(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 219 620 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
03.07.2002 Bulletin 2002/27

(51) Int Cl.⁷: **C07D 417/12**

(21) Application number: **02075969.2**

(22) Date of filing: **27.10.1998**

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
Designated Extension States:
AL LT LV RO SI

(30) Priority: **04.11.1997 GB 9723295**

(62) Document number(s) of the earlier application(s) in accordance with Art. 76 EPC:
98959834.7 / 1 028 960

(71) Applicant: **SMITHKLINE BEECHAM PLC**
Brentford, Middlesex TW8 9EP (GB)

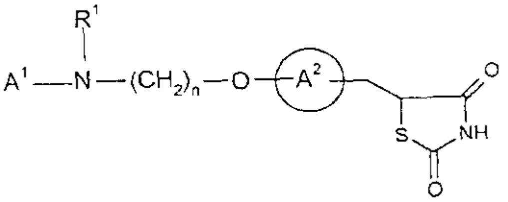
(72) Inventors:
- **Giles, Robert Gordon, c/o GlaxoSmithKline**
  Tonbridge, Kent TN11 9AN (GB)
- **Lewis, Norman John, c/o GlaxoSmithKline.**
  Tonbridge, Kent TN11 9AN (GB)
- **Quick, John Kirby, c/o GlaxoSmithKline**
  Tonbridge, Kent TN11 9AN (GB)

(74) Representative: **Rutter, Keith et al**
GlaxoSmithKline
Corporate Intellectual Property (CN9.25.1)
980 Great West Road
Brentford, Middlesex TW8 9GS (GB)

Remarks:
This application was filed on 13 - 03 - 2002 as a divisional application to the application mentioned under INID code 62.

(54) Process for the preparation of thiazolidinedione derivatives

(57) A process for preparing a compound of formula (I):



(I)

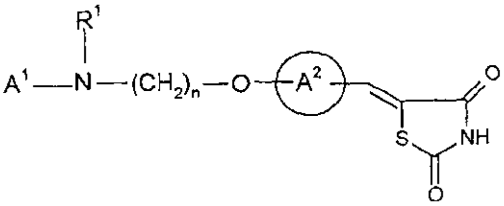
or a tautomeric form thereof or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, wherein:

A^1 represents a substituted or unsubstituted aromatic heterocyclyl group;
R^1 represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;
A^2 represents a benzene ring having in total up to five substituents; and
n represents an integer in the range of from 2 to 6,

which process comprises catalytically reducing a compound of formula (II):

Printed by Jouve, 75001 PARIS (FR)

(Cont. next page)



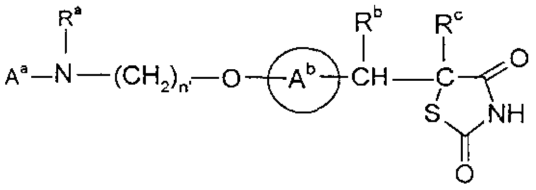
(II)

wherein A^1, R^1, A^2 and n are as defined in relation to formula (I), characterised in that the reduction reaction is carried out using a hydrogen pressure above 20psi; and thereafter if required forming a pharmaceutically acceptable salt and/ or a pharmaceutically acceptable solvate of the compound of formula (I).

Description

[0001] This invention relates to a novel process and in particular to a process for preparing certain substituted thiazolidinedione derivatives.

[0002] European Patent Application, Publication Number 0306228 discloses certain thiazolidinedione derivatives of formula (A):



(A)

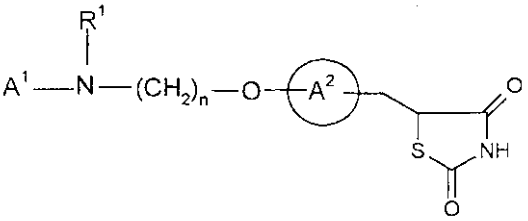
or a tautomeric form thereof or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, wherein:

A^a represents a substituted or unsubstituted aromatic heterocyclyl group;
R^a represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;
R^b and R^c each represent hydrogen or R^b and R^c together represent a bond;
A^b represents a benzene ring having in total up to five substituents; and
n' represents an integer in the range of from 2 to 6.

[0003] EP 0306228 also discloses a process for reducing the compounds of formula (A) wherein R^b and R^c together represent a bond (the 'benzylidene thiazolidine-2, 4-diones') to the corresponding compounds of formula (A) wherein R^b and R^c each represent hydrogen (the 'benzylthiazolidine-2, 4-diones'). The particular reduction methods disclosed in EP 0306228 are dissolving metal methods and catalytic hydrogenation methods.

