TREATMENT OF DIABETES WITH THIAZOLIDINEDIONE AND METFORMIN

This invention relates to a method of treatment, in particular to a method for the treatment of diabetes mellitus, especially non-insulin dependent diabetes (NIDDM) or Type II diabetes and conditions associated with diabetes mellitus.

Biguanide antihyperglycaemic agents are commonly used in the treatment of NIDDM (or Type II diabetes). 1,1 - Dimethylbiguanidine (or Metformin) is an example of a biguanides antihyperglycaemic agent.

European Patent Application, Publication Number 0,306,228 relates to certain thiazolidinedione derivatives disclosed as having antihyperglycaemic and hypolipidaemic activity. One particular thiazolidinedione disclosed in EP 0306228 is 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (hereinafter 'Compound (I)'). WO94/05659 discloses certain salts of Compound (I) including the maleate salt at example 1 thereof.

Compound (I) is an example of a class of anti-hyperglycaemic agents known as 'insulin sensitisers'. In particular Compound (I) is a thiazolidinedione insulin sensitiser.

European Patent Applications, Publication Numbers: 0008203, 0139421, 0032128, 0428312, 0489663, 0155845, 0257781, 0208420, 0177353, 0319189, 0332331, 0332332, 0528734, 0508740; International Patent Application, Publication Numbers 92/18501, 93/02079, 93/22445 and United States Patent Numbers 5104888 and 5478852, also disclose certain thiazolidinedione insulin sensitisers.

Another series of compounds generally recognised as having insulin sensitiser activity are those typified by the compounds disclosed in International Patent Applications, Publication Numbers WO93/21166 and WO94/01420. These compounds are herein referred to as 'acyclic insulin sensitisers'. Other examples of acyclic insulin sensitisers are those disclosed in United States Patent Number 5232945 and International Patent Applications, Publication Numbers WO92/03425 and WO91/19702.

Examples of other insulin sensitisers are those disclosed in European Patent Application, Publication Number 0533933, Japanese Patent Application Publication Number 05271204 and United States Patent Number 5264451.

The above mentioned publications are incorporated herein by reference.

It is now surprisingly indicated that Compound (I) in combination with a biguanide antihyperglycaemic agent provides a particularly beneficial effect on glycaemic control with no observed adverse effects, such combination is therefore particularly useful for the treatment of diabetes mellitus, especially Type II diabetes and conditions associated with diabetes mellitus.

Accordingly, the invention provides a method for the treatment of diabetes mellitus, especially Type II diabetes and conditions associated with diabetes mellitus in a mammal, such as a human, which method comprises administering an effective non-toxic and pharmaceutically acceptable amount of an insulin sensitiser, such as Compound (I), and a biguanide antihyperglycaemic agent, to a mammal in need thereof.

In another aspect the invention provides an insulin sensitiser, such as Compound (I), together with a biguanide antihyperglycaemic agent, for use in a method for the treatment of diabetes mellitus, especially Type II diabetes and conditions associated with diabetes mellitus.

The method comprises either co-administration of an insulin sensitiser, such as Compound (I), and a biguanide antihyperglycaemic agent or the sequential administration thereof.

Co-administration includes administration of a formulation which includes both an insulin sensitiser, such as Compound (I), and a biguanide antihyperglycaemic agent or the essentially simultaneous administration of separate formulations of each agent.

In another aspect the invention provides the use of an insulin sensitiser, such as Compound (I), and a biguanide antihyperglycaemic agent, for use in the manufacture of a composition for the treatment of diabetes mellitus, especially Type II diabetes and conditions associated with diabetes mellitus.

A suitable biguanide antihyperglycaemic agent is metformin, buformin or phenformin, especially metformin.

A suitable thiazolidinedione insulin sensitiser is Compound (I).

Other suitable thiazolidinedione insulin sensitisers include (+) -5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]benzyl] thiazolidine-2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl] thiazolidine-2,4-dione (or pioglitazone) or 5-[(2-benzyl-2,3-dihydrobenzopyran)-5-ylmethyl)thiazolidine-2,4-dione (or englitazone)

In one particular aspect, the method comprises the administration of 2 to 12 mg of Compound (I), especially when administered per day.

