

COMMONWEALTH of AUSTRALIA
Patents Act 1952

APPLICATION FOR A STANDARD PATENT

611079

I/We

Beecham Group p.l.c.

of

Beecham House, Great West Road, Brentford, Middlesex, TW8 9BD, United Kingdom

hereby apply for the grant of a Standard Patent for an invention entitled:

"Thiazolidinedione derivatives".

which is described in the accompanying complete specification.

Details of basic application(s):-

<u>Number</u>	<u>Convention Country</u>	<u>Date</u>
8720825	United Kingdom	4 September 1987
8727987	United Kingdom	30 November 1987
8802454	United Kingdom	4 February 1988

The address for service is care of DAVIES & COLLISON, Patent Attorneys, of 1 Little Collins Street, Melbourne, in the State of Victoria, Commonwealth of Australia.

DATED this SECOND day of SEPTEMBER 1988

To: THE COMMISSIONER OF PATENTS

Keith Collison

.....
a member of the firm of
DAVIES & COLLISON for
and on behalf of the
applicant(s)

MO2510 02/09/88



Davies & Collison, Melbourne

AU/1

COMMONWEALTH OF AUSTRALIA
PATENTS ACT 1952
DECLARATION IN SUPPORT OF CONVENTION
APPLICATION FOR A PATENT

In support of the Application made for a patent for an invention
entitled:
NOVEL COMPOUNDS

I, David Roberts of Beecham Pharmaceuticals, Great Burgh, Yew Tree Bottom
Road, Epsom, Surrey, KT18 5XQ, England,
do solemnly and sincerely declare as follows:-

1. I am authorised by Beecham Group p.l.c. the applicant for the patent
to make this declaration on its behalf.
2. Richard Mark Hindley

Of Post Office address:

Beecham Pharmaceuticals, Great Burgh, Yew Tree Bottom Road, Epsom,
Surrey KT18 5XQ, England

A/All British Subject(s)

is/~~are~~ the actual inventor(~~s~~) of the invention and the facts upon which
the applicant is entitled to make the application are as follows:-

by virtue of the employment of the actual inventor(~~s~~) by Beecham Group
p.l.c., the applicant would, if a patent were granted upon an application
made by the said actual inventor(~~s~~), be entitled to have the patent
assigned to it.

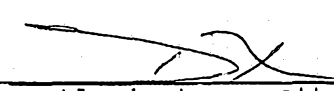
3. The basic application(s) as defined by Section 141 of the Act
~~was~~/were made in United Kingdom by Beecham Group p.l.c. as follows:

Great Britain Patent Appln. No. 8720825	filed on 4th September 1987
Great Britain Patent Appln. No. 8727987	filed on 30th November 1987
Great Britain Patent Appln. No. 8802454	filed on 4th February 1988

4. The basic application(s) referred to in the paragraph 3 of this
Declaration was/were the first application(s) made in a Convention country
in respect of the invention the subject of the application.

Declared at Epsom, Surrey, England

this 4th day of August 1988.

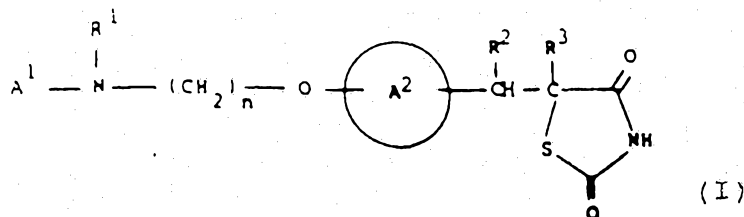

David Roberts, as Attorney for and on behalf
of the said Beecham Group p.l.c.

Witness: *E. n Ferguson*

(12) PATENT ABRIDGMENT (11) Document No. AU-B-21738/88
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 611938

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PHARMACEUTICAL 5-SUBSTITUTED-2,4-THIAZOLIDINEDIONES
- International Patent Classification(s)
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A61K 031/425 A61K 031/495
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- (21) Application No. : 21738/88 (22) Application Date : 02.09.88
- (30) Priority Data
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| (31) Number | (32) Date | (33) Country |
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| 8727987 | 30.11.87 | GB UNITED KINGDOM |
| 8802454 | 04.02.88 | GB UNITED KINGDOM |
- (43) Publication Date : 09.03.89
(44) Publication Date of Accepted Application : 27.06.91
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(56) Prior Art Documents
US 4340605
(57) Claim

1. A compound of formula (I):



or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, characterised in that:

A¹ represents an optionally substituted single or fused ring aromatic heterocyclyl group comprising up to 4 heteroatoms in each ring selected from oxygen, sulphur or nitrogen, in which the optional substituents are selected from the group consisting of C₁₋₁₂ alkyl, C₁₋₁₂ alkoxy, phenyl, naphthyl, halogen or any two substituents on adjacent carbon atoms, together with the carbon atoms to which they are attached, form a benzene ring; and wherein the carbon atoms or benzene ring represented by the two said substituents may themselves be optionally substituted with up to three groups selected from

(11) AU-B-21738/88

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halogen, C₁₋₁₂ alkyl, phenyl, C₁₋₁₂ alkoxy, halo C₁₋₁₂ alkyl, hydroxy, amino, nitro, carboxy, C₁₋₁₂ alkoxy-carbonyl, C₁₋₁₂ alkoxy-carbonyl-C₁₋₁₂-alkyl, C₁₋₁₂ alkyl-carbonyloxy or C₁₋₁₂ alkyl-carbonyl;

R¹ represents a hydrogen atom, a C₁₋₁₂ alkyl group, an acyl group, a phenyl C₁₋₁₂ alkyl, naphthyl C₁₋₁₂ alkyl, phenyl or naphthyl group, wherein the phenyl or naphthyl moiety may be optionally substituted with up to five groups selected from halogen, C₁₋₁₂ alkyl, phenyl, C₁₋₁₂ alkoxy, halo C₁₋₁₂ alkyl, hydroxy, amino, nitro, carboxy, C₁₋₁₂ alkoxy-carbonyl, C₁₋₁₂ alkoxy-carbonyl-C₁₋₁₂-alkyl, C₁₋₁₂ alkyl-carbonyloxy or C₁₋₁₂ alkyl-carbonyl;

R² and R³ each represents hydrogen, or R² and R³ together represent a bond;

A² represents a benzene ring having in total up to three optional substituents selected from the group consisting of halogen, C₁₋₁₂ alkyl or C₁₋₁₂ alkoxy optionally substituted with up to five groups selected from halogen, C₁₋₁₂ alkyl, phenyl, C₁₋₁₂ alkoxy, halo C₁₋₁₂ alkyl, hydroxy, amino, nitro, carboxy, C₁₋₁₂ alkoxy-carbonyl, C₁₋₁₂ alkoxy-carbonyl-C₁₋₁₂ alkyl, C₁₋₁₂ alkyl, carbonyloxy or C₁₋₁₂ alkyl-carbonyl; and n represents an integer in the range of from 2 to 6.

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

COMPLETE SPECIFICATION

61 1938

NAME & ADDRESS
OF APPLICANT:

Beecham Group p.l.c.
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Great West Road
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NAME(S) OF INVENTOR(S):

Richard Mark Hindley

ADDRESS FOR SERVICE:

DAVIES & COLLISON
Patent Attorneys
1 Little Collins Street, Melbourne, 3000.

COMPLETE SPECIFICATION FOR THE INVENTION ENTITLED:

"Thiazolidinedione derivatives".

The following statement is a full description of this invention, including the best method of performing it known to me/us:-



B2368

Thiazolidinedione derivatives
NOVEL COMPOUNDS

This invention relates to certain substituted thiazolidinedione derivatives, to a process for preparing such compounds, to pharmaceutical compositions containing such compounds and to the use of such compounds and compositions in medicine.

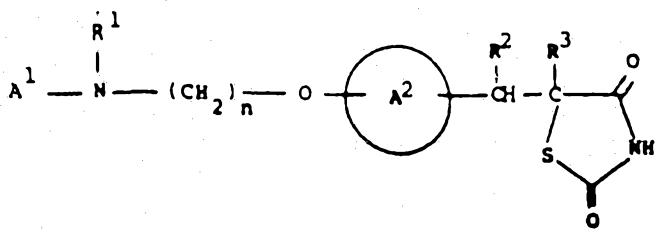
European Patent Applications, Publication Numbers 0008203, 0139421, 0155845, 0177353, 0193256, 0207581 and 0208420 relate to thiazolidinedione derivatives which are disclosed as having hypoglycaemic and hypolipidaemic activity. Chem. Pharm. Bull 30 (10) 3580-3600 also relates to certain thiazolidinedione derivatives having hypoglycaemic and hypolipidaemic activities.

It has now surprisingly been discovered that certain novel substituted-thiazolidinedione derivatives show improved blood-glucose lowering activity and are therefore of potential use in the treatment and/or prophylaxis of hyperglycaemia and are of particular use in the treatment of Type II diabetes.

These compounds are also indicated to be of potential use for the treatment and/or prophylaxis of other diseases including hyperlipidaemia, hypertension, cardiovascular disease and certain eating disorders.

Accordingly, the present invention provides a compound of formula (I):





(I)

or a tautomeric form thereof and/or a pharmaceutically
10 acceptable salt thereof and/or a pharmaceutically
acceptable solvate thereof, characterised in that:

A¹ represents an optionally substituted single or fused ring aromatic heterocyclyl group comprising up to 4 heteroatoms in each ring selected from oxygen, sulphur or nitrogen, in which the optional substituents are selected from the group consisting of C₁₋₁₂ alkyl, C₁₋₁₂ alkoxy, phenyl, naphthyl, halogen or any two substituents on adjacent carbon atoms, together with the carbon atoms to which they are attached, form a benzene ring; and wherein the carbon atoms or benzene ring represented by the two said substituents may themselves be optionally substituted with up to three groups selected from halogen, C₁₋₁₂ alkyl, phenyl, C₁₋₁₂ alkoxy, halo C₁₋₁₂ alkyl, hydroxy, amino, nitro, carboxy, C₁₋₁₂ alkoxycarbonyl, C₁₋₁₂ alkoxycarbonyl-C₁₋₁₂-alkyl, C₁₋₁₂ alkylcarbonyloxy or C₁₋₁₂ alkylcarbonyl;

R¹ represents a hydrogen atom, a C₁₋₁₂ alkyl group, an acyl group, a phenyl C₁₋₁₂ alkyl, naphthyl C₁₋₁₂ alkyl, phenyl or naphthyl group, wherein the phenyl or naphthyl moiety may be optionally substituted with up to five groups selected from halogen, C₁₋₁₂ alkyl, phenyl, C₁₋₁₂ alkoxy, halo C₁₋₁₂ alkyl, hydroxy, amino, nitro, carboxy, C₁₋₁₂ alkoxycarbonyl, C₁₋₁₂ alkoxycarbonyl-C₁₋₁₂-alkyl, C₁₋₁₂ alkylcarbonyloxy or C₁₋₁₂ alkylcarbonyl;

R^2 and R^3 each represents hydrogen, or R^2 and R^3 together represent a bond;

A^2 represents a benzene ring having in total up to three optional substituents selected from the group consisting of halogen, C_{1-12} alkyl or C_{1-12} alkoxy optionally substituted with up to five groups selected from halogen, C_{1-12} alkyl, phenyl, C_{1-12} alkoxy, halo C_{1-12} alkyl, hydroxy, amino, nitro, carboxy, C_{1-12} alkoxycarbonyl, C_{1-12} alkoxycarbonyl- C_{1-12} alkyl, C_{1-12} alkyl, carbonyloxy or C_{1-12} alkylcarbonyl; and n represents an integer in the range of from 2 to 6.

Favoured aromatic heterocyclyl groups include substituted or unsubstituted single ring aromatic heterocyclyl groups having 4 to 7 ring atoms, preferably 5 or 6 ring atoms.

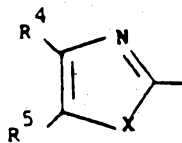
In particular, the aromatic heterocyclyl group comprises 1, 2 or 3 heteroatoms, especially 1 or 2, selected from oxygen, sulphur or nitrogen.

Suitable values for A^1 when it represents a 5-membered aromatic heterocyclyl group include thiazolyl and oxazolyl, especially oxazolyl.

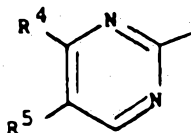
Suitable values for A^1 when it represents a 6-membered aromatic heterocyclyl group include pyridyl or pyrimidinyl.

Suitably R^2 and R^3 each represent hydrogen.

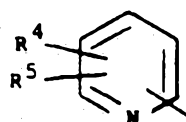
Preferably, A^1 represents a moiety of formula (a), (b) or (c):



(a)



(b)

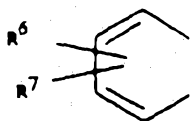


(c)



wherein:

R⁴ and R⁵ each independently represents a hydrogen atom,
an C₁₋₁₂ alkyl group or a phenyl or naphthyl group
optionally substituted with up to five groups selected
5 from halogen, C₁₋₁₂ alkyl, phenyl, C₁₋₁₂ alkoxy, halo
C₁₋₁₂ alkyl, hydroxy, amino, nitro, carboxy, C₁₋₁₂
alkoxycarbonyl, C₁₋₁₂ alkoxycarbonyl C₁₋₁₂ alkyl, C₁₋₁₂
alkylcarbonyloxy or C₁₋₁₂ alkylcarbonyl; or when R⁴ and
R⁵ are each attached to a carbon atom, then R⁴ and R⁵
10 together represent a moiety of formula (d):



(d)

15

wherein R₆ and R₇ each independently represent hydrogen,
halogen or C₁₋₁₂ alkyl, optionally substituted with up to
five groups selected from halogen, C₁₋₁₂ alkyl, phenyl,
20 C₁₋₁₂ alkoxy, halo C₁₋₁₂ alkyl, hydroxy, amino, nitro,
carboxy, C₁₋₁₂ alkoxycarbonyl, C₁₋₁₂ alkoxycarbonyl-
C₁₋₁₂ alkyl, C₁₋₁₂ alkylcarbonyloxy or C₁₋₁₂
alkylcarbonyl; or C₁₋₁₂ alkoxy and in the moiety of
formula (a), X represents oxygen or sulphur.

25

Aptly, A¹ represents a moiety of the abovedefined formula
(a).

30

Aptly, A¹ represents a moiety of the abovedefined formula
(b).

Aptyl, A¹ represents a moiety of the abovedefined formula
(c).

35

Favourably, R⁶ represents hydrogen. Favourably, R⁷
represents hydrogen.

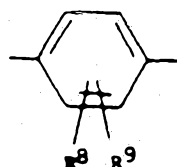


Preferably, R^6 and R^7 both represent hydrogen.

Preferably, for the moieties of formula (b) or (c), R^4 and R^5 both represent hydrogen.

Suitable substituents for the moiety A^2 include halogen, substituted or unsubstituted alkyl or alkoxy.

