopropanol, at high temperature of around 80-100°C. Compound – 12, is generally subjected to hydrolysis without isolation to form Pioglitazone hydrochloride 7.

p-Fluoro nitrobenzene is known to dimerize under the conditions described in the publications. Formation of impurities due to dimerization of fluoro nitrobenzene are difficult to isolate making such processes unattractive.

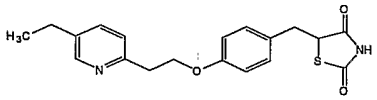
Other methods for the preparation of derivatives of thiazolidinedione are given in publications JPA-S63 (1988)-139182; EP-A-257781; *Chem. Pharm. Bull.,* 39, 1440, (1991); JP-A H5 (1993)-112483; and EP-A 506273 represented by scheme-3.

SCHEME- 3

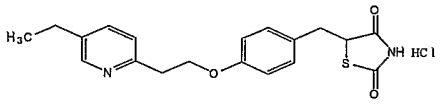




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Here 2-(2-pyridyl)ethyl alkane sulfonate compound of formula-8 in Scheme-3 is reacted with p-hydroxy benzaldehyde in a suitable solvent selected from aliphatic halogenated hydrocarbons, aromatic hydrocarbons, ethers, water, ethyl acetate and dimethyl formamide or in a suitable mixture of them in the present of a base. When the reaction is conducted in non-aqueous organic solvent the reaction takes approximately 25-30h. for completion. Due to β-elimination reaction as the side reaction, 2-vinyl pyridine is produced thereby lowering the yield and purity of the benzaldehyde compound in subsequent reaction steps. If the reaction needs to be conducted in aqueous and non-aqueous solvent, a phase transfer catalyst is required. The formation of thick slurry creates problems of inhomogeneous mixing thereby affecting the yield (as low 50-60%) and purity of the benzaldehyde compound 4. Further the reduction of double bond in the compound of formula 5 in Scheme-3 requires expensive noble metal catalysts, high pressure and high temperature. The process described as per Scheme-3 has serious limitations for industrial application.

U.S. Patent No. 6, 100, 403 describes a process where attempt has been made to overcome drawbacks of earlier processes by employing ethanol or isopropanol for the condensation of p-hydroxy benzaldehyde with 5-ethylpyridine-2-ethanol and the subsequent condensation of the aldehyde derivative in toluene or ethyl acetate. This approach significantly reduces the formation of 2-vinyl pyridine. The major draw back in the process described is the reduction of compound of formula - 5 in Scheme-3, viz. 5-[4-[2-(ethyl-2-pyridyl) ethoxy] benzylidene] 2,4-thiazolidinedione using palladium on carbon as catalyst is that it requires hydrogen pressure of 50 kg/cm and temperature of

110°C for 5 hours for completion of the reduction. The yield obtained is about 66% with substantial quantities of impurities that need extensive purification. The high hydrogen pressures and temperatures used in this reaction make this process unsuitable for effective industrial use.

U. S. Pat. No. 5,585,495 discloses an attempt to circumvent the high-pressure reduction of double bond in compound -5 in Scheme-3 using sodium borohydride, cobalt salts like cobaltous chloride or cobaltous di acetate and dimethyl glyoxime as a ligand meant for complexing their metal ion. The yields in this process are inconsistent. The work up is cumbersome and requires the isolation of cobalt salts. The process has not found favor for industrial use.

Several references disclose cobalt catalyzed reduction of compound 5-[4-(2-(-5-ethyl-2pyridyl ethoxy] benzylidene] 2,4-thiazolidinedione, prepared by the condensation of 5-ethyl pyridine-2-ethanol with p-hydroxy benzaldehyde following Scheme-3. [Ref; U. Leuteneggar., *Agnew. Chem Int Ed. Eng.*, 28:60, 1989, M. Ricroch *et al., J. org. met Chem.,* 67, 119, (1974); J. O. Oshy *et a.*, JACS, 108, 67-72, (1986). These methods have the inherent disadvantage of preparing cobalt complexes of sodium borohydride either with semicorrin, pyridinato cobaloxime, chloro pyridinato cobaloxime or Vitamin B 12. Reductions have also been reported using lithium aluminum hydride.