Particularly, the method comprises the administration of 2 to 4 , 4 to 8 or 8 to 12 mg of Compound (I) per day.

Particularly, the method comprises the administration of 2 to 4mg of Compound (I), especially when administered per day.

Particularly, the method comprises the administration of 4 to 8mg of Compound (I), especially when administered per day.

Particularly, the method comprises the administration of 8 to 12 mg of Compound (I), especially when administered per day.

Preferably, the method comprises the administration of 2 mg of Compound (I), especially when administered per day.

Preferably, the method comprises the administration of 4 mg of Compound (I), especially when administered per day.

Preferably, the method comprises the administration of 8 mg of Compound (I), especially when administered per day.

It will be understood that the insulin sensitiser, such as Compound (I) and the biguanide antihyperglycaemic agent are each administered in a pharmaceutically acceptable form, including pharmaceutically acceptable derivatives such as pharmaceutically acceptable salts, esters and solvates thereof, as appropriate of the relevant pharmaceutically active agent. In certain instances herein the names used for the relevant biguanide may relate to a particular pharmaceutical form of the relevant active agent: It will be understood that all pharmaceutically acceptable forms of the active agents per se are encompassed by this invention.

Suitable pharmaceutically acceptable forms of insulin sensitisers include those described in the above mentioned publications.

Suitable pharmaceutically acceptable forms of Compound (I) include those described in EP 0306228 and WO94/05659, especially pharmaceutically acceptable salted forms. A preferred pharmaceutically acceptable salt is a maleate.

Suitable pharmaceutically acceptable solvated forms of Compound (I) include those described in EP 0306228 and WO94/05659, in particular hydrates.

Suitable pharmaceutically acceptable forms of the biguanide antihyperglycaemic agent depend upon the particular agent used but includes known pharmaceutically acceptable forms of the particular compound chosen. Such derivatives are found or are referred to in standard reference texts such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), The Extra Pharmacopoeia (London, The Pharmaceutical Press) (for example see the 31st Edition page 341 and pages cited therein).

A suitable pharmaceutically acceptable form of metformin is an acid addition salt, such as a hydrochloride.

Compound (I) or, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, may be prepared using known methods, for example those disclosed in EP 0306228 and WO94/05659. The disclosures of EP 0306228 and WO94/05659 are incorporated herein by reference.

Compound (I) may exist in one of several tautomeric forms, all of which are encompassed by the term Compound (I) as individual tautomeric forms or as mixtures

thereof. Compound (I) contains a chiral carbon atom, and hence can exist in up to two stereoisomeric forms, the term Compound (I) encompasses all of these isomeric forms whether as individual isomers or as mixtures of isomers, including racemates.

The insulin sensitiser or the biguanide antihyperglycaemic agent of choice is prepared according to known methods, such methods are found or are referred to in standard reference texts, such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press) (for example see the 31st Edition page 341 and pages cited therein) or as described in the above mentioned publications.

When used herein the term 'conditions associated with diabetes' includes those conditions associated with the pre-diabetic state, conditions associated with diabetes mellitus itself and complications associated with diabetes mellitus.

When used herein the term 'conditions associated with the pre-diabetic state' includes conditions such as insulin resistance, including hereditary insulin resistance, impaired glucose tolerance and hyperinsulinaemia.

'Conditions associated with diabetes mellitus itself' include hyperglycaemia, insulin resistance, including acquired insulin resistance and obesity. Further conditions associated with diabetes mellitus itself include hypertension and cardiovascular disease, especially atherosclerosis and conditions associated with insulin resistance. Conditions associated with insulin resistance include polycystic ovarian syndrome and steroid induced insulin resistance and gestational diabetes.

'Complications associated with diabetes mellitus' includes renal disease, especially renal disease associated with Type II diabetes, neuropathy and retinopathy.

Renal diseases associated with Type II diabetes include nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

As used herein the term 'pharmaceutically acceptable' embraces both human and veterinary use: for example the term 'pharmaceutically acceptable' embraces a veterinarily acceptable compound.