10 Favourably, A^2 represents a moiety of formula (e):



(e)

15

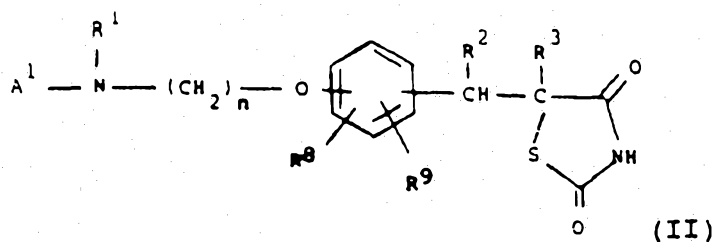
wherein R_8 and R_9 each independently represent hydrogen, halogen, C_{1-12} alkyl or C_{1-12} alkoxy optionally substituted with up to five groups selected from halogen, C_{1-12} alkyl, phenyl, C_{1-12} alkoxy, halo C_{1-12} alkyl, hydroxy, amino, nitro, carboxy, C_{1-12} alkoxy carbonyl, C_{1-12} alkoxy carbonyl- C_{1-12} alkyl, C_{1-12} alkyl, carbonyloxy or C_{1-12} alkyl carbonyl; and n represents an integer in the range of from 2 to 6.

20

25 Preferably, R^8 and R^9 each represent hydrogen.

Favourably, X represents oxygen. Favourably, X represents sulphur.

30 In one preferred aspect the present invention provides a class of compounds, which fall wholly within the scope of formula (I), of formula (II):



35

- or a tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, wherein A^1 , R^1 , R^2 , R^3 , and n are as defined in relation to formula (I) and R^8 and R^9 are as defined in relation to formula (e).

Suitably, n represents an integer 2, 3 or 4, notably 2 or 3 and especially 2.

- 10 Suitably, R^1 represents hydrogen, alkyl, acyl, especially acetyl, or benzyl.

Preferably, R^1 represents a methyl group.

- 15 As indicated above a compound of formula (I) may exist in one of several tautomeric forms, all of which are encompassed by the present invention. It will be appreciated that the present invention encompasses all of the isomeric forms of the compounds of formula (I) and
20 the pharmaceutically acceptable salts thereof, including any stereoisomeric forms thereof, whether as individual isomers or as mixtures of isomers.

- When used herein the term 'halogen' refers to fluorine,
25 chlorine, bromine and iodine; preferably chlorine.

- When used herein the terms ' C_{1-12} alkyl' and ' C_{1-12} alkoxy' relate to groups having straight or branched carbon chains.

- 30 Suitable alkyl groups are C_{1-12} alkyl groups, especially C_{1-6} alkyl groups e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or tert-butyl groups.

- 35 Suitable pharmaceutically acceptable salts include salts of the thiazolidinedione moiety, and, where appropriate,



salts of carboxy groups.

Suitable pharmaceutically acceptable salts of the thiazolidineone moiety include metal salts especially

- 5 alkali metal salts such as the lithium, sodium and potassium salts.

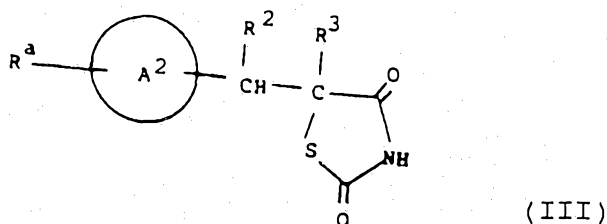
Suitable pharmaceutically acceptable salts of carboxy groups include metal salts, such as for example

- 10 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-
15 hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine, cycloalkylamines such as bicyclohexylamine, or with procaine, dibenzylpiperidine, N-benzyl- β -phenethylamine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine or
20 bases of the pyridine type such as pyridine, collidine or quinoline.



Suitable pharmaceutically acceptable solvates include hydrates.

In a further aspect the present invention also provides a process for the preparation of a compound of formula (I), or a tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable hydrate thereof, which process comprises reacting a compound of formula (III):



wherein R², R³ and A² are as defined in relation to formula (I), and R^a is a moiety convertible to a moiety of formula (f):



wherein R¹, A¹, and n are as defined in relation to formula (I), with an appropriate reagent capable of converting R^a to the said moiety (f) and thereafter, if required, carrying out one or more of the following optional steps:

- (i) converting a compound of formula (I) to a further compound of formula (I);
- (ii) preparing a pharmaceutically acceptable salt of the compound of formula (I) and/or a pharmaceutically acceptable solvate thereof.

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Suitably, R^a represents $R^1HN-(CH_2)_nO-$ wherein R^1 and n are as defined in relation to formula (I).

Suitably, when R^a is $R^1HN-(CH_2)_nO-$, an appropriate reagent capable of converting R^a to a moiety (f) is a compound of formula (IV):

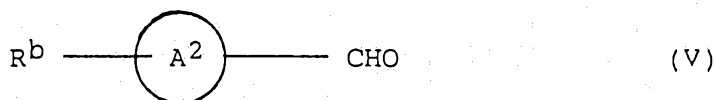


wherein A^1 is as defined in relation to formula (I) and R^X represents a leaving group.

A suitable leaving group R^X includes a halogen atom, preferably a chlorine or bromine atom, or a thioalkyl group for example a thiomethyl group.

The reaction between the compound of formula (III) and the appropriate reagent may be carried out under conditions suitable to the particular compound of formula (III) and the reagent chosen; thus for example the abovementioned reaction between a compound of formula (III) wherein R^a represents $R^1HN-(CH_2)_nO-$ and the compound of formula (IV), may be carried out in any suitable solvent, for example tetrahydrofuran, at a temperature in the range of between 0 and 60°C.

A compound of formula (III) may be prepared from a compound of formula (V):



wherein A^2 is as defined in relation to the compound of formula (I) and R^b is a moiety R^a , or a moiety convertible to a moiety R^a ; by reaction of the compound of formula (V) with 2,4-thiazolidinedione; and

thereafter if required carrying out one or more of the following optional steps:

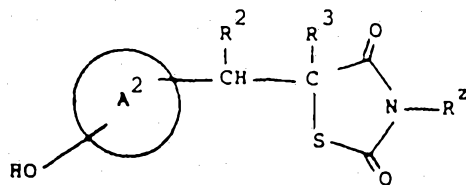
(i) reducing a compound of formula (III) wherein R^2 and R^3 together represent a bond, into a compound of formula (III) wherein R^2 and R^3 each represent hydrogen;

(ii) converting a moiety R^b to a moiety R^a .

The reaction between the compound of formula (V) and 2,4-thiazolidinedione will of course be carried out under conditions suitable to the nature of the compound of formula (V), in general the reaction being carried out in a solvent such as toluene, suitably at an elevated temperature such as the reflux temperature of the solvent and preferably in the presence of a suitable catalyst such as piperidinium acetate or benzoate. Favourably, in the reaction between the compound of formula (V) and 2,4-thiazolidinedione, the water produced in the reaction is removed from the reaction mixture, for example by means of a Dean and Stark apparatus.

When R^a represents $R^1HN-(CH_2)_n-O-$, a suitable value for R^b is a hydroxyl group.

The moiety R^b may be converted to the moiety R^a by any suitable means, for example when R^b represents a hydroxyl group and R^a represents $R^1HN(CH_2)_n-O-$ the appropriate conversion may be carried out by coupling a compound of formula (VA):



(VA)

wherein R^2 , R^3 and A^2 are as defined in relation to formula (I) and R^2 is hydrogen or a nitrogen protecting group, with a compound of formula (VI):



wherein R^1 and n are as defined in relation to formula (I) and R^X is hydrogen or a nitrogen protecting group, in the presence of a suitable coupling agent; and thereafter, if required, carrying out one or more of the following optional steps:

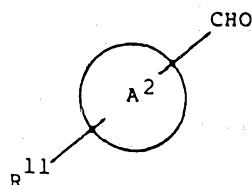
(i) reducing a compound of formula (III) wherein R^2 and R^3 together represent a bond, to a compound of formula (III) wherein R^2 and R^3 each represent hydrogen;

(ii) removing any nitrogen protecting group.

A suitable coupling agent for the coupling reaction between the compound of formula (VA) and (VI) is provided by diethylazodicarboxylate and triphenylphosphine. The coupling reaction may be carried out in any suitable solvent at a low to medium temperature, for example in tetrahydrofuran at a temperature in the range of between 0 and 60°C.

One example of the preparation of a compound of formula (VA) is that wherein a compound falling within formula

- 12 -
(V) of particular formula (VII):



(VII)

wherein A^2 is as defined in relation to formula (I), and R^{11} represents a hydroxyl group or a protected hydroxyl group, is reacted with 2,4-thiazolidinedione; and thereafter if required removing any protecting group.

Preferably, R^{11} represents a benzyloxy group.

Suitable conditions for the reaction between a compound of formula (VII) and 2,4-thiazolidinedione are those defined above in relation to the reaction between the compounds of formula (V) and 2,4-thiazolidinedione.

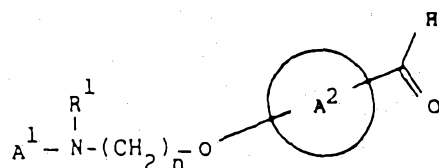
The compounds of formula (IV), (VI) and (VII) are either known compounds or are prepared using methods analogous to those used to prepare known compounds.

Suitable protecting groups in any of the abovementioned reactions are those used conventionally in the art. Thus, for example, a suitable nitrogen protecting group is a benzyl group or a benzyloxycarbonyl group and a suitable hydroxyl protecting group is a benzyl group.

The methods of formation and removal of such protecting groups are those conventional methods appropriate to the molecule being protected. Thus for example when R^{11} represents a benzyloxy group such group may be prepared by treatment of the appropriate compound of

formula (VII), wherein R^{11} is a hydroxyl group with a benzyl halide, such as benzyl bromide, and thereafter when required the benzyl group may be conveniently removed using a mild ether cleavage reagent such as trimethylsilyliodide.

A compound of formula (I), or a tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may also be prepared by reacting a compound of formula (VIII):



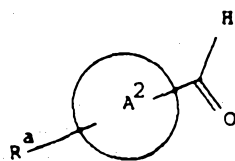
(VIII)

wherein R^1 , A^1 , A^2 , and n are as defined in relation to formula (I) with 2,4-thiazolidinedione; and thereafter if required carrying out one or more of the following optional steps:

- (i) converting a compound of formula (I) into a further compound of formula (I);
- (ii) preparing a pharmaceutically acceptable salt of a compound of formula (I) and/or a pharmaceutically acceptable solvate thereof.

The reaction between a compound of formula (VIII) and 2,4-thiazolidinedione may suitably be carried out under analogous conditions to those used in the reaction between a compound of formula (V) and 2,4-thiazolidinedione.

A compound of formula (VIII) may be prepared by reacting a compound of formula (IX):



(IX)

wherein A^2 is as defined in relation to formula (I) and R^a is as defined in relation to formula (III), with an appropriate reagent capable of converting R^a to the above defined moiety (f).

Suitable values for R^a include those described above in relation to the compound of formula (III). Thus R^a may represent $R^1HN-(CH_2)_nO-$, as defined above, and hence the appropriate compound of formula (IX) may be reacted with a reagent of the abovedefined formula (IV) to provide the required compound of formula (VIII).

Suitable reaction conditions for the reaction of the compound of formula (IX) and the appropriate reagent may include those described above in relation to the preparation of compound (III) with the said appropriate reagent.

Preferably, for the compound of formula (IX), R^a represents a leaving group, especially a fluorine atom. When R^a represents a leaving group, preferably a fluorine atom, a particularly appropriate reagent is a compound of formula (X):

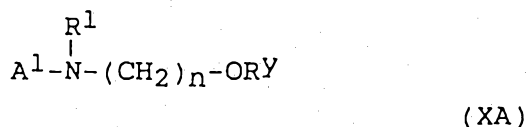


wherein R^1 , A^1 , and n are as defined in relation to formula (I).

The reaction between the compounds of formulae (IX) and (X) may be carried out under any suitable conditions, for example in a solvent such as dimethylformamide or dimethylsulphoxide at an elevated temperature for example in the range of between 100 to 150°C, suitably in the presence of a base such as sodium hydride or potassium carbonate.

In the compound of formula (IX) R^a may also represent a hydroxyl group.

When R^a , in the compound of formula (IX), represents a hydroxyl group a particularly appropriate reagent is a compound of the abovedefined formula (X) or a compound of formula (XA):



wherein A^1 , R^1 and n are as defined in relation to formula (X) and R^Y represents a tosylate or mesylate group.

The reaction between the compound of formula (IX) wherein R^a is a hydroxyl group and the reagent of the abovedefined formula (X) may suitably be carried out in an aprotic solvent, such as tetrahydrofuran, at low to medium temperature, for example at ambient temperature, and preferably in the presence of a coupling agent such as that provided by triphenylphosphine and diethylazodicarboxylate.

The reaction between the compound of formula (IX), wherein R^a is a hydroxyl group, and the reagent of the abovedefined formula (XA) may be carried out in an aprotic solvent, such as dimethylformamide, at a low to elevated temperature, for example in the range of from 50°C to 120°C and preferably in the presence of a base, such as sodium hydride.

The compound of formula (XA) may be prepared from the corresponding compound of formula (X) by reaction with either a tosyl halide or a mesyl halide in a solvent such as pyridine.

The compounds of formula (IX) are known compounds or compounds prepared by methods analogous to those used to prepare known compounds, for example 4-fluorobenzaldehyde and 4-hydroxybenzaldehyde are known commercially available compounds.

The reagent of formula (X) may be prepared by reacting a compound of the hereinabove defined formula (IV), with a compound of the hereinbefore defined formula (VI) and thereafter if required removing any nitrogen protecting group using the appropriate conventional conditions.

The reaction between the compounds of formula (IV) and (VI) may be carried out under any suitable conditions, such as in solvent, for example in an aprotic solvent such as tetrahydrofuran, at a low to medium temperature, for example a temperature in the range of from 0 to 60°C.

Favourably when R^1 represents hydrogen the reaction is carried out using the compound of formula (VI) as a solvent at a low to elevated temperature, suitably an

elevated temperature such as in the range of between 100 and 170°C.

The abovementioned conversion of a compound of formula (I) into a further compound of formula (I) includes the following conversions:

(a) reducing a compound of formula (I) wherein R^2 and R^3 together represent a bond, to a compound of formula (I) wherein R^2 and R^3 each represent hydrogen; and

(b) converting one group R^1 into another group R^1 .

The conversion of a compound of formula (I) to a further compound of formula (I) may be carried out by using any appropriate conventional procedure.

A suitable reduction method for the abovementioned conversion (a) includes catalytic reduction or the use of a metal/solvent reducing system.

Suitable catalysts for use in the catalytic reduction are palladium on carbon catalysts, preferably a 10% palladium on charcoal catalyst; the reduction being carried out in a solvent, for example dioxan, suitably at ambient temperature.