Drugs of Future., 9, (1991), 16, 9, discloses a multi step process via carbon alkylation for the preparation of thiazolidinedione.

All the processes described in the prior art are cumbersome needing extensive workup with high pressures/temperatures, low yielding, hazardous, expensive and therefore remain unattractive for industrial use.

It has been a long-standing need of the industry to develop industrially viable processes that are cost effective, simple, efficient and safe to implement in the industrial scale.

The present invention is a step in the desired direction as it provides method for the preparation of pharmaceutically active compounds, such as thiazolidinedione derivatives including Pioglitazone, Cglitazone, Englitazone and Rosiglitazone etc and their pharmaceutically acceptable salts.

The invention further provides for high yielding process for the preparation of Pioglitazone intermediates and subsequent conversion to Pioglitazone hydrochloride without resorting to extensive and cumbersome purification procedures.

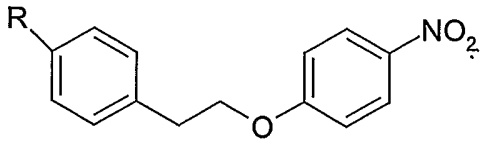
Objects of the invention

The main object of the present invention is to provide a novel method for the preparation of thiazolidinedione derivatives of formula including their pharmacologically acceptable salts such as the acid salts including hydrochloride, hydro bromide, sulfate, organic acid salts like succinate, maleate, fumarate, laclate, tartrate, sulfonates like methane sulfonates, toluene sulfonates, benzene sulfonates and basic salts including alkali metal salts such as the sodium salt, potassium salt, alkaline earth metal salts like calcium salt etc.

Another object of the present invention is to provide method for the preparation of such compounds having desirable pharmacological activity, broad safety margins, without toxicity or unfavorable side reaction.

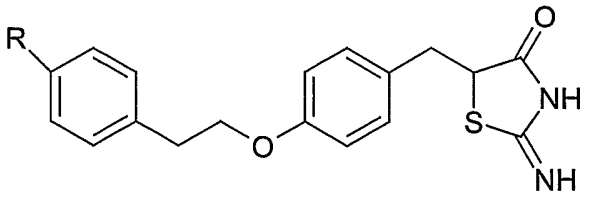
Yet another object of the invention is to provide process for the preparation of a compound of the general formula 10A by employing readily available raw materials like p-nitro phenol as the reagent.

Another object of the present invention is to provide efficient and high yielding process for the converting the nitro group in general formula 10A to the corresponding amino group under controlled reduction using effective catalysts.



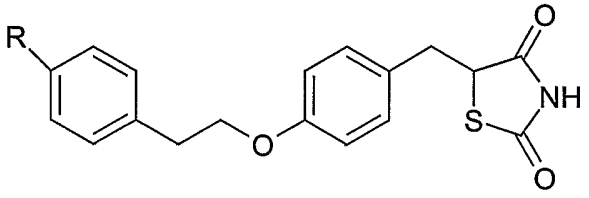
10A

Yet another object of the present invention is to provide a method for converting the compound of general formula-13A to compound of general formula-7A by hydrolysis using mineral acid and with/without employing any other organic liquid or alcoholic solvents as co solvents.



13A

Yet another object of the invention is to provide efficient and cost effective process for preparation of pioglitazone hydrochloride.