[0004] It has now been discovered that when the catalytic hydrogenation of the benzylidene thiazolidine-2, 4-diones is carried out using an elevated pressure of hydrogen that the reaction can be effected with a surprising reduction in the catalytic loading and reaction time and, most surprisingly, produces a significant reduction in by-product formation.

[0005] Accordingly, the present invention provides a process for preparing a compound of formula (I):

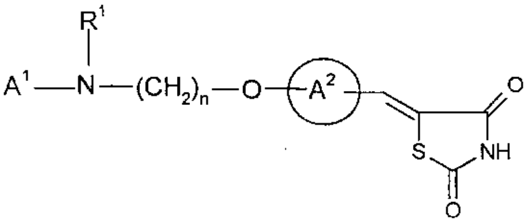


(I)

or a tautomeric form thereof or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, wherein:

A^1 represents a substituted or unsubstituted aromatic heterocyclyl group;
R^1 represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;
A^2 represents a benzene ring having in total up to five substituents; and
n represents an integer in the range of from 2 to 6,

which process comprises catalytically reducing a compound of formula (II):



(II)

wherein A^1, R^1, A^2 and n are as defined in relation to formula (I), characterised in that the reduction reaction is carried out using a hydrogen pressure above 20psi, and thereafter, if required, forming a pharmaceutically acceptable salt and/or a pharmaceutically acceptable solvate of the compound of formula (I).

[0006] Suitably the reaction is carried out at a pressure in the range of from 50 to 1500 psi, such as 60 to 1500 psi, 75 to 1500psi, 200 to 1500psi, 70 to 1000psi or 200 to 1000psi, suitably 70 to 1000psi.

[0007] Examples of reaction pressures include 70, 75, 80, 500 and 1000psi.

[0008] A suitable hydrogenation catalyst is a noble metal catalyst, suitably a palladium catalyst.

[0009] Favoured catalysts are supported noble metal catalysts, such as a palladium-on-carbon catalyst, typically comprising 5% to 10% of palladium.

[0010] A preferred catalyst is a 10% palladium-on-carbon catalyst.

[0011] Catalyst loadings (expressed as w/w% of catalyst to substrate) in the reaction are typically in the range of from 5 to 100%, usually 10 to 50% and preferably 25 to 50%.

[0012] The reaction may be carried out using any suitable solvent such as acetic acid, or an alkanol, such as methanol or ethanol, preferably admixed with an aqueous mineral acid such as hydrochloric acid; or tetrahydrofuran, preferably admixed with an aqueous mineral acid such as hydrochloric acid. Preferably the solvent is acetic acid or aqueous acetic acid, for example a 1:2 acetic acid:water mixture.

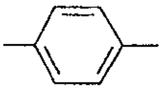
[0013] The reaction is carried out at a temperature which provides a suitable rate of formation of the required product, suitably at an elevated temperature, preferably above 70°C, for example in the range of from 80°C to 115°C.

[0014] The compounds of formula (I) are isolated from the reaction and subsequently purified by use of conventional isolation and purification methods such as chromatography and crystallization/recrystalliazation.

[0015] The suitable, apt, favoured and preferred values of the variables A^1, A^2, R^1 and n in formulae (I) and (II) are as defined in relation to formula (I) of EP 0306228.

[0016] A most preferred value of A^1 is a 2-pyridyl group.

[0017] A most preferred value of A^2 is a moiety of formula:



[0018] A most preferred value of R^1 is a methyl group.

[0019] A most preferred value of n is 2.

[0020] A most preferred value of formula (I) is 5-{4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl}-2,4-thiazolidinedione, or a tautomeric form thereof or a salt thereof, or a solvate thereof.

[0021] Crystalline 5-{4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzylidene}-2,4-thiazolidinedione is isolated from the present reaction and as such forms a further aspect of the present invention. A suitable crystallization/recrystallization solvent is denatured ethanol, the crystallization is favourably effected from refluxing solvent which is allowed to cool to provide the required compound.

[0022] A most preferred value of formula (II) is 5-{4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzylidene}-2,4-thiazolidinedione or a tautomeric form thereof or a salt thereof, or a solvate thereof.

[0023] Suitable salts are pharmaceutically acceptable salts.

[0024] Suitable pharmaceutically acceptable salts include metal salts, such as for example aluminium, alkali metal salts such as sodium or potassium, alkaline earth metal salts such as calcium or magnesium and ammonium or substituted ammonium salts, for example those with lower alkylamines such as triethylamine, hydroxy alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine, cycloalkylamines such as bicyclohexylamine, or with procaine, dibenzylpiperidine, N-benzyl-b-phenethylamine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine or bases of the pyridine type such as pyridine, collidine or quinoline.