Suitable metal/solvent reducing systems include magnesium in methanol.

The abovementioned reduction of a compound of formula (III) wherein R^2 and R^3 together represent a bond to a compound of formula (III) wherein R^2 and R^3 each represent hydrogen, may be carried out under analogous

conditions to those referred to above in conversion (a) of the compound of formula (I).

In the abovementioned conversion (b), suitable conversions of one group R^1 into another group R^1 includes converting a group R^1 which represents hydrogen into a group R^1 which represents an acyl group.

The conversion of a compound of formula (I) wherein R^1 represents hydrogen into a compound of formula (I) wherein R^1 represents acyl may be carried out using any appropriate conventional acylation procedure, such as by treating an appropriately protected compound of formula (I) with an acylating agent. For example acetic anhydride may be used to prepare the compound of formula (I) wherein R^1 is acetyl.

It will be appreciated that in the abovementioned conversions (a) and (b), any reactive group in the compound of formula (I) would be protected, according to conventional chemical practice, where necessary.

Where appropriate the isomeric forms of the compounds of formula (I) and the pharmaceutically acceptable salts thereof may be prepared as individual isomers using conventional chemical procedures.

As mentioned above the compounds of the invention are indicated as having useful therapeutic properties:

The present invention accordingly provides a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use as an active therapeutic substance.

Thus the present invention provides a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment of and/or prophylaxis of hyperglycaemia.

In a further aspect the present invention also provides a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment and/or prophylaxis of hyperlipidaemia.

As indicated hereinbefore the present invention also provides a compound of formula (I) or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof for use in the treatment of hypertension, cardiovascular disease and certain eating disorders.

A compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier.

Accordingly, the present invention also provides a pharmaceutical composition comprising a compound of the general formula (I), or a tautomeric form thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier therefor.

As used herein the term 'pharmaceutically acceptable' embraces compounds, compositions and ingredients for

both human and veterinary use: for example the term 'pharmaceutically acceptable salt' embraces a veterinarily acceptable salt.

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

Usually the pharmaceutical compositions of the present invention will be adapted for oral administration, although compositions for administration by other routes, such as by injection and percutaneous absorption are also envisaged.

Particularly suitable compositions for oral administration are unit dosage forms such as tablets and capsules. Other fixed unit dosage forms, such as powders presented in sachets, may also be used.

In accordance with conventional pharmaceutical practice the carrier may comprise a diluent, filler, disintegrant, wetting agent, lubricant, colourant, flavourant or other conventional adjuvant.

Typical carriers include, for example, microcrystalline cellulose, starch, sodium starch glycollate, polyvinylpyrrolidone, polyvinylpolypyrrolidone, magnesium stearate, sodium lauryl sulphate or sucrose.

Most suitably the composition will be formulated in unit dose form. Such unit dose will normally contain an amount of the active ingredient in the range of from 0.1 to 1000 mg, more usually 0.1 to 500 mg, and more especially 0.1 to 250 mg.

The present invention further provides a method for the treatment and/or prophylaxis of hyperglycaemia in a human or non-human mammal which comprises administering an effective, non-toxic, amount of a compound of the general formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof to a hyperglycaemic human or non-human mammal in need thereof.

The present invention further provides a method for the treatment of hyperlipidaemia in a human or non-human mammal, which comprises administering an effective, non-toxic, amount of a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, to a hyperlipidaemic human or non-human mammal in need thereof.

Conveniently, the active ingredient may be administered as a pharmaceutical composition hereinbefore defined, and this forms a particular aspect of the present invention.

In the treatment and/or prophylaxis of hyperglycaemic humans, and/or the treatment and/or prophylaxis of hyperlipidaemic human, the compound of the general formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may be taken in doses, such as those described above, one to six times a day in a manner such that the total daily dose for a 70 kg adult will generally be in the range of from 0.1 to 6000 mg, and more usually about 1 to 1500 mg.

In the treatment and/or prophylaxis of hyperglycaemic non-human mammals, especially dogs, the active ingredient may be administered by mouth, usually once or twice a day and in an amount in the range of from about 0.025 mg/kg to 25 mg/kg, for example 0.1 mg/kg to 20 mg/kg. Similar dosage regimens are suitable for the treatment and/or prophylaxis of hyperlipidaemia in non-human mammals.

The dosages regimens for the treatment of hypertension, cardiovascular disease and eating disorders will generally be those mentioned above in relation to hyperglycaemia.

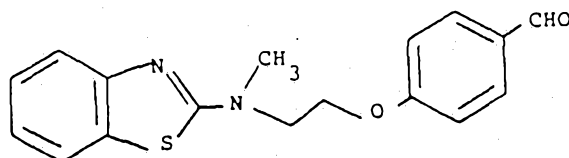
In a further aspect the present invention provides the use of a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of hyperglycaemia.

The present invention also provides the use of a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of hyperlipidaemia, hypertension, cardiovascular disease or certain eating disorders.

The following Procedures and Examples illustrate the invention but do not limit it in any way.

Preparation 1

4-[2-(N-Methyl-N-(2-benzothiazolyl)amino)ethoxy]-
benzaldehyde



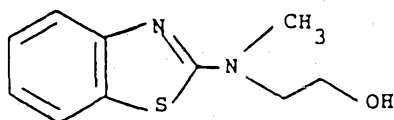
A mixture of 4-fluorobenzaldehyde (1.5g) and 2-[N-methyl-N-(2-benzothiazolyl)amino]ethanol (2.4g) in dimethyl sulfoxide (50ml) containing anhydrous potassium carbonate (2g) was stirred at 100°C for 24 hours. The mixture was cooled to room temperature and added to water (300ml). The aqueous solution was extracted with diethyl ether (2x300ml). The organic extracts were washed with brine (1x300ml), dried (MgSO₄), filtered and evaporated to dryness. The title compound was obtained as a waxy solid following chromatography on silica-gel in 1% methanol in dichloromethane.

¹H NMR δ (CDCl₃)

3.2 (3H, s); 3.8 (2H, t); 4.2 (2H, t);
6.8-7.8 (8H, complex); 9.8 (1H, s).

Preparation 2

2-[N-Methyl-N-(2-benzothiazolyl)amino]ethanol



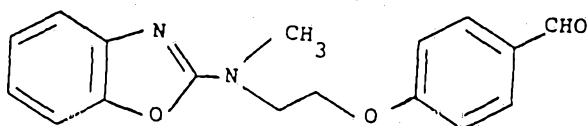
A mixture of 2-chlorobenzothiazole (8.5g) and 2-methylaminoethanol (20ml) was heated at 120°C under pressure in a sealed, glass lined, stainless steel reaction vessel for 18 hours. After cooling, the oil was added to water (100ml), extracted with dichloromethane (2x100ml), the organic extracts were dried (MgSO₄), filtered and evaporated to dryness. Chromatography of the residual oil on silica-gel in 2% methanol in dichloromethane gave the title compound which was used in Preparation 1 without further purification.

¹H NMR δ (CDCl₃)

3.15 (3H, s); 3.4-4.0 (4H, m); 4.7 (1H, broad s, exchanges with D₂O); 6.8-7.6 (4H, complex).

Preparation 3

4-[2-(N-Methyl-N-(2-benzoxazolyl)amino)ethoxy]-
benzaldehyde



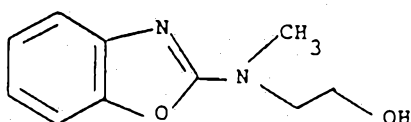
To a solution of 2-[N-methyl-N-(2-benzoxazolyl)amino]ethanol (9.6g), triphenylphosphine (13.1g) and 4-hydroxybenzaldehyde (6.1g) in dry tetrahydrofuran (150ml) was added dropwise a solution of diethyl azodicarboxylate (9.0g) in dry tetrahydrofuran (30ml), under a blanket of nitrogen with stirring at room temperature. The solution was stirred overnight at room temperature following which the solvent was removed under reduced pressure. The residue was dissolved in diethyl ether (300ml), filtered and the ether solution was washed with dilute sodium hydroxide solution (200 ml), saturated brine (200ml), dried (MgSO_4), filtered and the solvent evaporated. The title compound (mp 97-98°C) was obtained after chromatography on silica-gel, eluting with dichloromethane.

^1H NMR δ (CDCl_3)

3.30 (3H, s); 3.85 (2H, t); 4.30 (2H, t) 6.80-7.85 (8H, complex); 9.85 (1H, s).

Preparation 4

2-[N-Methyl-N-(2-benzoxazolyl)amino]ethanol



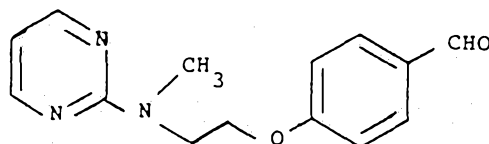
A solution of 2-chlorobenzoxazole (15.4g) in dry tetrahydrofuran (50ml) was added dropwise to an ice cooled solution of 2-methylaminoethanol (15.0g) in dry tetrahydrofuran (100ml) with stirring and protection from atmospheric moisture. The mixture was stirred at 0°C for 1 hour, allowed to warm to room temperature and stirred for a further 2 hours. The solvent was removed under reduced pressure, the product was dissolved in ethyl acetate (200ml) and washed with brine (2x150ml). The organic layer was dried (MgSO₄), filtered and the solvent evaporated. Chromatography of the residue on silica-gel in dichloromethane gave the title compound (mp 62-3°C) which was used in Preparation 3 without further purification.

¹H NMR δ (CDCl₃)

3.12 (3H s); 3.4-4.0 (4H, m); 4.7 (1H, s, exchanges with D₂O); 6.8-7.4 (4H, complex).

Preparation 5

4-[2-(N-Methyl-N-(2-pyrimidinyl)amino)ethoxy]-
benzaldehyde



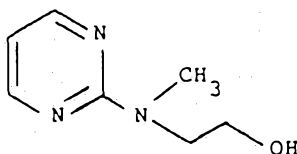
A mixture of 4-fluorobenzaldehyde (12ml) and 2-[N-methyl-N-(2-pyrimidinyl)amino]ethanol (10.05g) in dry dimethyl sulfoxide (50ml) containing anhydrous potassium carbonate (15g) was stirred at 120°C for 6 hours. The mixture was cooled to room temperature and added to water (200ml). The aqueous solution was extracted with ethyl acetate (2 x 300ml), the organic extracts washed with brine, dried (MgSO₄) and evaporated. The title compound was obtained as an oil following chromatography on silica-gel in 2% methanol in dichloromethane.

¹H NMR δ (CDCl₃)

3.3 (3H, s); 3.8-4.4 (4H, complex); 6.5 (1H, t);
7.0 (2H, d); 7.8 (2H, d); 8.3 (2H, d); 9.9 (1H, s).

Preparation 6

2-[N-Methyl-N-(2-pyrimidinyl)amino]ethanol



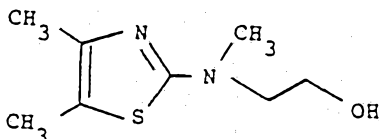
A mixture of 2-chloropyrimidine (10g) and 2-methylaminoethanol in dry tetrahydrofuran (100ml) was boiled under reflux for 3 hours. The solution was cooled, water (200ml) was added, the mixture extracted with dichloromethane, the organic extracts were dried (MgSO_4), filtered and evaporated to dryness. The residual oil was used in Preparation 5 without further purification.

^1H NMR δ (CDCl_3)

3.2 (3H, s); 3.5-3.9 (4H, m); 4.6 (1H, s, exchanges with D_2O); 6.4 (1H, t); 8.2 (2H, d).

Preparation 7

2-[N-Methyl-N-(2-[4,5-dimethylthiazolyl])amino]ethanol



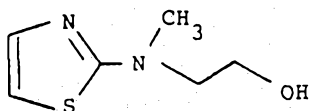
A solution of 2-chloro-4,5-dimethylthiazole (13.2g) and 2-methylaminoethanol (40ml) in pyridine (100ml) was boiled under reflux for 20 hours. After cooling, the oil was added to water (300ml) and extracted with ethyl acetate (3x200ml). The organic extracts were washed with brine (2x200ml), dried (MgSO₄), filtered and evaporated to dryness to leave the title compound which was used in Preparation 14 without further purification.

¹H NMR δ (CDCl₃)

2.15 (3H, s); 2.20 (3H, s); 3.1 (3H, s); 3.4-3.9 (4H, m); 5.25 (1H, broad s, exchanges with D₂O).

Preparation 8

2-[N-Methyl-N-(2-thiazolyl)amino]ethanol



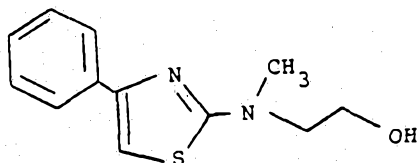
The title compound was prepared as an oil from 2-bromothiazole (15g) and 2-methylaminoethanol (45ml) by an analogous procedure to that described in Preparation 7

¹H NMR δ (CDCl₃)

3.1 (3H, s); 3.4-3.9 (4H, m); 4.8 (1H, broad s, exchanges with D₂O); 6.4 (1H, d); 7.0 (1H, d).

Preparation 9

2-[N-Methyl-N-(2-(4-phenylthiazolyl))amino]ethanol



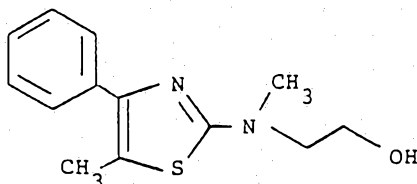
The title compound was prepared as an oil from 2-chloro-4-phenylthiazole (13.5g) and 2-methylaminoethanol (40ml) by an analogous procedure to that described in Preparation 7.

¹H NMR δ (CDCl₃)

3.15 (3H, s); 3.6-4.0 (4H, m); 4.6 (1H, broad s, exchanges with D₂O); 6.7 (1H, s); 7.2-7.9 (5H, complex).

Preparation 10

2-[N-Methyl-N-(2-(4-phenyl-5-methylthiazolyl))amino]ethanol



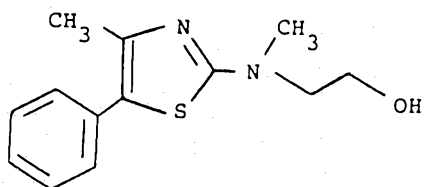
The title compound was prepared as an oil from 2-chloro-4-phenyl-5-methylthiazole (18.9g) and 2-methylaminoethanol (50ml) by an analogous procedure to that described in Preparation 7.

¹H NMR δ (CDCl₃)

2.38 (3H, s); 3.0 (3H, s); 3.45-3.85 (4H, m); 5.1 (1H, broad s, exchanges with D₂O); 7.1-7.7 (5H, complex).