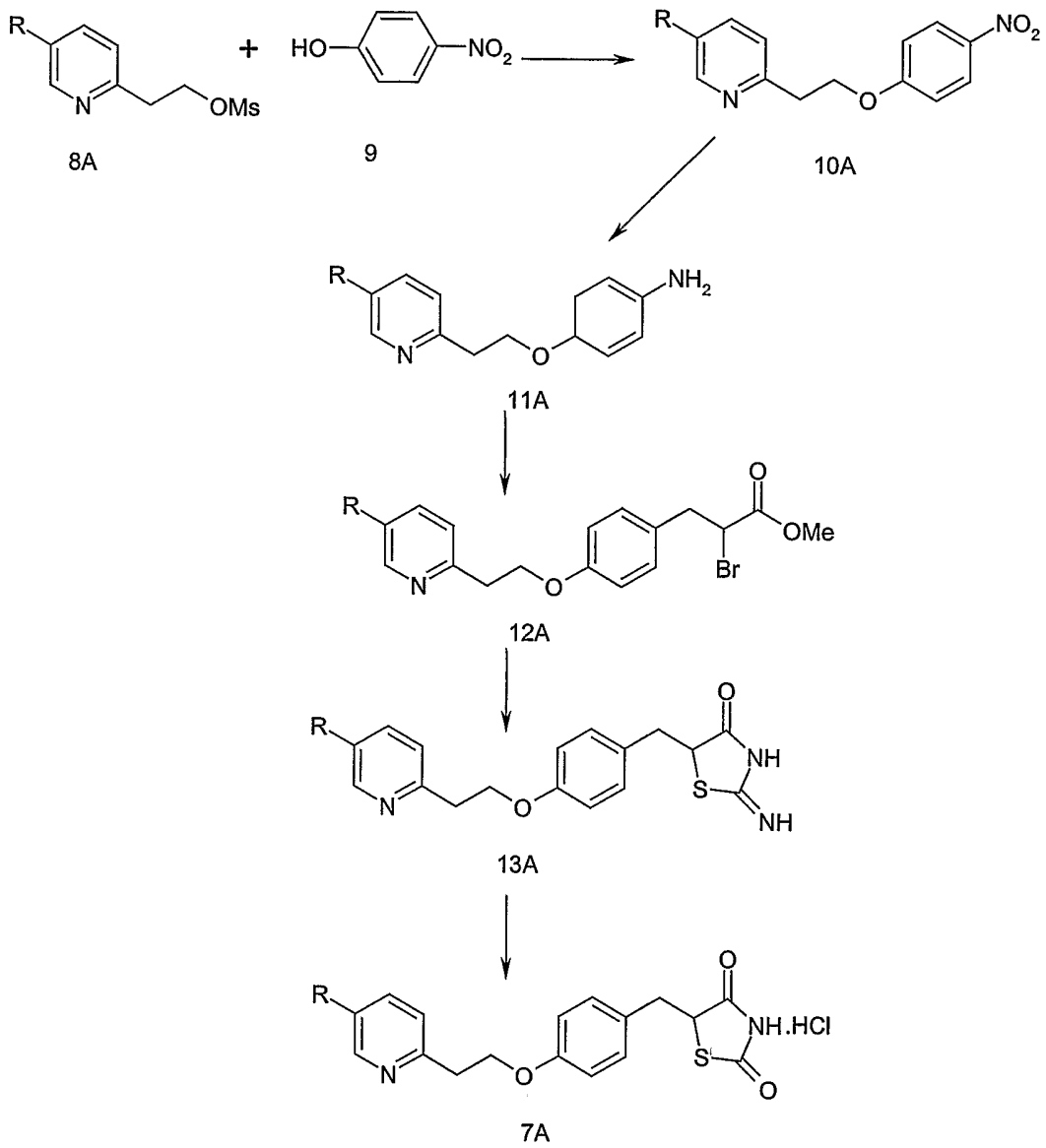
7A

Another object of the present invention is to provide a commercially viable process for the preparation of pharmaceutically acceptable salts of thiazolidinedione and the like. It may be noted that 'R' may vary from n-alkyl, acyl, aryl, heteroaryl or trifluormethyl groups.

Summary of the invention;

The process of this invention is illustrated in Scheme-4

SCHEME 4



where R is alkyl, acyl, aryl, heteroaryl or trifluormethyl.

In accordance with this invention the process of preparation of thiazolidinedione derivatives and their pharmaceutically acceptable salts comprise

- reacting 2-(5-R-2-pyridine) ethyl methane sulfonate of general formula 8A, where R is alkyl, aryl, aryl or heteroaryl with p-nitro phenol in an organic solvent and in presence of suitable base
- Conversion of the adduct thus obtained viz. 4-(2-(5-R-pyridine) ethoxy nitro benzene of general formula 10A to the corresponding amine by catalytic reduction employing noble metal catalysts or Raney nickel and hydrogen.