For the avoidance of doubt, when reference is made herein to scalar amounts, including mg amounts, of Compound (I) in a pharmaceutically acceptable form, the scalar amount referred to is made in respect of Compound (I) *per se*: For example 2 mg of Compound (I) in the form of the maleate salt is that amount of maleate salt which contains 2 mg of Compound (I).

Diabetes mellitus is preferably Type II diabetes.

The particularly beneficial effect on glycaemic control provided by the treatment of the invention is indicated to be a synergistic effect relative to the control expected for the sum of the effects of the individual active agents.

Glycaemic control may be characterised using conventional methods, for example by measurement of a typically used index of glycaemic control such as fasting plasma glucose or glycosylated haemoglobin (Hb A1c). Such indices are determined using standard methodology, for example those described in: Tuescher A, Richterich, P., Schweiz. med. Wschr. 101 (1971), 345 and 390 and Frank P., 'Monitoring the Diabetic Patent with Glycosolated Hemoglobin Measurements', Clinical Products 1988.

In a preferred aspect, the dosage level of each of the active agents when used in accordance with the treatment of the invention will be less than would have been required from a purely additive effect upon glycaemic control.

There is also an indication that the treatment of the invention will effect an improvement, relative to the individual agents, in the levels of advanced glycosylation end products (AGEs), leptin and serum lipids including total cholesterol, HDL-cholesterol, LDL-cholesterol including improvements in the ratios thereof, in particular an improvement in serum lipids including total cholesterol, HDL-cholesterol, LDL-cholesterol including improvements in the ratios thereof.

In the method of the invention, the active medicaments are preferably administered in pharmaceutical composition form. As indicated above, such compositions can include both medicaments or one only of the medicaments.

Accordingly, in one aspect of the invention there is provided a pharmaceutical composition comprising an insulin sensitiser, such as Compound (I) especially 2 to 12 mg thereof, a biguanide antihyperglycaemic agent and a pharmaceutically acceptable carrier therefor.

Such compositions may be prepared by admixing an insulin sensitiser, such as Compound (I) especially 2 to 12 mg thereof, the biguanide antihyperglycaemic agent and a pharmaceutically acceptable carrier therefor.

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

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

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

Unit dose presentation forms for oral administration may be tablets and capsules and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine;

tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable wetting agents such as sodium lauryl sulphate.

The compositions are preferably in a unit dosage form in an amount appropriate for the relevant daily dosage.

Suitable unit dosages of the Compound of formula (I) comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 mg of Compound (I).

The composition of the invention may be administered from 1 to 6 times a day, but most preferably 1 or 2 times per day.

Particular dosages of Compound (I) are are 2mg/day, 4mg/day, including 2mg twice per day, and 8 mg/day, including 4mg twice per day.

Suitable unit dosages of the insulin sensitiser or the biguanide antihyperglycaemic agent, such as metformin, include the known doses for these compounds as described or referred to in reference texts such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press) (for example see the 31st Edition page 341 and pages cited therein) or the above mentioned publications.

Suitable dosages of metformin include up to 3000mg per day, in unit doses of 500mg (for example two or three times per day) or 850mg (for example two times per day), one example of a dosage for metformin is 500mg once building to five times per day per day.

Thus, one example of the method comprises the administration of 4 or 8mg of Compound (I) (at 2mg twice per day or 4mg twice per day respectively) and 1000mg or 2500mg of metformin (at 500mg twice per day or 500mg five times per day respectively).

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

Oral liquid preparations may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan

monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, and, depending on the concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, a preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the Compound (I)s suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

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

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

The compositions are formulated according to conventional methods, such as those disclosed in standard reference texts, for example the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press) (for example see the 31st Edition page 341 and pages cited therein) and Harry's Cosmeticology (Leonard Hill Books).

In a further aspect, the present invention also provides a pharmaceutical composition comprising an insulin sensitiser such as Compound (I) especially 2 to 12 mg thereof, a biguanide antihyperglycaemic agent and a pharmaceutically acceptable carrier therefor, for use as an active therapeutic substance.

In particular, the present invention provides a pharmaceutical composition comprising an insulin sensitiser such as Compound (I) especially 2 to 12 mg thereof, a biguanide antihyperglycaemic agent and a pharmaceutically acceptable carrier therefor, for use in the treatment of diabetes mellitus, especially Type II diabetes and conditions associated with diabetes mellitus.