Preparation 11

2-[N-Methyl-N-(2-(4-methyl-5-phenylthiazolyl))amino]-
ethanol



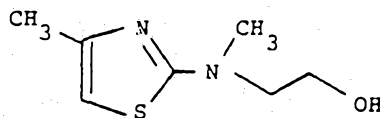
The title compound was prepared as an oil from
2-chloro-4-methyl-5-phenylthiazole (14.8g) and
2-methylaminoethanol (40ml) by an analogous procedure
to that described in Preparation 7.

^1H NMR δ (CDCl_3)

2.35 (3H, s); 3.1 (3H, s); 3.5-4.0 (4H, m);
5.1 (1H, broad s, exchanges with D_2O);
7.1-7.5 (5H, complex).

Preparation 12

2-[N-Methyl-N-(2-(4-methylthiazolyl))amino]ethanol



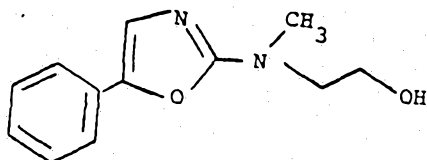
The title compound was prepared, by an analogous procedure to that described in Preparation 7, and was used in the next stage without further purification.

¹H NMR δ (CDCl₃)

2.25 (3H, s); 3.1 (3H, s); 3.55-3.95 (4H, m);
4.9 (1H, broad s, exchanges with D₂O); 6.1 (1H, s).

Preparation 13

2-[N-Methyl-N-[2-(5-phenyloxazolyl)]amino]ethanol



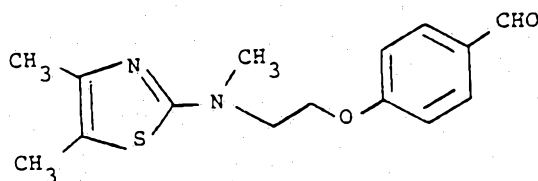
A solution of 2-chloro-5-phenyloxazole (8.3g) and 2-methylaminoethanol (30ml) was stirred at 50°C for 10 minutes. After cooling the oil was added to water (250ml) and extracted with ethyl acetate (2x150ml). The organic extracts were washed with brine (2x100ml), dried (MgSO₄), filtered and evaporated to dryness to leave the title compound (m.p. 73-75°C).

¹H NMR δ (CDCl₃)

3.2 (3H, s); 3.6 (2H, t); 3.85 (2H, t); 3.9 (1H, broad s, exchanges with D₂O); 7.0 (1H, s); 7.2-7.55 (5H, complex).

Preparation 14

4-[2-(N-Methyl-N-(2-(4,5-dimethylthiazolyl)amino)ethoxy)]benzaldehyde



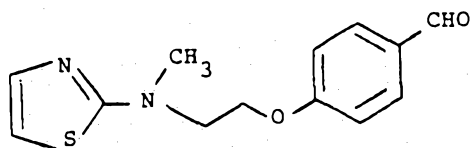
The title compound was prepared from 2-[N-methyl-N-(2-(4,5-dimethylthiazolyl)amino)ethanol (13.2g) and 4-fluorobenzaldehyde (23.1g) by an analogous procedure to that described in Preparation 5.

¹H NMR δ (CDCl₃)

2.15 (3H, s); 2.2 (3H, s); 3.18 (3H, s); 3.8 (2H, t);
4.3 (2H, t); 7.0 (2H, d); 7.8 (2H, d); 10.0 (1H, s).

Preparation 15

4-[2-(N-Methyl-N-(2-thiazolyl)amino)ethoxy]benzaldehyde



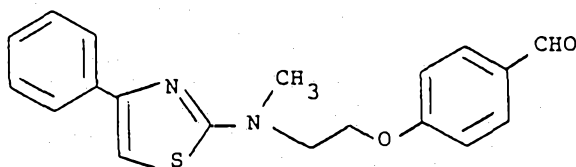
The title compound was prepared from 2-[N-methyl-N-(2-thiazolyl)amino]ethanol (10.7g) and 4-fluorobenzaldehyde (15.9g) by an analogous procedure to that described in Preparation 5.

¹H NMR δ (CDCl₃)

3.15 (3H, s); 3.9 (2H, t); 4.4 (2H, t); 6.5 (1H, d);
7.0 (2H, d); 7.15 (1H, d); 7.8 (2H, d); 9.9 (1H, s).

Preparation 16

4-[2-(N-Methyl-N-(2-(4-phenylthiazolyl)amino)ethoxy)]
benzaldehyde



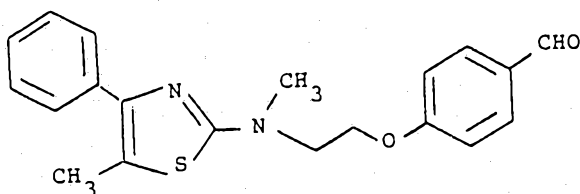
The title compound was prepared from 2-[N-methyl-N-(2-(4-phenylthiazolyl))amino]ethanol (16.1g) and 4-fluorobenzaldehyde (17.4g) by an analogous procedure to that described in Preparation 5.

¹H NMR δ (CDCl₃)

3.2 (3H, s); 3.95 (2H, t); 4.3 (2H, t); 6.7 (1H, s);
6.95-7.9 (9H, complex); 9.9 (1H, s).

Preparation 17

4-[2-(N-Methyl-N-(2-(4-phenyl-5-methylthiazolyl)amino)ethoxy)]benzaldehyde



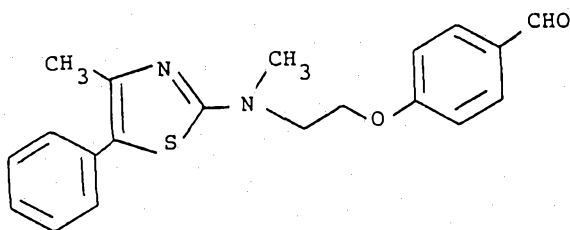
The title compound was prepared from 2-[N-methyl-N-(2-(4-phenyl-5-methylthiazolyl))amino]ethanol (13g) and 4-fluorobenzaldehyde (9.8g) by a similar procedure to that described in Preparation 5.

¹H NMR δ (CDCl₃)

2.35 (3H, s); 3.1 (3H, s); 3.8 (2H, t); 4.2 (2H, t);
6.85-7.8 (9H, complex); 9.85 (1H, s).

Preparation 18

4-[2-(N-Methyl-N-(2-(4-methyl-5-phenyl-thiazolyl)amino)ethoxy)]benzaldehyde



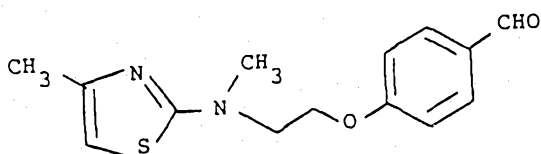
The title compound was prepared from 2-[N-methyl-N-(2-(4-methyl-5-phenylthiazolyl);amino]ethanol (13g) and 4-fluorobenzaldehyde (13g) by an analogous procedure to that described in Preparation 5.

¹H NMR δ (CDCl₃)

2.36 (3H, s); 3.2 (3H, s); 3.9 (2H, t); 4.35 (2H, t);
7.05 (2H, d); 7.2-7.5 (5H, complex); 7.85 (2H, d);
9.95 (1H, s).

Preparation 19

4-[2-(N-Methyl-N-(2-(4-methylthiazolyl))amino)ethoxy]
benzaldehyde



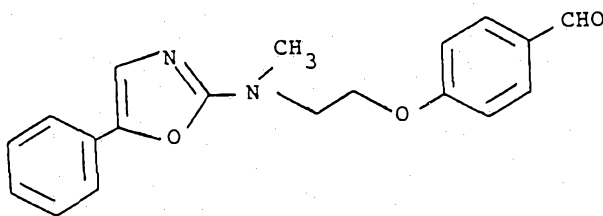
The title compound was prepared from 2-[N-methyl-N-(2-(4-methylthiazolyl))amino]ethanol (12g) and 4-fluorobenzaldehyde (14.3g) by an analogous procedure to that described in Preparation 5.

¹H NMR 4 (CDCl₃)

2.25 (3H, s); 3.2 (3H, s); 3.9 (2H, t); 4.3 (2H, t);
6.1 (1H, s); 7.05 (2H, d); 7.85 (2H, d); 9.95 (1H, s).

Preparation 20

4-[2-(N-Methyl-N-[2-(5-phenyloxazolyl)]amino)ethoxy]
benzaldehyde



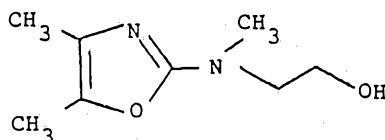
The title compound was prepared from
2-[N-methyl-N-(2-(5-phenyloxazolyl))amino]ethanol
(9.3g) and 4-fluorobenzaldehyde (7.9g) by an analogous
procedure to that described in Preparation 5.

¹H NMR δ (CDCl₃)

3.25 (3H, s); 3.85 (2H, t); 4.3 (2H, t); 6.95-7.6 (8H,
complex); 7.8 (2H, d); 9.9 (1H, s).

Preparation 21

2-[N-Methyl-N-[2-(4,5-dimethyloxazolyl)]amino]ethanol.



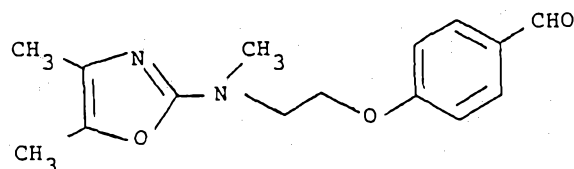
A solution of 2-chloro-4,5-dimethyloxazole (5g) and 2-methylaminoethanol (15ml) was stirred at 120°C for 40 minutes. After cooling the oil was added to water (200ml) and extracted with dichloromethane (3x200ml). The organic extracts were washed with brine (2x100ml), dried (MgSO₄), filtered and evaporated to dryness to leave the title compound as a waxy solid, which was used in Preparation 22 without further purification.

¹H NMR δ (CDCl₃)

1.95 (3H, s); 2.10 (3H, s); 3.05 (3H, s); 3.5 (2H, t);
3.8 (2H, t); 4.4 (1H, broad s, exchanges with D₂O).

Preparation 22

4-[2-(N-Methyl-N-[2-(4,5-dimethyloxazolyl)]amino)ethoxy]benzaldehyde



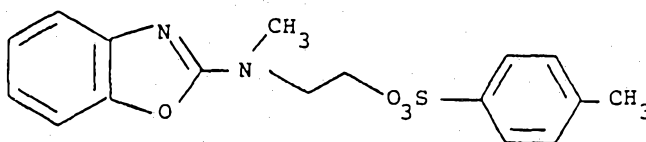
To a stirred solution of 2-[N-methyl-N-[2-(4,5-dimethyloxazolyl)amino]ethanol (2.7g) in DMF (60ml), under an atmosphere of nitrogen, was added portionwise sodium hydride (0.7g; 60% dispersion in oil). After the vigorous reaction had subsided, 4-fluorobenzaldehyde (2.9g) was added and the reaction mixture was heated to 80°C for 16 hours. After cooling, the mixture was added to water (400ml). The aqueous solution was extracted with diethyl ether (3x250ml). The organic extracts were washed with brine (2x100ml), dried (MgSO₄), filtered and evaporated to dryness. The title compound was obtained as an oil following chromatography of the residue on silica-gel in 1% methanol in dichloromethane.

¹H NMR δ (CDCl₃)

1.95 (3H, s); 2.15 (3H, s); 3.15 (3H, s); 3.8 (2H, t); 4.25 (2H, t); 7.0 (2H, d); 7.9 (2H, d); 10.0 (1H, s).

Preparation 23

2-(N-(2-Benzoxazolyl)-N-methylamino)ethanol 4-toluene-
sulphonyl ester



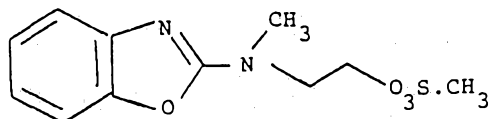
4-Toluenesulphonyl chloride (19.0g) was added portion-wise to a solution of N-(2-benzoxazolyl)-N-methylaminoethanol (19.2g) in dry pyridine (100 ml) at room temperature. The mixture was stirred at room temperature for 3 hours, added to water (500 ml) and extracted with dichloromethane (3x250 ml). The combined extracts were washed with 2M hydrochloric acid (3x250 ml), saturated sodium bicarbonate solution (250 ml) and brine (250 ml), dried (MgSO₄), filtered and evaporated. The title compound was obtained pure following crystallisation from ethanol (m.p. 119-121°C).

¹H NMR δ (DMSO-d₆)

2.25 (3H, s); 3.05 (3H, s); 3.75 (2H, t); 4.35 (2H, t);
7.0 - 7.4 (6H, complex); 7.70 (2H, d).

Preparation 24

2-(N-(2-Benzoxazolyl)-N-methylamino)ethanol methane-
sulphonyl ester



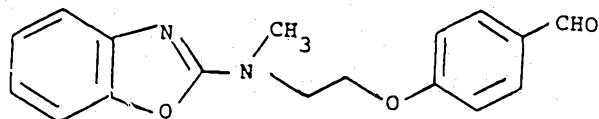
The title compound (m.p. 97-8°C) was prepared from N-(2-benzoxazolyl)-N-methylaminoethanol (19.2g) and methanesulphonyl chloride (11.5g) by a similar procedure to that used in Preparation 23.

¹H NMR δ (CDCl₃)

2.90 (3H, s); 3.25 (3H, s); 3.7 (2H, t);
4.5 (2H, t); 6.90 - 7.4 (4H, complex).

Preparation 25

4-[2-(N-Methyl-N-(2-benzoxazolyl)amino)ethoxy]-
benzaldehyde



To a solution of 4-hydroxybenzaldehyde (7.32g) in dry

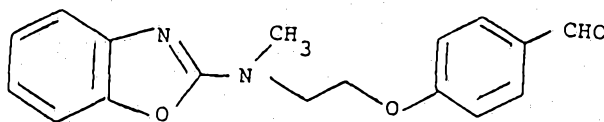
dimethylformamide (100ml) was added portionwise sodium hydride (60%, 2.4g) with stirring at room temperature under nitrogen. When gas evolution ceased a solution of 2-(N-methyl-N-(2-benzoxazolyl)amino)ethanol 4-toluenesulphonyl ester (17.3g) in dry dimethylformamide was added dropwise. The mixture was heated to 80°C and stirred at this temperature overnight. After cooling, the solution was poured into iced water (1 litre), extracted with ethyl acetate (3x500ml), and the combined extracts were washed with sodium hydroxide solution (2M; 500ml) and brine (500ml), dried (MgSO₄), filtered and evaporated. The title compound (m.p. 96-98°C) was obtained pure after crystallisation from ethanol.

¹H NMR δ (DMSO-d₆)

3.25 (3H, s); 3.95 (2H, t); 4.40 (2H, t);
6.90-7.40 (6H, complex); 7.85 (2H, d); 9.90 (1H, s).