- The amine viz. 4-(2-(5-R-pyridine) ethoxyaniline of general formula 11A is diazotized in a manner known to those skilled in the art. The diazo compound is allowed to undergo Meerwein arylation using ethyl acrylate to obtain 2-bromo-3-(4-2-5-R-2-pyridyl) ethoxyphenyl) propionate of general formula 12A.
- The Meerwein arylated product 12A is allowed to react with thiourea in situ with out isolation of 12A to give the imino thiazolidinone viz. 5-(4-(2-(5-R-2-pyridyl) ethoxy) benzyl-2-imino-4-thiazolidinone of general formula 13A.
- The imino thiazolidinone under suitable acidic condition is converted to the thiazolidinedione derivative represented by the general formula 7A.
- When R=ethyl (C_2H_5), in formula 7A and using dilute hydrochloric acid, the imino thiazolidinone 13A is converted to pioglitazone hydrochloride.

Detailed Description of the Invention

The process as per scheme-4 is described in detail for pioglitazone hydrochloride where R is ethyl (CH_2CH_3) as a preferred embodiment.

The present invention provides a process for preparing a compound of the formula-10, by reacting 2-(5-ethyl-2-pyridyl) ethyl-p-methyl sulfonate of formula –8, with p-nitro phenol in an organic solvent comprising of any aromatic hydrocarbons e.g. Toluene, xylene or benzene or any aliphatic nitriles like acetonitrile, propionitrile etc or any aprotic solvent like dimethyl formamide or dimethyl sulfoxide, the preferred solvent being aliphatic nitriles, especially acetonitrile. The reaction is carried out in presence of an inorganic base selected from any alkali metal carbonates, bicarbonates like sodium, potassium carbonate or bicarbonate or alkaline earth metal carbonates like calcium carbonate preferably potassium carbonate. The reaction is generally conducted at elevated temperature ranging from about 20 to about 80°C, preferably from about 30 to about 50°C. The compound thus prepared is isolated using aromatic hydrocarbon solvents like toluene, benzene or xylene and purified using an aliphatic solvent selected from pentane, hexane or heptanes and ethers like isopropyl ether or diethyl ether. Resulting in the pure nitro compound without resorting to extensive recrystallization or chromatography.

The compound of formula 10 is converted to compound of formula 11, by reduction of the nitro group by catalytic hydrogenation using Raney Nickel. The reduction can also be carried out using conventional reagents like iron / hydrochloric acid, sodium

hydrogen sulfide, or even sodium sulfide. The catalyst of choice being Raney Nickel processed from Nickel Aluminum alloy with Ni content of 90-92% and aluminum content of 8-10% and particle sizes of the catalyst from about 150 to about 250 mesh for the controlled reduction of nitro group without affecting the more reactive pyridine ring. The hydrogen pressure is of about 3kg/cm^3 to about 5kg/cm^3, preferably of about 3kg/cm^3 to about 4kg/cm^3. The medium for hydrogenation is selected from a range of aliphatic alcohols such as methyl alcohol, ethyl alcohol, isopropyl alcohol, butyl alcohol, etc preferably methanol. The amine thus obtained can be isolated by evaporation of solvent , and subjected to subsequent reaction without resorting to exhaustive purification.

Compound of formula 12 is prepared by conventional Meerwein Arylation step, by diazotization of the compound of formula 11 in presence of aqueous hydrogen bromide and allowing the resultant diazo compound to react with acrylic acid or its lower alkyl ester in presence of copper catalyst. The compound thus obtained is purified by preferential extraction and water wash.

Compound of formula 12 is reacted with thiourea in presence of sodium or potassium acetate by any of the generally used methods. The imino thiazolidiene of formula 13 is hydrolyzed to pioglitazone base using any of the mineral acids selected form hydrochloric, sulfuric or even hydrobromic. The quantity of acid used range from about 1M to about 4M, preferably about 2M to about 3M with respect to the pioglitazone base. The base thus obtained is purified to pharmaceutical grade in a variety of solvents starting from DMF/water to other aliphatic solvents like ethyl acetate. The Pioglitazone base thus obtained needs to be converted to its hydrochloride salt in any alcoholic solvents using dry hydrogen chloride.

The process of this invention substitutes the expensive raw materials like p-fluoro nitro benzene or p-fluoro benzo nitrile as described in the prior art for the preparation of the amino compound required for building up the thiazolidinedione ring. The method also avoids cumbersome and difficult reduction of double bond in compounds known by the formula 5 in Scheme 3.