[0025] In addition should be mentioned those pharmaceutically acceptable salts provided by pharmaceutically acceptable acids including mineral acids, including salts provided by mineral acids, such as hydrobromic, hydrochloric and sulphuric acids, and organic acids, such as methanesulphonic, tartaric and maleic acids, especially tartaric and maleic acid. A preferred salt is a maleate salt.

[0026] Suitable solvates are pharmaceutically acceptable solvates, such as hydrates.

[0027] The compounds of formula (II) are prepared according to known methods, for example by use of the appropriate method disclosed in EP 0306228. The contents of EP 0306228 are incorporated herein by reference.

[0028] The following example illustrates the invention but does not limit it in any way.

Example

Reduction of (Z)-5-{4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzylidene}-2,4-thiazolidinedione to 5-{4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl}-2,4-thiazolidinedione.

[0029] To a solution of (Z)-5-{[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzylidene}-2,4-thiazolidinedione (123 kg) in glacial acetic acid (1232 L) is added 10% palladium on charcoal (Johnson-Matthey type 87L, 123 kg, catalyst contains ~ 50% w/w water and hence the catalyst loading was 50%w/w). The resulting mixture is hydrogenated at 70-80 p.s.i. hydrogen pressure at about 95°C. After the starting material is consumed (15 - 20 hours), the reaction mixture is cooled to about 65°C and the catalyst is removed by filtration. The resulting solution is concentrated under reduced pressure to low volume and the residue is dissolved in denatured ethanol (500 L) at 60°C. The solution is heated to reflux and then cooled to ambient temperature to effect crystallisation. The product, 5-{[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy] benzyl}-2,4-thiazolidinedione, is isolated by filtration, and dried *in vacuo* at 45°C. Typical yields are 70-80%.

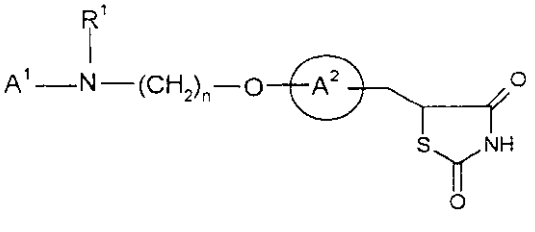
Effect of Change of Reaction Pressure

[0030] The above reaction can be performed over a range of pressures resulting in a significant reduction in reaction time and catalyst loading, as shown below.

Reaction number	Conditions	Reaction Time (hours.)
1	(75psi, 100% catalyst)	15 - 20
2	1000 psi, 100% catalyst	< 2
3	1000 psi, 50% catalyst	7
4	500 psi, 100% catalyst	4
5	500 psi, 50% catalyst	ca.12

Claims

1. A process for preparing a compound of formula (I):



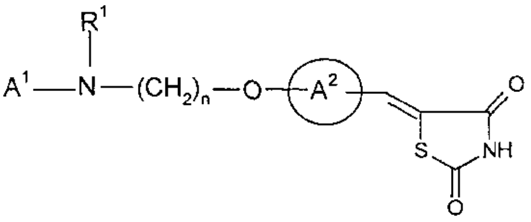
(I)

or a tautomeric form thereof or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, wherein:

A^1 represents a substituted or unsubstituted aromatic heterocyclyl group;

R^1 represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;
A^2 represents a benzene ring having in total up to five substituents; and
n represents an integer in the range of from 2 to 6,

which process comprises catalytically reducing a compound of formula (II):



(II)

wherein A^1, R^1, A^2 and n are as defined in relation to formula (I), **characterised in that** the reduction reaction is carried out using a hydrogen pressure above 20psi; and thereafter if required forming a pharmaceutically acceptable salt and/or a pharmaceutically acceptable solvate of the compound of formula (I).

2. A process according to claim 1, wherein the reaction is carried out using a hydrogen pressure in the range of from 50 to 1500psi, 60 to 1500psi, 75 to 1500psi, 70 to 1000psi or 200 to 1500psi.

3. A process according to claim 1 or claim 2, wherein the reaction hydrogen pressure is in the range of from 70 to 1000psi.

4. A process according to any one of claims 1 to 3, wherein the reaction hydrogen pressure is 70, 75, 80, 500 or 1000psi.

5. A process according to any one of claims 1 to 4, wherein the hydrogenation catalyst is a 10% palladium-on-carbon catalyst.

6. A process according to any one of claims 1 to 5, wherein the catalyst loading is 5 to 100%, (%w/w of catalyst to substrate).