Preparation 26

4-[2-(N-Methyl-N-(2-benzoxazolyl)amino)ethoxy]-
benzaldehyde

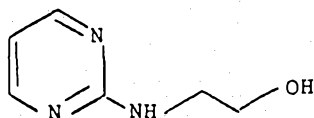


The title compound was prepared from 4-hydroxy

benzaldehyde (1.22g) and 2-(N-methyl-N-(2-benzoxazolyl)-amino)ethanol methanesulphonyl ester (2.7g) in a similar manner to that described in Preparation 25.

Preparation 27

2-(2-Pyrimidinylamino)ethanol



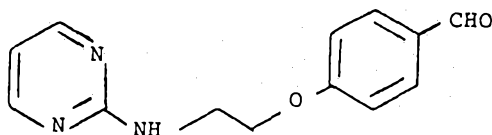
2-Chloropyrimidine (5g) and ethanolamine (15ml) were stirred for 2 hours at 140°C. After cooling, the mixture was added to water (200ml) and continuously extracted with ethyl acetate (500ml) for 16 hours. The organic extract was dried (MgSO₄), filtered and evaporated to dryness. The title compound was obtained as a solid (m.p. 66°C), following chromatography on silica-gel in 3% methanol in dichloromethane.

¹H NMR δ (CDCl₃)

3.55 (2H, complex); 3.8 (2H, t); 4.3 (1H, broad s, exchanges with D₂O); 6.1 (1H, broad s, exchanges with D₂O); 6.55 (1H, t); 8.3 (2H, d).

Preparation 28

4-[2-(2-Pyrimidinylamino)ethoxy]benzaldehyde



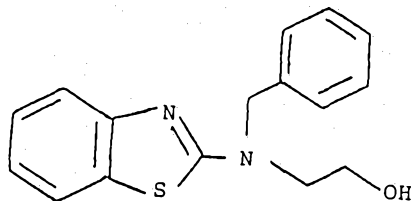
Sodium hydride (1.2g; 60% dispersion in oil) was added portionwise to a stirred solution of 2-(2-pyrimidinyl amino)ethanol (4g) in DMF (140ml) under an atmosphere of nitrogen. After the vigorous reaction had subsided 4-fluorobenzaldehyde (5.35g) was added and the solution heated to 80°C for 20 hours. After cooling the mixture was added to water (500ml) and extracted with diethyl ether (3x300ml). The organic extracts were washed with brine (2x200ml), dried (MgSO₄), filtered and evaporated to dryness. Chromatography of the residue on silica gel in 2% methanol in dichloromethane afforded the title compound, which was used in the next stage without further purification.

¹H NMR δ (CDCl₃)

3.8 (2H, complex); 4.2 (2H, t); 5.7 (1H, broad s, exchanges with D₂O); 6.5 (1H, t); 7.0 (2H, d); 7.8 (2H, d); 8.3 (2H, d); 9.9 (1H, s).

Preparation 29

2-(N-(2-Benzothiazolyl)-N-benzylamino)ethanol



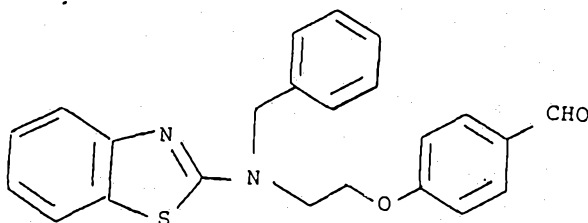
2-Chlorobenzothiazole (13g) and 2-(benzylamino)ethanol (29g) were heated together in a sealed vessel at 120°C for 20h.. After cooling, the reaction mixture was dissolved in ethyl acetate (200ml) and the solution was washed with saturated aqueous sodium hydrogen carbonate (3x100ml), water (3x100ml) and brine (100ml), dried over anhydrous magnesium sulphate and evaporated to give the title compound (m.p. 95-96°C; dichloromethane/hexane).

¹H NMR δ (CDCl₃)

3.8 (4H, m); 4.5 (1H, broad s, exchanges with D₂O); 4.7 (2H, s); 6.9-7.7 (9H, complex).

Preparation 30

4-(2-(N-(2-Benzothiazolyl)-N-benzylamino)ethoxy)-benzaldehyde



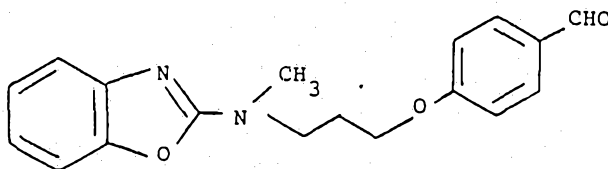
The title compound was prepared from 2-(N-(2-benzothiazolyl)-N-benzylamino)ethanol (8.25g) and 4-fluorobenzaldehyde (3.6g) by an analogous procedure to that described in Preparation 22.

^1H NMR δ (CDCl_3)

4.0 (2h, t); 4.4 (2H, t); 4.9 (2H, s); 6.9-8.0 (13H, complex); 10.0 (1H, s).

Preparation 31

4-[3-(N-Methyl-N-(2-benzoxazolyl)-amino)propoxy]benzaldehyde



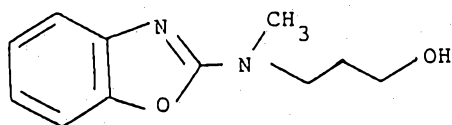
The title compound was prepared from 3-[(N-(2-benzoxazolyl)-N-methyl)amino]propan-1-ol (7.5g) and 4-fluorobenzaldehyde (6.78g) by a similar procedure to that described in Preparation 22.

¹H NMR δ (CDCl₃)

2.0-2.4 (2H, complex); 3.2 (3H, s); 3.75 (2H, t); 4.2 (2H, t); 6.8-7.5 (6H, complex); 7.8 (2H, d); 9.9 (1H, s).

Preparation 32

3-[(N-(2-Benzoxazolyl)-N-methyl)amino]propan-1-ol



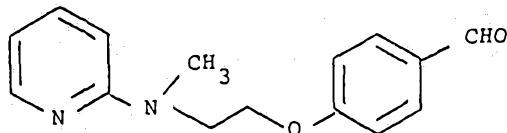
2-Chlorobenzoxazole (15.36g) in dry tetrahydrofuran (50ml) was added dropwise to a mixture of 3-N-methylaminopropan-1-ol (9.8g) and triethylamine (20.2g) in dry tetrahydrofuran (130ml) with stirring, at room temperature. After stirring at room temperature overnight the solvent was evaporated. The residue was dissolved in dichloromethane (150ml), washed with water (3x100ml), brine (150ml), dried (MgSO₄), filtered and evaporated. The title compound was obtained as an oil following chromatography on silica-gel in 2.5-3% methanol in dichloromethane.

¹H NMR δ (CDCl₃)

1.8-2.1 (2H, complex); 3.2 (3H, s); 3.5-3.85 (4H, complex); 4.3 (1H, broad s, exchanges with D₂O); 6.8-7.5 (4H, complex).

Preparation 33

4-[2-(N-Methyl-N-(2-pyridyl)amino)ethoxy]benzaldehyde



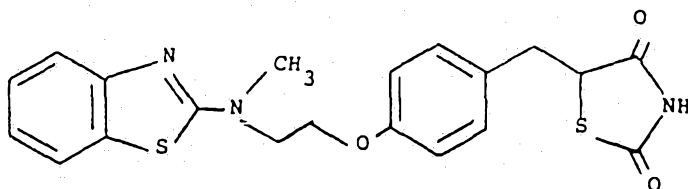
The title compound was prepared from 2-(N-methyl-N-(2-pyridyl)amino)ethanol (8.9g) and 4-fluorobenzaldehyde by a similar procedure to that described in Preparation 22.

^1H NMR δ (CDCl_3)

3.2 (3H, s); 3.8 (2H, t); 4.2 (2H, t); 6.4 (2H, t); 6.9 (2H, d); 7.3 (1H, complex); 7.75 (2H, d); 8.15 (1H, d); 9.9 (1H, s).

Example 1

5-(4-[2-(N-Methyl-N-(2-benzothiazolyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione.



5-(4-[2-(N-Methyl-N-(2-benzothiazolyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione (2g) in dry

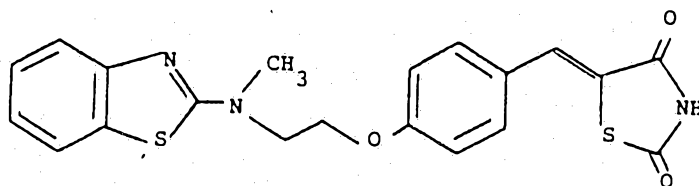
1,4-dioxan (70ml) was reduced under hydrogen in the presence of 10% palladium on charcoal (3g) at ambient temperature and atmospheric pressure until hydrogen uptake ceased. The solution was filtered through diatomaceous earth, the filter pad was washed exhaustively with dioxan and the combined filtrates were evaporated to dryness under vacuum. The title compound (m.p. 167-8°C) was obtained after crystallisation from methanol.

¹H NMR δ (DMSO-d₆)

2.9-3.4 (2H, complex); 3.25 (3H, s); 3.9 (2H, complex); 4.25 (2H, complex); 4.8 (1H, complex); 6.8-7.75 (8H, complex); 12.0 (1H, s, exchanges with D₂O).

Example 2

5-(4-[2-(N-Methyl-N-(2-benzothiazolyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione.



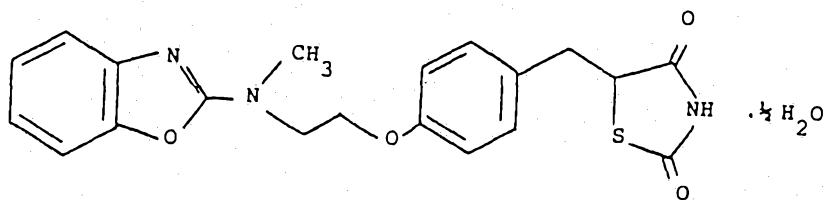
A solution of 4-[2-(N-methyl-N-(2-benzothiazolyl)amino)ethoxy]benzaldehyde (1.9g) and 2,4-thiazolidinedione (0.8g) in toluene (100ml) containing a catalytic quantity of piperidinium acetate was boiled under reflux in a Dean and Stark apparatus for 2 hours. The mixture was cooled and filtered and the filtered solid was dried to give the title compound (mp 219°C).

¹H NMR δ (DMSO - d₆)

3.2 (3H, s); 3.9 (2H, t); 4.35 (2H, t);
6.8 - 7.7 (10H, complex).

Example 3

5-(4-[2-(N-Methyl-N-(2-benzoxazolyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione hemihydrate



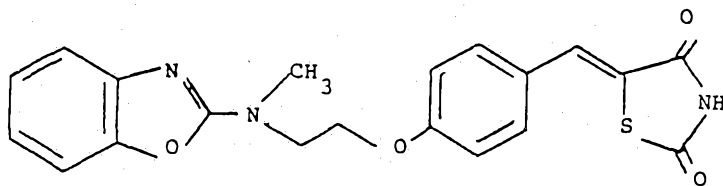
5-(4-[2-(N-Methyl-N-(2-benzoxazolyl)amino)ethoxy]-benzylidene)-2,4-thiazolidinedione (1.5g) in dry 1,4-dioxan (80 ml) was reduced under hydrogen in the presence of 10% palladium on charcoal (2g) at ambient temperature and atmospheric pressure until hydrogen uptake ceased. The solution was filtered through diatomaceous earth, the filter pad was washed exhaustively with dioxan and the combined filtrates were evaporated to dryness under vacuum. The title compound (mp 147 - 9°C) was obtained after crystallisation from methanol.

¹H NMR δ (DMSO-d₆+D₂O)

3.1-3.5 (2H, complex); 3.3 (3H,s); 3.95 (2H, complex);
4.25 (2H, complex); 4.5 (1H, complex); 6.8-7.3 (8H,
complex).

Example 4

5-(4-[2-(N-Methyl-N-(2-benzoxazolyl)amino)ethoxy]
benzylidene)-2,4-thiazolidinedione



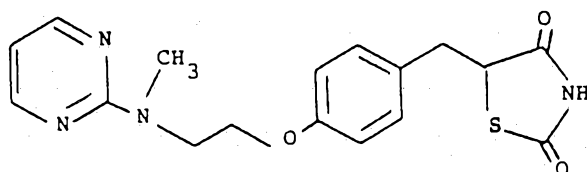
A solution of 4-[2-(N-methyl-N-(2-benzoxazolyl)amino)ethoxy]benzaldehyde (1.6g) and 2,4-thiazolidinedione (0.63g) in toluene (100ml) containing a catalytic quantity of piperidinium acetate was boiled under reflux in a Dean and Stark apparatus for 2 hours. The mixture was cooled and filtered to give the title compound (mp 227 - 9°C).

¹H NMR δ (DMSO-d₆)

3.20 (3H, s); 3.90 (2H, t); 4.30 (2H, t); 6.9 - 7.75
(10H, complex).

Example 5

5-(4-[2-(N-Methyl-N-(2-pyrimidinyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione



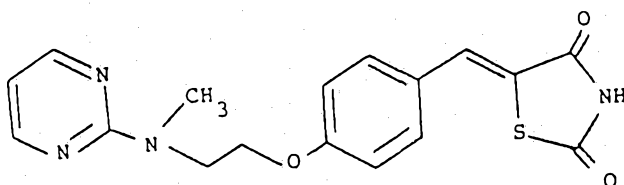
5-(4-[2-(N-Methyl-N-(2-pyrimidinyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione (2.4g) in dry 1,4-dioxan (150ml) was reduced under hydrogen in the presence of 10% palladium on charcoal (3g) until hydrogen uptake ceased. The solution was filtered through diatomaceous earth, the filter pad was washed exhaustively with dioxan and the combined filtrates were evaporated to dryness under vacuum. The title compound (mp 150-51°C) was obtained after crystallisation from methanol.

¹H NMR δ (DMSO-d₆)

2.9-3.4 (2H, complex); 3.2 (3H, s); 3.9 (2H, complex); 4.2 (2H, complex); 4.9 (1H, complex); 6.6 (1H, t); 6.9 (2H, d); 7.2 (2H, d); 8.4 (2H, d); 12.0 (1H, broad s, exchanges with D₂O).

Example 6

5-(4-[2-(N-Methyl-N-(2-pyrimidinyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione



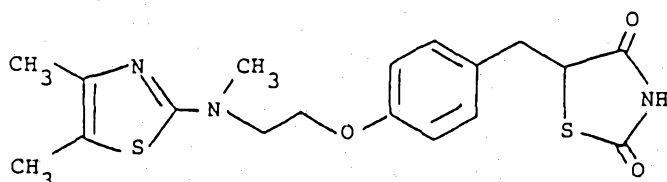
A solution of 4-[2-(N-methyl-N-(2-pyrimidinyl)amino)ethoxy]benzaldehyde (1.7g) and 2,4-thiazolidinedione (0.7g) in toluene (100ml) containing a catalytic quantity of piperidinium acetate was boiled under reflux in a Dean and Stark apparatus for 2 hours. The mixture was cooled and filtered to give the title compound (mp 189 - 90°C).