Furthermore, the preparation of other salts of pioglitazone can be achieved by the reaction of compound of formula 13 with various mineral acids like hydrochloric acid,

sulfuric acid, or organic acids like methane sulfonic acid or maleic acid or fumaric acid etc.

In the case of the organic acids, the thiazolidinone base is taken in an organic solvent such as aliphatic alcohol preferably methanol, ethanol or isopropanol in molar ratio of minimum 1:1 with respect to the thiazolidinone base. The reaction mixture is refluxed to dissolve the thiazolidinone base and the temperature is maintained for 1h then cooled to room temperature and further to about 10°C. The precipitated solid is filtered and washed with an aliphatic alcohol such as isopropyl alcohol and dried at 50°C to obtain thiazolidienedione acid salt as a white solid.

The present invention is illustrated by means of following non-limiting examples.

Example – 1:

Preparation of 4-(2-(5-ethyl-pyridine) ethoxy) nitrobenzene

p-Nitro phenol (57.45g, 0.42mol), acetonitrile (450ml) and potassium carbonate (67.80, 0.488 mol) are mixed and heated to 60°C. 2-(5-ethyl-2-pyridine)ethylmethanesulfonate (85.95, 0.375 mol) in acetonitrile (75ml) is added to the above solution over a period of 2h. The resulting reaction mixture is heated under stirring for 5-6hrs. After completion of the reaction, the system is cooled to room temperature and filtered. The filtrate is collected and the acetonitrile is removed under vacuum. The residue thus obtained is dissolved in ethyl acetate and the ethyl acetate layer is washed with water and then with 10% sodium hydroxide solution and finally with water. The solvent is removed under vacuum and the residue is taken in petroleum ether (300ml) and heated to 50°C. Activated charcoal is added at this stage and filtered to obtain a clear solution. The solution is cooled to 0-5°C under stirring and filtered. The solid obtained is dried at room temperature in air to obtain the product (50.0g, 47.0%). The compound is re-crystallized from ethyl acetate –hexane to give colorless prisms, m. p. 53-55°C.

Example –2:

Preparation of 4-(2-(5-ethyl-2-pyridyl)ethoxy aniline

In a stainless steel autoclave 4-(2-(5-ethyl-2-pyridyl)ethoxy)nitrobenzene (500g, 6.94 m mol) is charged in methanol (2500 ml) followed by Raney Nickel (5.00g dry weight) and

stirred for 10-15 min. The system is charged with hydrogen to a pressure of 4kg/cm^2 and the reaction is carried out in the stirred autoclave for 8-10 hours or until the reduction of nitro compound to amino compound is completed as indicated by HPLC or TLC.

After the completion of the reaction, the residual hydrogen is vented off and the autoclave is pressurized with nitrogen. After venting the nitrogen, the solution is filtered to remove the Raney nickel. The filtrate is concentrated under vacuum at 40-45°C. The product is collected as pale yellow oil. Yield 430g (97%)

Example – 3:

Preparation of 2-bromo-3—[4-2-5-ethyl-2-pyridyl) ethoxy phenyl propionate

4-(2-(5-ethyl-pyridine) ethoxy) aniline (73.0g, 0.3mol) in a mixture of acetone/water (8:3) {1050 ml} is cooled to 0°C. 48% hydrobromic acid (225g) is added slowly so as to keep the temperature below 5°C. On completion of the addition of hydrobromic acid the reaction mixture is stirred for 30min and aqueous solution of sodium nitrate (25.0g, 0.36 mol) is slowly added. The reaction mixture is maintained at 0-5°C for 2hr and methyl acrylate (153g, 1.8 mol) is added. The reaction mixture is slowly brought to room temperature under stirring. The reaction mixture is heated to 40°C and portions of cuprous oxide (3.0g, 0.021 mol) are slowly added in a period of 1-3 hr. After the addition is completed stirring is continued for 2-3 hrs to complete the reaction.

The reaction mixture is concentrated under vacuum to remove methanol and acetone. To the residue thus obtained water is charged then cooled to 10-15°C and ammonia solution (25%) is slowly added to bring pH of the solution to 9.00. After the addition of ammonia is completed, stirring is continued for 30min. and ethyl acetate (375ml) is added followed by separation of the layers. The aqueous layer is extracted few times with ethyl acetate and combined with the organic layer. The organic layer is washed with water and the acetate is distilled off under vacuum to obtain the product (102g, 86.7%). No purification is needed at this stage.