7. A process according to any one of claims 1 to 6, wherein the reaction solvent is acetic acid, aqueous acetic acid, an alkanol, an alkanol admixed with an aqueous mineral acid, tetrahydrofuran or tetrahydrofuran admixed with an aqueous mineral.

8. A process according to claim 7, wherein the reaction solvent is acetic acid.

9. A process according to any one of claims 1 to 8, wherein the reaction temperature is in the range of from 80°C to 115°C.

10. A process according to any one of claims 1 to 9, wherein the compound of formula (II) is 5-{4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzylidene}-2,4-thiazolidinedione or a tautomeric form thereof or a salt thereof, or a solvate thereof, and the compound of formula (I) is 5-{4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl}-2,4-thiazolidinedione, or a tautomeric form thereof or a salt thereof, or a solvate thereof.

European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 02 07 5969

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
D,X	EP 0 306 228 A (BEECHAM GROUP PLC) 8 March 1989 (1989-03-08) * examples 23,31 * ---	1-5	C07D417/12
Y	WO 92 07838 A (BEECHAM GROUP PLC) 14 May 1992 (1992-05-14) * examples 3,9 * ---	1-5	
Y	WO 92 07839 A (BEECHAM GROUP PLC) 14 May 1992 (1992-05-14) * example 4 * -----	1-5	
			TECHNICAL FIELDS SEARCHED (Int.Cl.7)
			C07D

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	3 May 2002	Hass, C

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 02 07 5969

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

03-05-2002

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 306228 A	08-03-1989	AT 186724 T	15-12-1999
		AU 2173888 A	09-03-1989
		BR 1100841 A3	20-06-2000
		CA 1328452 A1	12-04-1994
		CA 1339902 A1	09-06-1998
		CZ 9103916 A3	17-03-1993
		DE 3856378 D1	23-12-1999
		DE 3856378 T2	11-05-2000
		DK 490288 A	05-03-1989
		DK 200001556 A	18-10-2000
		EP 0306228 A1	08-03-1989
		EP 0842925 A1	20-05-1998
		ES 2137915 T3	01-01-2000
		GR 3031873 T3	29-02-2000
		HK 1011029 A1	03-11-2000
		JP 10194970 A	28-07-1998
		JP 10194971 A	28-07-1998
		JP 1131169 A	24-05-1989
		JP 2614497 B2	28-05-1997
		JP 2817840 B2	30-10-1998
		JP 9183771 A	15-07-1997
		JP 2837139 B2	14-12-1998
		JP 9183726 A	15-07-1997
		JP 9183772 A	15-07-1997
		KR 164207 B1	15-01-1999
		KR 164275 B1	15-01-1999
		KR 169463 B1	15-01-1999
		LU 90711 A9	05-03-2001
		NZ 226027 A	26-03-1992
		PT 88410 A ,B	31-07-1989
		SG 59988 A1	22-02-1999
		SK 391691 A3	11-12-2000
		US 6288095 B1	11-09-2001
		US 5646169 A	08-07-1997
		US 5002953 A	26-03-1991
		US 5521201 A	28-05-1996
		US 5232925 A	03-08-1993
		US 5194443 A	16-03-1993
		US 5756525 A	26-05-1998
		US 5260445 A	09-11-1993
		ZA 8806536 A	26-07-1989
WO 9207838 A	14-05-1992	AU 8734791 A	26-05-1992
		EP 0555251 A1	18-08-1993
		WO 9207838 A1	14-05-1992
		JP 6502145 T	10-03-1994

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 02 07 5969

03-05-2002

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9207839 A	14-05-1992	AU 650296 B2	16-06-1994
		AU 8734591 A	26-05-1992
		CA 2095146 A1	01-05-1992
		EP 0555249 A1	18-08-1993
		WO 9207839 A1	14-05-1992
		JP 6502146 T	10-03-1994
		US 5478850 A	26-12-1995

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

制備噻唑烷二酮衍生物的方法

撮錄

一种制備結構式（Ⅰ）或其互變體形式的化合物或其藥用容許的鹽，或其藥用容許的溶劑化物的方法，其中：

A^1代表取代或未被取代的芳族雜環基；
R^1代表氫原子、烷基、酰基、芳烷基，其中芳基部分可以是取代或未被取代的、或取代或未被取代芳基；
A^2代表具有總數高達5個取代基的苯環；和
n代表從2-6範圍内的整數，

該方法包括催化還原結構式（Ⅱ）的化合物：

其中A^1、R^1、A^2和n如同關於結構式（Ⅰ）的規定，其特徵在於催化還原是使用20psi（磅/英寸^2）以上氫壓力進行的；其後如果需要，形成結構式（Ⅰ）的化合物的藥用容許的鹽和/或藥用容許的溶劑化物。