¹H NMR δ (DMSO-d₆ + D₂O)

3.2 (3H, s); 3.7-4.4 (4H, complex); 6.6 (1H, t); 7.1 (2H, d), 7.5 (2H, d); 7.7 (1H, s); 8.4 (2H, d).

Example 7

5-(4-(2-(N-Methyl-N-[2-(4,5-dimethylthiazolyl)]amino)ethoxy]benzyl)-2,4-thiazolidinedione



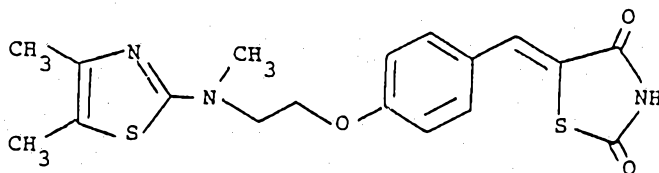
5-(4-[2-(N-Methyl-N-[2-(4,5-dimethylthiazolyl)]amino)ethoxy]benzylidene-2,4-thiazolidinedione (1.6g) was dissolved in a mixture of methanol (50ml) and dioxan (50ml). Magnesium turnings (1.5g) were added and the solution stirred until no more effervescence was observed. The mixture was added to water (300ml), acidified (2M HCl) to form a solution, neutralised (saturated NaHCO₃ solution), filtered and dried. The solid was dissolved in dioxan (100ml), adsorbed onto silica (20g) and the title compound (m.p. 177°C; MeOH) obtained following chromatography on silica-gel in 5% dioxan in dichloromethane.

¹H NMR δ (DMSO-d₆)

2.05 (3H, s); 2.15 (3H, s); 3.0 (3H, s); 3.0-3.4 (2H, complex); 3.8 (2H, t); 4.2 (2H, t); 4.85 (1H, complex); 6.9 (2H, d); 7.1 (2H, d); 12.0 (1H, broad s exchanges with D₂O).

Example 8

5-(4-[2-(N-Methyl-N-[2-(4,5-dimethylthiazolyl)]amino)ethoxy]benzylidene)-2,4-thiazolidinedione



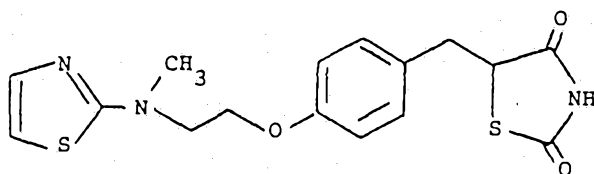
The title compound (m.p. 175°C) was prepared by a similar procedure to that described in Example 4.

¹H NMR δ (DMSO-d₆)

2.0 (3H, s); 2.1 (3H, s); 3.0 (3H, s); 3.7 (2H, t);
4.25 (2H, t); 7.1 (2H, d); 7.55 (2H, d); 7.75 (1H, s);
12.0 (1H, broad s, exchanges with D₂O).

Example 9

5-(4-[2-(N-Methyl-N-(2-thiazolyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione



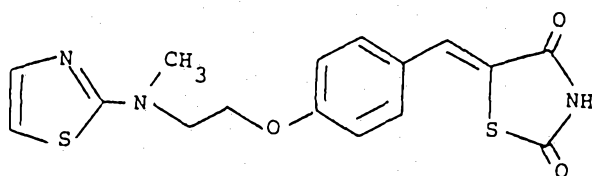
The title compound (m.p. 186°C; MeOH) was prepared by an analogous procedure to that described in Example 7.

¹H NMR δ (DMSO-d₆)

3.0-3.4 (2H, complex) 3.1 (3H, s); 3.8 (2H, t);
4.2 (2H, t); 4.85 (1H, complex); 6.7-7.3 (6H, complex);
12.0 (1H, broad s, exchanges with D₂O).

Example 10

5-(4-[2-(N-Methyl-N-(2-thiazolyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione



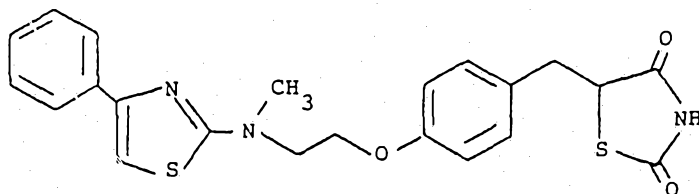
The title compound (m.p. 212°C) was prepared by a similar procedure to that described in Example 4.

¹H NMR δ (DMSO-d₆)

3.1 (3H, s); 3.85 (2H, t); 4.3 (2H, t); 6.75 (1H, s);
7.1-7.3 (3H, complex); 7.6 (2H, d); 7.75 (1H, s);
12.0 (1H, broad s, exchanges with D₂O).

Example 11

5-[4-(2-(N-Methyl-N-(2-(4-phenylthiazolyl))amino)ethoxy)benzyl]-2,4-thiazolidinedione



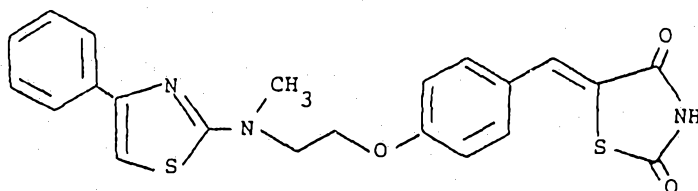
The title compound was obtained as a foam (m.p. 62-65°C) from 5-[4-(2-(N-methyl-N-(2-(4-phenylthiazolyl))amino)ethoxy)benzylidene]-2,4-thiazolidinedione (1.7g) by a similar procedure to that described in Example 7.

¹H NMR δ (DMSO-d₆)

3.15 (3H, s); 3.0-3.4 (2H, complex); 3.9 (2H, t); 4.25 (2H, t); 4.85 (1H complex); 6.9 (2H, d); 7.1-7.45 (6H, complex); 7.85 (2H, d); 12.0 (1H, broad s, exchanges with D₂O).

Example 12

5-(4-[2-(N-Methyl-N-(2-(4-phenylthiazolyl))amino)ethoxy]benzylidene)-2,4-thiazolidinedione



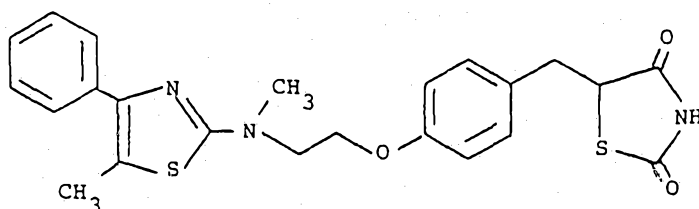
The title compound (m.p. 134°C) was prepared from 4-[2-(N-methyl-N-(2-(4-phenylthiazolyl))amino)ethoxy]benzaldehyde by a similar procedure to that described in Example 4.

¹H NMR δ (DMSO-d₆)

3.2 (3H, s); 3.9 (2H, t); 4.35 (2H, t); 7.1-7.95 (11H, complex); 12.0 (1H broad s, exchanges with D₂O).

Example 13

5--(4-[2-(N-Methyl-N-[2-(4-phenyl-5-methylthiazolyl)]
amino)ethoxy]benzyl)-2,4-thiazolidinedione



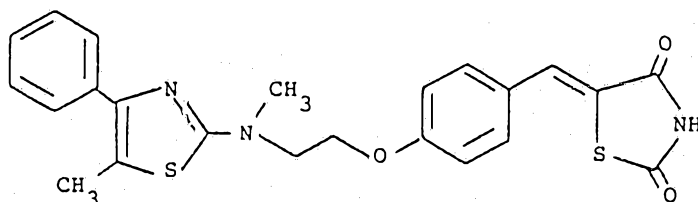
The title compound, obtained as a foam
(m.p. 60-62°C), was prepared by an analogous procedure
to that described in Example 7.

¹H NMR δ (DMSO-d₆)

2.35 (3H, s); 3.1 (3H, s); 3.0-3.4 (2H, complex);
3.8 (2H, t); 4.2 (2H, t); 4.85 (1H, complex);
6.9 (2H, d); 7.2 (2H, d); 7.25-7.5 (3H, complex);
7.65 (2H, d); 12.0 (1H, broad s, exchanges with D₂O).

Example 14

5-(4-[2-(N-Methyl-N-[2-(4-phenyl-5-methylthiazolyl)]
amino)ethoxy]benzylidene)-2,4-thiazolidinedione



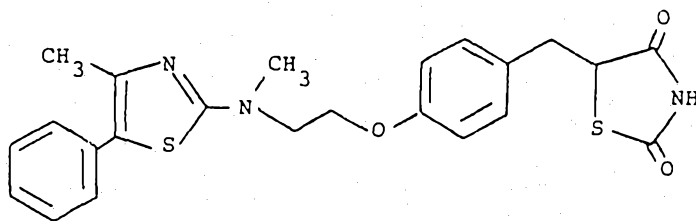
The title compound was prepared from 4-[2-(N-methyl-N-[2-(4-phenyl-5-methylthiazolyl)]amino)ethoxy] benzaldehyde by a similar procedure to that described in Example 4, and was used in Example 13 without further purification.

¹H NMR δ (DMSO-d₆)

2.4 (3H, s); 3.1 (3H, s); 3.8 (2H, t); 4.35 (2H, t);
 7.1-7.75 (10H, complex); 12.0 (1H, broad s, exchanges
 with D₂O).

Example 15

5-(4-[2-(N-Methyl-N-[2-(4-methyl-5-phenylthiazolyl)]-amino)ethoxy]benzyl)-2,4-thiazolidinedione



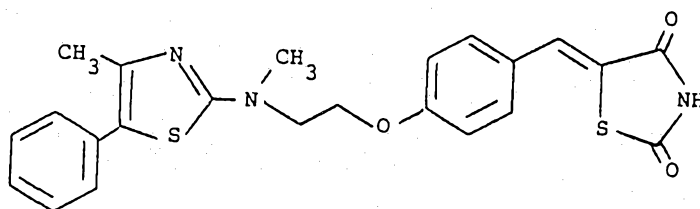
The title compound (m.p. 174°C; MeOH) was prepared from 5-(4-[2-(N-methyl-N-[2-(4-methyl-5-phenylthiazolyl)]-amino)ethoxy]benzylidene)-2,4-thiazolidinedione by an analogous procedure to that described in Example 7.

¹H NMR δ (DMSO-d₆)

2.3 (3H, s); 3.0-3.4 (2H, complex); 3.15 (3H, s);
3.85 (2H, t); 4.25 (2H, t); 4.85 (1H, complex);
6.95 (2H, d); 7.2 (2H, d); 7.45 (5H, complex);
12.0 (1H, broad s, exchanges with D₂O).

Example 16

5-(4-[2-(N-Methyl-N-[2-(4-methyl-5-phenylthiazolyl)]
amino)ethoxy]benzylidene)-2,4-thiazolidinedione



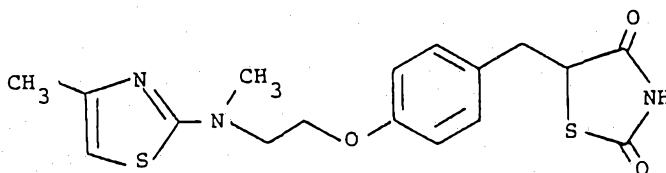
The title compound was prepared from
4-[2-(N-methyl-N-[2-(4-methyl-5-phenylthiazolyl)]
amino)ethoxy]benzaldehyde by a similar procedure to
that described in Example 4, and was used in Example 15
without further purification.

¹H NMR δ (DMSO- d_6)

2.3 (3H, s); 3.1 (3H, s); 3.85 (2H, t); 4.35 (2H, t);
7.15-7.75 (10H, complex); 12.0 (1H, broad s, exchanges
with D₂O).

Example 17

5-(4-[2-(N-Methyl-N-[2-(4-methylthiazolyl)]amino)ethoxy]benzyl)-2,4-thiazolidinedione



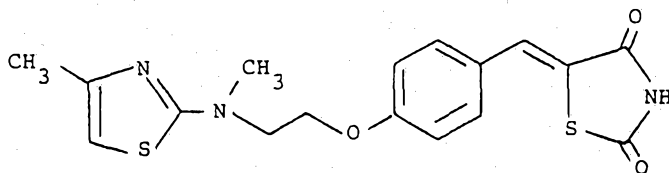
The title compound, was prepared from 5-(4-[2-(N-methyl-N-[2-(4-methylthiazolyl)]amino)ethoxy]benzylidene)-2,4-thiazolidinedione as a foam (m.p. 121°C), by a similar procedure to that described in Example 7.

¹H NMR δ (DMSO-d₆)

2.1 (3H, s); 3.0-3.4 (2H, complex); 3.1 (3H, s);
3.75 (2H, t); 4.15 (2H, t); 4.85 (1H, complex);
6.3 (1H, s); 6.9 (2H, d); 7.2 (2H, d);
12.0 (1H, broad s, exchanges with D₂O).

Example 18

5-(4-[2-(N-Methyl-N-[2-(4-methylthiazolyl)]amino)ethoxy]benzylidene)-2,4-thiazolidinedione



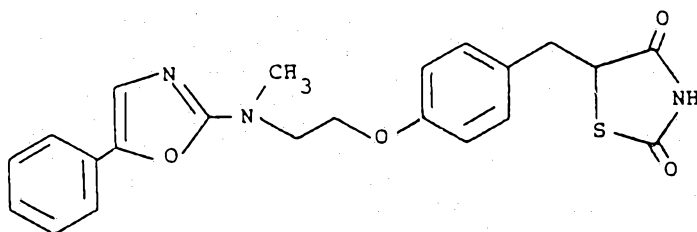
The title compound was prepared from 5-(4-[2-(N-methyl-N-[2-(4-methylthiazolyl)]amino)ethoxy]benzaldehyde by a similar procedure to that described in Example 4, and was used in the Example 17 without further purification.

¹H NMR δ (DMSO- d_6)

2.1 (3H, s); 3.1 (3H, s); 3.85 (2H, d); 4.3 (2H, d); 6.3 (1H, s); 7.15 (2H, d); 7.6 (2H, d); 7.75 (1H, s); 12.0 (1H, broad s, exchanges with D₂O).