A range of 2 to 4mg includes a range of 2.1 to 4, 2.2 to 4, 2.3 to 4, 2.4 to 4, 2.5 to 4, 2.6 to 4, 2.7 to 4, 2.8 to 4, 2.9 to 4 or 3 to 4mg.

A range of 4 to 8mg includes a range of 4.1 to 8, 4.2 to 8, 4.3 to 8, 4.4 to 8, 4.5 to 8, 4.6 to 8, 4.7 to 8, 4.8 to 8, 4.9 to 8, 5 to 8, 6 to 8 or 7 to 8mg.

A range of 8 to 12 mg includes a range of 8.1 to 12, 8.2 to 12, 8.3 to 12, 8.4 to 12, 8.5 to 12, 8.6 to 12, 8.7 to 12, 8.8 to 12, 8.9 to 12, 9 to 12, 10 to 12 or 11 to 12mg.

No adverse toxicological effects have been established for the compositions or methods of the invention in the abovementioned dosage ranges.

The following example illustrates the invention but does not limit it in any way.

Example

This study evaluated the pharmacokinetics (PK) of Compound (I) and metformin (M) administered alone and in combination. Sixteen male volunteers, aged 22 to 55 years, received oral Compound (I) (2 mg Q12h), M (500 mg Q12h), or the combination, each for 4 days. Plasma collected on day 4 of each regimen was assayed for Compound (I) and M concentrations. Oral doses of Compound (I) and M were safe and well tolerated alone or in combination. There were no episodes of hypoglycaemia and co-administration did not result in an increase in blood lactic acid concentration.

Parameter	M		Compound (I)	
[units]	Alone	Combn	Alone	Combn
AUC(0-12) [ng.h/mL]	626 (494-866)	629 (418-912)	6508 (4694-8705)	6575 (4773-9230)
Cmax [ng/mL]	105 (78.9-150.2)	104 (76.5-139.2)	901 (620-1251)	918 (635-1344)
Tmax [hours]	3.0 (2.0-4.0)	3.5 (1.5-4.0)	3.0 (1.0-6.0)	3.5 (1.5-6.0)
T1/2 [hours]	3.22 (2.45-5.01)	3.21 (2.56-4.64)	3.24 (2.56-4.19)	3.41 (2.64-4.58)

Combo = Compound (I) + M coadministration

Coadministration of Compound (I) and M did not affect the steady-state pharmacokinetics (AUC(0-12), Cmax, Tmax, or T1/2) of either drug. Because M plasma concentrations were unaffected, coadministration or Compound (I) will not accentuate the concentration-dependent toxicities of M.

COMPOUND (I) COMPOSITIONS

A Concentrate Preparation

Approximately two thirds of the lactose monohydrate is passed through a suitable screen and blended with the milled maleate salt of Compound (I). Sodium starch glycollate, hydoxypropyl methylcellulose, microcrystalline cellulose and the remaining lactose are passed through a suitable screen and added to the mixture. Blending is then continued. The resulting mixture is then wet granulated with purified water. The wet granules are then screened, dried on a fluid bed drier and the dried granules are passed through a further screen and finally homogenised.

% COMPOSITION OF GRANULAR CONCENTRATE

Ingredient	Quantity (%)
Milled Compound (I) as maleate salt	13.25 (pure maleate salt)
Sodium Starch Glycollate	5.00
Hydoxypropyl Methylcellulose 2910	5.00
Microcrystalline Cellulose	20.0
Lactose Monohydrate, regular grade	to 100
Purified water	*

* Removed during processing.

B Formulation of the concentrate into tablets.

The granules from above are placed into a tumble blender. Approximately two thirds of the lactose is screened and added to the blender. The microcrystalline cellulose, sodium starch glycollate, magnesium stearate and remaining lactose are screened and added to the blender and the mixture blended together. The resulting mix is then compressed on a rotary tablet press to a target weight of 150mg for the 1, 2 and 4mg tablets and to a target weight of 300mg for the 8mg tablets.