Example – 4:

Preparation of 5(4-(2-(5-ethyl-2-pyridyl) ethoxy) benzyl)-2-imino-4-thiazolidinone

To a solution 2-bromo-3-[4-2-5-ethyl-2-pyridyl) ethoxy phenyl propionate (59.0g, 0.15 mol) in methanol (450ml), thiourea (11.4 g, 0.15 mol) and sodium acetate (12.3g, 0.15 mol) is added and heated under stirring to reflux. Reflux is continued for 6-7 hrs or until the reaction is complete as indicated by TLC or HPLC. The reaction mixture is cooled to room temperature and finally to 0°C - 5 °C followed by filtration of the precipitated solid. The precipitate is washed with water (50ml X2) and finally a few times with acetone and dried at 70°C - 75 °C. (24.3g, 45.6%, HPLC purity is 98%).

Example – 5:

Preparation of Pioglitazone hydrochloride:

5(4-(2-(5-ethyl-2-pyridyl) ethoxy) benzyl)-2-imino-4-thiazolidinone (36.0g, 0.105 mol) and 2 N hydrochloric acid (300ml) is heated to reflux for 6h. After cooling to room temperature, pH of the reaction mixture is adjusted to about with aqueous sodium hydroxide solution. The precipitated solid is filtered and washed with water and dried at 75°C - 80 °C. (35.0g).

The material from the previous step mixed with dioxane (225ml) and heated to dissolve the material followed by addition of activated carbon and refluxing for 1 hr. The charcoal is filtered off under hot conditions and the solution is cooled to 0 °C over a period of 1h. The precipitate is filtered and washed with dioxane, and finally with water followed by drying at 75°C -80 °C to obtain pioglitazone base (33.0g, 88%), m.p. 183-184 °C.

The pioglitazone base (21.0g, 0.06 mol) is heated with 1 N hydrochloric acid (126ml) to 80 °C under stirring until the material dissolves completely. The heating is continued for 1h and the solution is filtered to remove any undissolved material. The filtrate is heated again to 80 °C and maintained at that temperature for 1h and finally cooled to

room temperature and further to about 10°C. The precipitated solid is filtered and washed with isopropyl alcohol (3X20ml) and dried at 50 ° to obtain pioglitazone hydrochloride as a white solid (20.5g, 87%).

Claims:

We claim

1. A process is for the preparation of Thiazolidinedione derivatives of general formula 5-(4-(2-(5-R-2-pyridyl) ethoxy) benzyl-2-imino-4-thiazolidinone including pioglitazone, cglitazone, englitazone and rosiglitazone and their pharmaceutically acceptable salts of general formula 5-(4-(2-(5-R-2-pyridyl) ethoxy) benzyl-2, 4-thiazolidinienedione.X, where R is alkyl, acyl, aryl, heteroaryl or trifluormethyl and X is a mono acid, comprising steps
   - reacting 2-(5-R-2-pyridine) ethyl methane sulfonate , where R is alkyl, acyl, aryl or heteroaryl with p-nitro phenol in an organic solvent and in presence of suitable base
   - Conversion of the adduct thus obtained viz. 4-(2-(5-R-pyridine) ethoxy nitro benzene to the corresponding amine by catalytic reduction employing noble metal catalysts or Raney nickel and hydrogen in an appropriate solvent
   - Diazotization of the amine viz. 4-(2-(5-R-pyridine) ethoxyaniline
   - Meerwein arylation of the diazo compound using ethyl acrylate to obtain 2-bromo-3- (4-2-5-R-2-pyridyl) ethoxyphenyl) propionate
   - Reaction of the Meerwein arylated product with thiourea to give the imino thiazolidinone viz. 5-(4-(2-(5-R-2-pyridyl) ethoxy) benzyl-2-imino-4-thiazolidinone
   - Conversion of the imino thiazolidinone under acidic condition to the corresponding thiazolidinedione salt