Example 19

5-[4-(2-(N-Methyl-N-[2-(5-phenyloxazolyl)]amino)ethoxy)benzyl]-2,4-thiazolidinedione



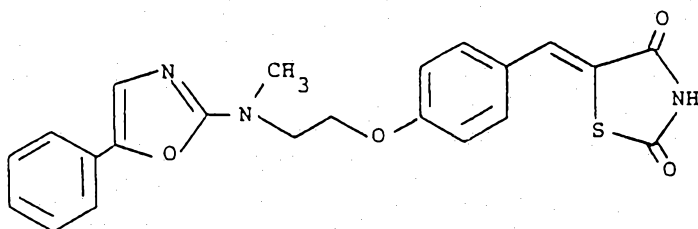
The title compound (m.p. 200°C, MeOH) was prepared from 5-[4-(2-(N-methyl-N-[2-(5-phenyloxazolyl)]amino)ethoxy)benzylidene]-2,4-thiazolidinedione by a similar procedure to that described in Example 7.

¹H NMR δ (DMSO-d₆)

3.0-3.4 (2H, complex); 3.15 (3H, s); 3.8 (2H, t);
4.2 (2H, t); 4.85 (1H, complex); 6.9 (2H, d);
7.1-7.4 (6H, complex); 7.5 (2H, d);
12.0 (1H, broad s, exchanges with D₂O).

Example 20

5-(4-[2-(N-Methyl-N-[2-(5-phenyloxazolyl)]amino)ethoxy]benzylidene)-2,4-thiazolidinedione



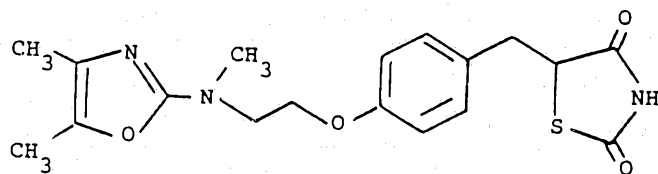
The title compound (m.p. 191°C) was prepared from 4-[2-(N-methyl-N-[2-(5-phenyloxazolyl)]amino)ethoxy]benzaldehyde by an analogous procedure to that described in Example 4.

¹H NMR δ (DMSO-d₆)

3.2 (3H, s); 3.8 (2H, t); 4.35 (2H, t); 7.1-7.7 (10H, complex); 7.8 (1H, s); 12.0 (1H, broad s, exchanges with D₂O).

Example 21

5-(4-[2-(N-Methyl-N-[2-(4,5-dimethyloxazolyl)]amino)ethoxy]benzyl)-2,4-thiazolidinedione



5-(4-[2-(N-Methyl-N-[2-(4,5-dimethyloxazolyl)]amino)-

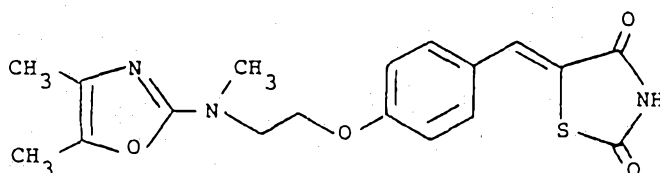
ethoxy]benzylidene)-2,4-thiazolidinedione (1.2g) in dry 1,4-dioxan (100ml) was reduced under hydrogen in the presence of 10% Palladium on charcoal (2.5g) until hydrogen uptake ceased. The solution was filtered through diatomaceous earth, the filter pad was washed exhaustively with dioxan and the combined filtrates evaporated to dryness under vacuum. The title compound was obtained as a foam (m.p. 53-54°C) following chromatography on silica-gel in 1% methanol in dichloromethane.

¹H NMR δ (DMSO-d₆)

1.85 (3H, s); 2.05 (3H, s); 3.0 (3H, s);
3.0-3.4 (2H, complex); 3.65 (2H, t); 4.1 (2H, t);
4.85 (1H, complex); 6.85 (2H, d); 7.15 (2H, d);
12.0 (1H, broad s, exchanges with D₂O).

Example 22

5-(4-[2-(N-Methyl-N-[2-(4,5-dimethyloxazolyl)]amino)-ethoxy]benzylidene)-2,4-thiazolidinedione



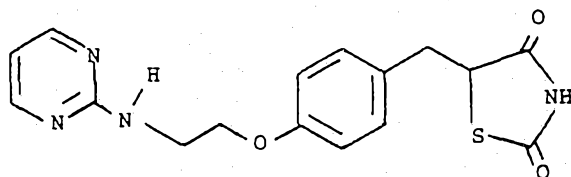
The title compound (softens at 149°C) was prepared by a similar procedure to that described in Example 4.

¹H NMR δ (DMSO-d₆)

1.85 (3H, s); 2.05 (3H, s); 3.0 (3H, s); 3.7 (2H, t);
4.25 (2H, t); 7.1 (2H, d); 7.5 (2H, d); 7.75 (1H, s);
12.0 (1H, broad s, exchanges with D₂O).

EXAMPLE 23

5-[4-(2-(2-Pyrimidinylamino)ethoxy)benzyl]-2,4-
thiazolidinedione



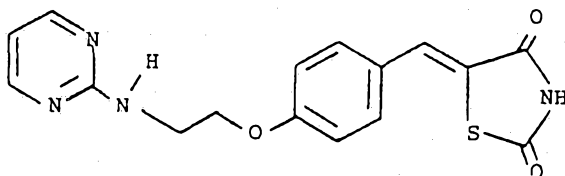
A mixture of 5-[4-(2-(2-pyrimidinylamino)ethoxy)benzylidene]-2,4-thiazolidinedione (3g) and 10% palladium on charcoal (9g) in DMF (70ml) was stirred under a pressure of 200 psi of hydrogen until hydrogen uptake ceased. The mixture was filtered through diatomaceous earth, and the filter pad washed exhaustively with DMF. The combined filtrates were evaporated to dryness and the title compound (m.p. 173°C) obtained following recrystallization from methanol.

¹H NMR δ (DMSO-d₆)

3.0 -3.4 (2H, complex); 3.65 (2H, complex); 4.1 (2H, t); 4.85 (1H, complex); 6.6 (1H, t); 6.85 (2H, d); 7.15 (2H, d); 7.25 (1H, t, exchanges with D₂O); 8.3 (2H, d); 12.0 (1H, broad s, exchanges with D₂O).

EXAMPLE 24

5-[4-(2-(2-Pyrimidinylamino)ethoxy)benzylidene]-2,4-thiazolidinedione



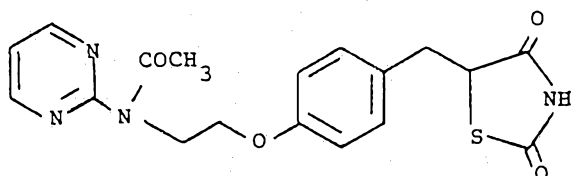
The title compound (m.p. 234°C) was obtained from 4-[2-(2-pyrimidinylamino)ethoxy]benzaldehyde and 2,4-thiazolidindione, by an analogous procedure to that described in Example 6.

¹H NMR δ (DMSO-d₆)

3.65 (2H, complex); 4.2 (2H, t); 6.6 (1H, t); 7.0-7.6 (5H, complex, one proton changes with D₂O); 7.7 (1H, s); 8.3 (2H, d); 12.0 (1H, broad s, exchanges with D₂O).

EXAMPLE 25

5-(4-[2-(N-Acetyl-N-(2-pyrimidinyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione



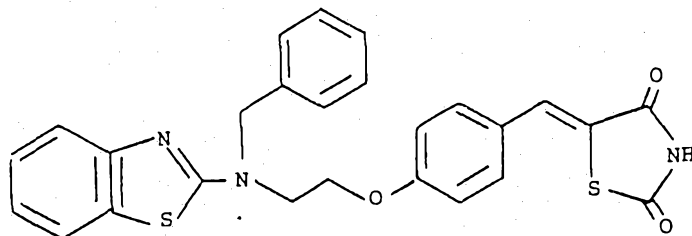
A stirred solution of 5-[4-(2-(2-pyrimidinylamino)ethoxy)benzyl]-2,4-thiazolidinedione (800mg) in acetic anhydride (15ml) and 1,4-dioxan (5ml) was boiled under reflux for 3 hours. After cooling, the mixture was added to water (300ml), neutralized (sodium bicarbonate) and extracted with dichloromethane (3x200ml). The organic extracts were washed with brine (100ml), dried (MgSO₄), filtered and evaporated to dryness. Chromatography on silica-gel in dichloromethane of the residual oil afforded the title compound (m.p. 137°C).

¹H NMR δ (DMSO-d₆)

2.3 (3H, s); 2.93.4 (2H, complex); 4.15 (2H, t);
4.35 (2H, t); 4.85 (1H, complex); 6.7 (2H, d);
7.1 (2H, d); 7.35 (1H, t); 8.8 (2H, d);
12.0 (1H, broad s, exchanges with D₂O).

EXAMPLE 26

5-(4-(2-(N-(2-Benzothiazolyl)-N-benzylamino)ethoxy)benzylidene)-2,4-thiazolidinedione



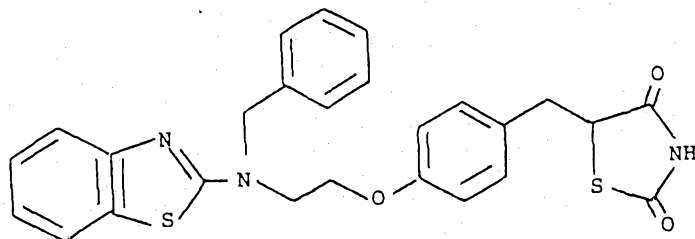
4-(2-(N-(2-Benzothiazolyl)-N-benzylamino)ethoxy)benzaldehyde (3g) and 2,4-thiazolidinedione (1g) were dissolved in toluene (200ml) containing piperidine (0.2ml) and benzoic acid (0.2g) and heated to reflux for 4h. in a Dean and Stark apparatus. On cooling, the solution was concentrated under vacuum to 50% of its volume and the title compound, which crystallised, was collected by filtration and dried in vacuo (m.p. 185-188°C). It was used in Example 27 without further purification.

¹H NMR δ (DMSO-d₆)

4.0 (2H, t); 4.4 (2H, t); 4.9 (2H, s); 7.1-7.9 (14H, complex); 12-13 (1H, broad s, exchanges with D₂O).

EXAMPLE 27

5-(4-(2-(N-(2-Benzothiazolyl)-N-benzylamino)ethoxy)benzylidene)-2,4-thiazolidinedione



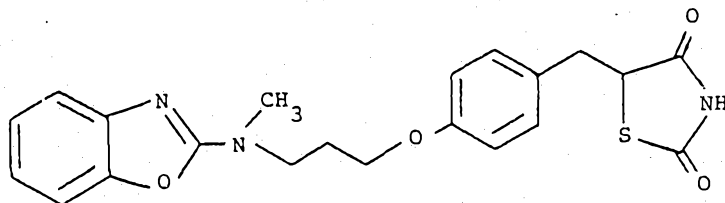
5-(4-(2-(N-(2-Benzothiazolyl)-N-benzylamino)ethoxy)benzylidene)-2,4-thiazolidinedione (2.4g) in dioxan (150ml) was hydrogenated in the presence of 10% palladium-charcoal (4.8g) for 3h. at room temperature and atmospheric pressure. A further portion of catalyst (2.4g) was added and the hydrogenation continued for a total of 20h. The mixture was filtered through diatomaceous earth and the solvent was evaporated. The residue was chromatographed on silica gel with 3% methanol-dichloromethane as eluant to afford the title compound as a foam, which collapsed at 78°C.

¹H NMR δ (CDCl₃)

3.1 (1H, dd); 3.4 (1H, dd); 4.0 (2H, t); 4.25 (2H, t); 4.5 (1H, dd); 4.9 (2H, s); 6.8-7.6 (13H, m); 8.3 (1H, broad s, exchanges with D₂O).

EXAMPLE 28

5-(4-[3-(N-Methyl-N-(2-benzoxazolyl)amino)propoxy]benzyl)-2,4-thiazolidinedione



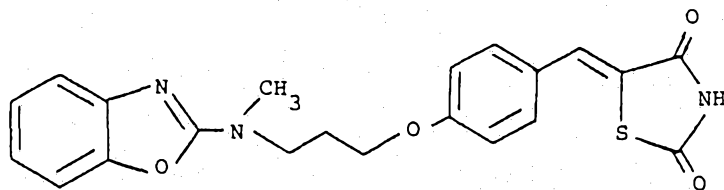
The title compound (m.p. 171-3°C; ethanol) was prepared from 5-(4-[3-(N-methyl-N-(2-benzoxazolyl)amino)-propoxy]benzylidene)-2,4-thiazolidinedione by a similar procedure to that described in Example 1.

¹H NMR δ (DMSO - d₆)

2.0-2.35 (2H, complex); 2.9-3.6 (2H, complex); 3.2 (3H, s); 3.7 (2H, t); 4.2 (2H, t); 4.9 (1H, complex); 6.8-7.4 (8H, complex); 12-12.5 (1H, broad s, exchanges with D₂O).

EXAMPLE 29

5-(4-[3-(N-Methyl-N-(2-benzoxazolyl)amino)propoxy]benzylidene)-2,4-thiazolidinedione



The title compound (m.p. 202-204°C) was prepared from

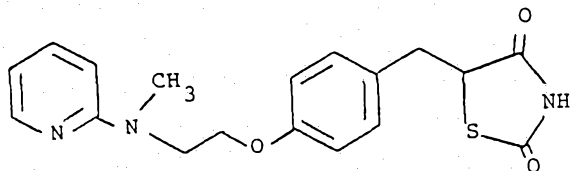
4-[3-(N-methyl-N-(2-benzoxazolyl)amino)propoxy]benzaldehyde (5.3g) and 2,4-thiazolidinedione (2.2g) by a similar procedure to that described in Example 4.

¹H NMR δ (DMSO - d₆)

2.0-2.35 (2H, complex); 3.15 (3H, s); 3.7 (2H, t); 4.2 (2H, t); 7.0-7.7 (8H, complex); 7.8 (1H, s); 12.0 (1H, broad s, exchanges with D₂O).

EXAMPLE 30

5-(4-[2-(N-Methyl-N-(2-pyridyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione



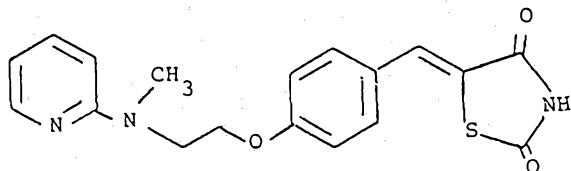
The title compound (m.p. 153-5°C; MeOH) was obtained from 5-(4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione by a similar procedure to that described in Example 1.

¹H NMR δ (DMSO - d₆)

2.9-3.4 (2H, complex); 3.1 (3H, s); 3.9 (2H, t); 4.15 (2H, t); 4.8 (1H, complex); 6.5-6.85 (2H, complex); 6.8 (2H, d); 7.2 (2H, d); 7.5 (1H, complex); 8.1 (1H, d); 12.05 (1H, broad s, exchanges with D₂O).