The tablet cores are then transferred to a tablet coating machine, pre-warmed with warm air (approximately 65°C) and film coated until the tablet weight has increased by 2.0% to 3.5%.

	Quantity (mg per Tablet)			
Tablet Strength	**1.0mg**	**2.0mg**	**4.0mg**	**8.0mg**
Active Ingredient:				
Compound (I) maleate Concentrate granules	10.00	20.00	40.00	80.00
Other Ingredients:				
Sodium Starch Glycollate	6.96	6.46	5.46	10.92
Microcrystalline Cellulose	27.85	25.85	21.85	43.70
Lactose monohydrate	104.44	96.94	81.94	163.88
Magnesium Stearate	0.75	0.75	0.75	1.50
Total Weight of Tablet Core	150.0	150.0	150.0	300.0
Aqueous film coating material	4.5	4.5	4.5	9.0
Total Weight of Film Coated Tablet	154.5	154.5	154.5	309.0

Claims

1. A method for the treatment of diabetes mellitus and conditions associated with diabetes mellitus in a mammal, which method comprises administering an effective non-toxic and pharmaceutically acceptable amount of an insulin sensitiser and a biguanide antihyperglycaemic agent, to a mammal in need thereof.

2. A method according to claim 1, wherein the biguanide antihyperglycaemic agent is metformin.

3. A method according to claim 1, wherein the biguanide antihyperglycaemic agent is metformin hydrochloride.

4. A method according to any one of claims 1 to 3, wherein the insulin sensitiser is 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (Compound I).

5. A method according to any one of claims 1 to 4, which comprises the administration of 2 to 12 mg of Compound (I).

6. A method according to any one of claims 1 to 5, which comprises the administration of 2 to 4, 4 to 8 or 8 to 12 mg of Compound (I).

7. A method according to any one of claims 1 to 6, which comprises the administration of 2 to 4mg of Compound (I)..

8. A method according to any one of claims 1 to 6, which comprises the administration of 4 to 8mg of Compound (I).

9. A method according to any one of claims 1 to 6, which comprises the administration of 8 to 12 mg of Compound (I).

10. A method according to any one of claims 1 to 6, which comprises the administration of 2 mg of Compound (I).



11. A method according to any one of claims 1 to 6, which comprises the administration of 4 mg of Compound (I).

12. A method according to any one of claims 1 to 6, which comprises the administration of 8 mg of Compound (I).

13. A method according to claim 1, wherein the insulin sensitiser is (+) -5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]benzyl] thiazolidine-2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl] thiazolidine-2,4-dione (or pioglitazone) or 5-[(2-benzyl-2,3-dihydrobenzopyran)-5-ylmethyl)thiazolidine-2,4-dione (or englitazone); or a pharmaceutically acceptable form thereof.

14. A pharmaceutical composition comprising an insulin sensitiser, a biguanide antihyperglycaemic agent and a pharmaceutically acceptable carrier therefor.

15. A composition according to claim 14, wherein the biguanide antihyperglycaemic agent is metformin.

16. A composition according to claim 14, wherein the biguanide antihyperglycaemic agent is metformin hydrochloride.

17. A composition according to any one of claims 14 to 16, which comprises 500mg or 850mg of metformin.

18. A composition according to any one of claims 14 to 17, wherein the insulin sensitiser is Compound (I)

19. A composition according to any one of claims 14 to 18, which comprises 2 to 12 mg of Compound (I).

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20. A pharmaceutical composition comprising an insulin sensitiser, a biguanide antihyperglycaemic agent and a pharmaceutically acceptable carrier therefor, for use as an active therapeutic substance.

21. A pharmaceutical composition comprising an insulin sensitiser a biguanide antihyperglycaemic agent and a pharmaceutically acceptable carrier therefor, for use in the treatment of diabetes mellitus and conditions associated with diabetes mellitus.

22. A composition according to any one of claims 14, 20 or 21, wherein the insulin sensitiser is (+) -5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]benzyl] thiazolidine-2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl] thiazolidine-2,4-dione (or pioglitazone) or 5-[(2-benzyl-2,3-dihydrobenzopyran)-5-ylmethyl)thiazolidine-2,4-dione (or englitazone); or a pharmaceutically acceptable form thereof.

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