2. A process wherein reaction of p-nitro phenol with 2-(5-R-2-pyridine) ethyl methane sulfonate is carried out in an organic solvent selected from aromatic hydrocarbon, such as toluene, xylene, benzene or any aliphatic nitriles such as acetonitrile, propionitrile etc or any aprotic solvent like dimethyl formamide or dimethyl sulfoxide, the preferred solvent being aliphatic nitriles, especially acetonitrile. aliphatic nitriles, aliphatic amides and sulfoxide in the presence of suitable base at temperatures ranging from 20°C - 80°C preferably between 30°C to 50°C, the base being selected from alkali or alkaline earth metals, preferably their carbonates or bicarbonates and the product of the reaction being separated using aromatic hydrocarbon solvents like toluene, benzene or xylene and purified using an aliphatic solvent selected from pentane, hexane or heptanes and ethers like isopropyl ether or diethyl ether.

3. A process as claimed in claims 1-2 wherein the base is preferably potassium carbonate.

4. A process for the conversion of the adduct 4-(2-(5-R-pyridine) ethoxy nitro benzene to the corresponding amine by catalytic reduction Raney nickel and hydrogen wherein the catalyst of choice being Raney nickel processed from Nickel Aluminum alloy with Ni content of 90-92% and aluminum content of 8-10% and particle sizes of the catalyst from about 150 to about 250 mesh.

5. A process as claimed in claim 1 and 4 wherein the hydrogenation is carried out in organic solvents selected from aliphatic alcohols such as methyl alcohol, ethyl alcohol, isopropyl alcohol, butyl alcohol, and the preferable solvent being methanol.

6. The hydrogenation in the process as claimed in claims 1, 4 and 5 wherein the pressure of hydrogen is about $3kg/cm^3$ to about $5kg/cm^3$, preferably of about $3kg/cm^3$ to about $4kg/cm^3$.

7. The reduction as claimed in claim 1 is optionally carried out using iron / hydrochloric acid, sodium hydrogen sulfide, or sodium sulfide.

8. A process wherein the amine viz. 4-(2-(5-R-pyridine) ethoxyaniline is diazotized and the diazo compound is allowed to undergo Meerwein arylation in aqueous hydrogen bromide and allowing the resultant diazo compound to react with acrylic acid or its lower alkyl ester such as ethyl acrylate in presence of copper catalyst to obtain 2-bromo-3- (4-2-5-R-2-pyridyl) ethoxyphenyl) propionate which is purified by preferential extraction and water wash.

9. A process for the reaction of the Meerwein arylated product with thiourea to give the imino thiazolidinone in presence of sodium or potassium acetate and further hydrolyzed to thiazolidinone base using any of the mineral acids selected form hydrochloric, sulfuric or even hydrobromic acid in any alcoholic solvents.

10. A process as claimed in claim 1 wherein the thiazolidinone base is converted to the corresponding organic acid salts such as the succinate, maleate, fumarate, laclate, tartrate, sulfonates like methane sulfonates, toluene sulfonates, benzene sulfonates with various organic acids such as succinic acid, maelaic acid, fumaric acid, lactic

acid, tartaric acid, methane sulfonic acid para toulene sulphonic acid etc respectively.

11. A process as claimed in claims 1 and 10 wherein the thiazolidinone base is converted to the corresponding organic acid salts by refluxing the organic acid with the thiazolidinone base with in molar ratio of minimum 1:1 with respect to the thiazolidinone base in an organic solvent such as aliphatic alcohol preferably methanol, ethanol or isopropanol for a period of at least 1 hr followed by cooling to about about 10°C, filtering, washing of the product with an aliphatic alcohol such as isopropyl alcohol and drying at around 50°C to obtain thiazolidinedione acid salt.

12. A process as claimed in claim 1 and 9 -10 wherein the acid used range from about 1 M to about 4 M, preferably about 2 M to about 3 M with respect to the thiazolidinone base.

13. A process as claimed in claim 1 and 9 wherein the thiazolidinone base is purified to pharmaceutical grade using solvents selected from starting from DMF/water mixtures, aliphatic solvents such as ethyl acetate.

14. Process for preparation of pioglitazone hydrochloride and the mineral acid used is dilute hydrochloric acid for the conversion of imino thiazolidinone where R=ethyl to pioglitazone hydrochloride.