EXAMPLE 31

5-(4-[2-(N-Methyl-N-(2-pyridyl)amino)ethoxy]benzyl-
idene)-2,4-thiazolidinedione



The title compound (m.p. 177-9°C) was obtained from 4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzaldehyde (3.2g) and 2,4-thiazolidinedione (1.1g) by a similar procedure to that described in Example 4.

¹H NMR δ (DMSO-D₂O)

3.1 (3H, s); 3.9 (2H, t); 4.2 (2H, t); 6.4-7.5 (7H, complex); 7.7 (1H, s); 8.1 (1H, d)

DEMONSTRATION OF EFFICACY OF COMPOUNDS

Obese Mice, Oral Glucose Tolerance Test.

C57bl/6 obese (ob/ob) mice were fed on powdered oxoid diet. After at least one week, the mice continued on a powdered oxoid diet or were fed powdered oxoid diet containing the test compound. After 6 days on the supplemented diet all of the mice were fasted for 5 hours prior to receiving an oral load of glucose (3 g/kg). Blood samples for glucose analysis were taken 0, 45, 90 and 135 minutes after glucose administration and the results appear below as the percentage reduction in area under the blood glucose curve where test compound treated groups are compared with the control groups. 7 mice were used for each treatment.

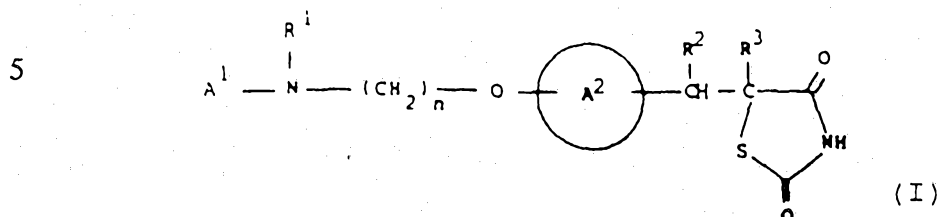
EXAMPLE NO:	LEVEL IN DIET ($\mu\text{mol kg}^{-1}$ of DIET)	%REDUCTION IN AREA UNDER BLOOD GLUCOSE CURVE
1	100	51
2	300	30
3	10	39
4	300	30
5	100	40
7	50	47
9	100	58
11	100	34
13	100	37
15	100	39
17	100	34
19	30	22
21	30	33
24	30	15
25	30	19
27	300	56
29	300	32

Toxicology

No toxicological effects were indicated for any of the compounds of the invention in any of the abovementioned tests.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of formula (I):



10 or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, characterised in that:

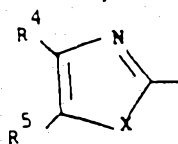
15 A¹ represents an optionally substituted single or fused ring aromatic heterocyclyl group comprising up to 4 heteroatoms in each ring selected from oxygen, sulphur or nitrogen, in which the optional substituents are selected from the group consisting of C₁-₁₂ alkyl, C₁-₁₂ alkoxy, phenyl, naphthyl, halogen or any two substituents on adjacent carbon atoms, together with the carbon atoms to which they are attached, form a benzene ring; and wherein the carbon atoms or benzene ring represented by the two said substituents may themselves be optionally substituted with up to three groups selected from halogen, C₁-₁₂ alkyl, phenyl, C₁-₁₂ alkoxy, halo C₁-₁₂ alkyl, hydroxy, amino, nitro, carboxy, C₁-₁₂ alkoxy carbonyl, C₁-₁₂ alkoxy carbonyl-C₁-₁₂-alkyl, C₁-₁₂ alkyl carbonyloxy or C₁-₁₂ alkyl carbonyl;

30 R¹ represents a hydrogen atom, a C₁-₁₂ alkyl group, an acyl group, a phenyl C₁-₁₂ alkyl, naphthyl C₁-₁₂ alkyl, phenyl or naphthyl group, wherein the phenyl or naphthyl moiety may be optionally substituted with up to five groups selected from halogen, C₁-₁₂ alkyl, phenyl, C₁-₁₂ alkoxy, halo C₁-₁₂ alkyl, hydroxy, amino, nitro, carboxy, C₁-₁₂ alkoxy carbonyl, C₁-₁₂ alkoxy carbonyl-C₁-₁₂-alkyl, C₁-₁₂ alkyl carbonyloxy or C₁-₁₂ alkyl carbonyl;

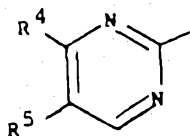
R^2 and R^3 each represents hydrogen, or R^2 and R^3 together represent a bond;

A^2 represents a benzene ring having in total up to three optional substituents selected from the group consisting of halogen, C_{1-12} alkyl or C_{1-12} alkoxy optionally substituted with up to five groups selected from halogen, C_{1-12} alkyl, phenyl, C_{1-12} alkoxy, halo C_{1-12} alkyl, hydroxy, amino, nitro, carboxy, C_{1-12} alkoxycarbonyl, C_{1-12} alkoxycarbonyl- C_{1-12} alkyl, C_{1-12} alkyl, carbonyloxy or C_{1-12} alkylcarbonyl; and n represents an integer in the range of from 2 to 6.

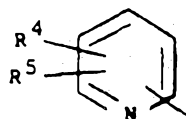
2. A compound according to claim 1 wherein A^1 represents a moiety of formula (a), (b) or (c):



(a)



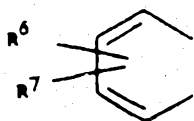
(b)



(c)

wherein:

R^4 and R^5 each independently represents a hydrogen atom, an C_{1-12} alkyl group or a phenyl or naphthyl group optionally substituted with up to five groups selected from halogen, C_{1-12} alkyl, phenyl, C_{1-12} alkoxy, halo C_{1-12} alkyl, hydroxy, amino, nitro, carboxy, C_{1-12} alkoxycarbonyl, C_{1-12} alkoxycarbonyl C_{1-12} alkyl, C_{1-12} alkylcarbonyloxy or C_{1-12} alkylcarbonyl; or when R^4 and R^5 are each attached to a carbon atom, then R^4 and R^5 together represent a moiety of formula (d):

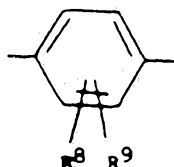


(d)

wherein R_6 and R_7 each independently represent hydrogen, halogen or C_{1-12} alkyl, optionally substituted with up to five groups selected from halogen, C_{1-12} alkyl, phenyl, C_{1-12} alkoxy, halo C_{1-12} alkyl, hydroxy, amino, nitro, carboxy, C_{1-12} alkoxy carbonyl, C_{1-12} alkoxy carbonyl- C_{1-12} alkyl, C_{1-12} alkyl carbonyloxy or C_{1-12} alkyl carbonyl; or C_{1-12} alkoxy and in the moiety of formula (a), X represents oxygen or sulphur.

3. A compound according to claim 2, wherein R^6 and R^7 both represent hydrogen.

4. A compound according to any one of claims 1 to 3 wherein A_2 represents a moiety of formula (e)

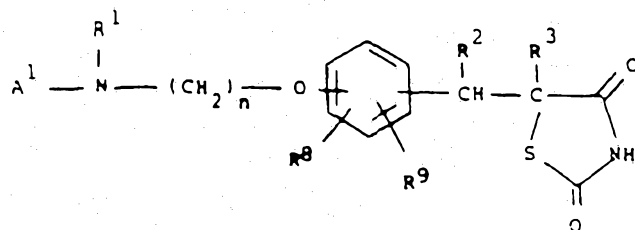


(e)

wherein R_8 and R_9 each independently represent hydrogen, halogen, C_{1-12} alkyl or C_{1-12} alkoxy optionally substituted with up to five groups selected from halogen, C_{1-12} alkyl, phenyl, C_{1-12} alkoxy, halo C_{1-12} alkyl, hydroxy, amino, nitro, carboxy, C_{1-12} alkoxy carbonyl, C_{1-12} alkoxy carbonyl- C_{1-12} alkyl, C_{1-12} alkyl carbonyloxy or C_{1-12} alkyl carbonyl; and n represents an integer in the range of from 2 to 6.

5. A compound according to claim 4, wherein R^8 and R^9 each represent hydrogen.

6. A compound according to claim 1, of formula (II):



(II)

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, wherein A^1 , R^1 , R^2 , R^3 and n are as defined in relation to formula (I) in claim 1 and
5 R^8 and R^9 are as defined in relation to formula (e) in claim 4.

7. A compound according to any one of claims 1 to 6, wherein n represents an integer 2 or 3.

10

8. A compound according to any one of claims 1 to 7, wherein R^1 represents a methyl group.

15

9. A compound according to claim 1, selected from the list consisting of:

5-(4-[2-(N-methyl-N-(2-benzothiazolyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-(2-benzothiazolyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-(2-benzoxazolyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-(2-benzoxazolyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-(2-pyrimidinyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-(2-pyrimidinyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione;

5-(4-(2-(N-methyl-N-[2-(4,5-dimethylthiazolyl)]amino)ethoxy]benzyl)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-[2-(4,5-dimethylthiazolyl)]amino)ethoxy]benzylidene)-2,4-thiazolidinedione;



5-(4-[2-(N-methyl-N-(2-thiazolyl)amino)ethoxy]benzyl)
-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-(2-thiazolyl)amino)ethoxy]
benzylidene)-2,4-thiazolidinedione;

5-[4-(2-(N-methyl-N-(2-(4-phenylthiazolyl))amino)
ethoxy]benzyl]-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-(2-(4-phenylthiazolyl))amino)
ethoxy]benzylidene)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-[2-(4-phenyl-5-methylthiazolyl)]
amino)ethoxy]benzyl)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-[2-(4-phenyl-5-methylthiazolyl)]
amino)ethoxy]benzylidene)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-[2-(4-methyl-5-phenylthiazolyl)]
amino)ethoxy]benzyl)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-[2-(4-methyl-5-phenylthiazolyl)]
amino)ethoxy]benzylidene)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-[2-(4-methylthiazolyl)]
amino)ethoxy]benzyl)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-[2-(4-methylthiazolyl)]amino)
ethoxy]benzylidene)-2,4-thiazolidinedione;

5-[4-(2-(N-methyl-N-[2-(5-phenyloxazolyl)]amino)
ethoxy]benzyl]-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-[2-(5-phenyloxazolyl)]amino)
ethoxy]benzylidene)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-[2-(4,5-dimethyloxazolyl)]amino)ethoxy]benzyl)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-[2-(4,5-dimethyloxazolyl)]amino)-ethoxy]benzylidene)-2,4-thiazolidinedione;

5-[4-(2-(2-pyrimidinylamino)ethoxy)benzyl]-2,4-thiazolidinedione;

5-[4-(2-(2-pyrimidinylamino)ethoxy)benzylidene]-2,4-thiazolidinedione;

5-(4-[2-(N-ccetyl-N-(2-pyrimidinyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione;

5-(4-(2-(N-(2-benzothiazolyl)-N-benzylamino)ethoxy)benzylidene)-2,4-thiazolidinedione;

5-(4-(2-(N-(2-benzothiazolyl)-N-benzylamino)ethoxy)benzyl)-2,4-thiazolidinedione;

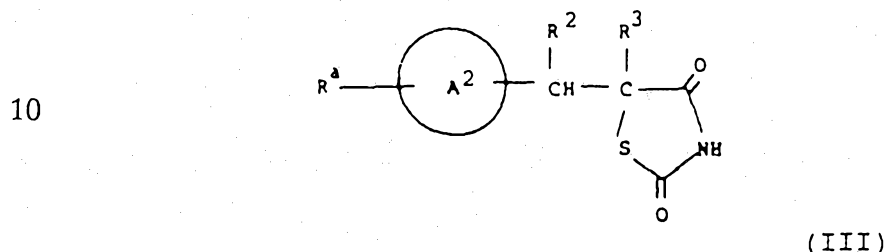
5-(4-[3-(N-methyl-N-(2-benzoxazolyl)amino)propoxy]benzyl)-2,4-thiazolidinedione;

5-(4-[3-(N-methyl-N-(2-benzoxazolyl)amino)propoxy]benzylidene)-2,4-thiazolidinedione;

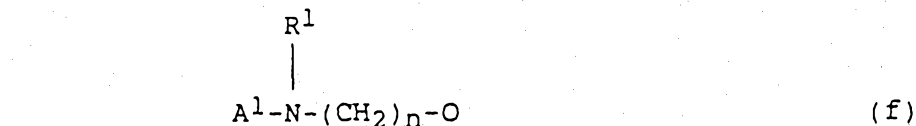
5-(4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione; and

5-(4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

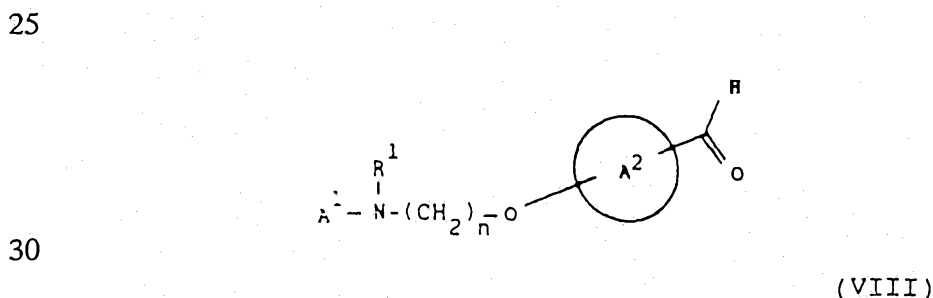
10. A process for the preparation of a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, characterised in that the process comprises either:
- (a) reacting a compound of formula (III):



- wherein R^2 , R^3 and A^2 are as defined in relation to formula (I), and R^a is a moiety convertible to a moiety of formula (f):



- wherein R^1 , A^1 , and n are as defined in relation to formula (I), with an appropriate reagent capable of converting R^a to the said moiety (f); or
- (b) reacting a compound of formula (VIII):



- wherein R^1 , A^1 , A^2 , and n are as defined in relation to formula (I) with 2,4-thiazolidinedione; and thereafter, if required, carrying out one or more of the following

optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

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(ii) preparing a pharmaceutically acceptable salt of the compound of formula (I) and/or a pharmaceutically acceptable solvate thereof.

10 11. A pharmaceutical composition comprising a compound of formula (I) according to claim 1, or a tautomeric form thereof or a pharmaceutically acceptable salt thereof or pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier therefor.

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12. A method for the treatment and/or prophylaxis of hyperglycaemia and/or hyperlipidaemia in a human or non-human mammal which comprises administering an effective, non-toxic, amount of a compound of the general formula(I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, to a hyperglycaemic human or non-human mammal in need thereof.

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25 13. Compounds of formula (I), methods for their manufacture or pharmaceutical compositions or methods of treatment involving them substantially as hereinbefore described with reference to the Examples.

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DATED this 3rd day of April, 1991

Beecham Group p.l.c

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By Its Patent Attorneys

DAVIES & COLLISON

