I/We being the person(s) identified below as the Applicant(s), request the grant of a patent to the person(s) identified below as the Nominated Person(s), for an invention described in the accompanying standard complete specification.

Full application details follow:

[71/70] Applicant(s)/Nominated Person(s):

**Synthelabo**

of

22, avenue Galilee, 92350 Le Plessis-Robinson, France

[54] Invention Title:

5,6-Dihydro-4H-thieno[3,4-c]pyrrole derivatives, their preparation and their therapeutic application

[72] Name(s) of actual inventor(s):

Manuel BENDOYA ZURITA
Juan Antonio DIAZ MARTIN
Gregorio DEL SOL MORENO
Ulpiano MARTIN ESCUDERO PEREZ
Maria Dolores JIMENEZ BARGUENO
Magali ROMANACH FERRER

[74] Address for service in Australia:

DAVIES COLLISON CAVE, Patent Attorneys, 1 Little Collins Street, Melbourne, Victoria, Australia.

Attorney Code:  DM

Basic Convention Application(s) Details:


94 05716  France  FR  10 May 1994

DATED this NINTH day of MAY 1995

....................

Keith L. Walsh

a member of the firm of DAVIES COLLISON CAVE for and on behalf of the applicant(s)
We, Synthelabo, the applicant/Nominated Person named in the accompanying Patent Request state the following:-

The Nominated Person is entitled to the grant of the patent because the Nominated Person would, on the grant of a patent for the invention to the inventors, be entitled to have the patent assigned to the Nominated Person.

The Nominated Person is entitled to claim priority from the basic application listed on the patent request because the Nominated Person made the basic application.

DATED this NINTH day of MAY 1995

..............................

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

(DCC ref: 1738717)
5,6-DIHYDRO-4H-THIENO[3,4-C]PYRROLE DERIVATIVES, THEIR PREPARATION AND THEIR THERAPEUTIC APPLICATION.

A 5,6-dihydro-4H-thieno[3,4-c]pyrrole derivative of formula (I)

![Chemical Structure](image)

in which R₁ represents a cyano group; a C₄ alkoxy group; a C₄ alkylthio group; a C₃ alkylsulphonyl group; a pyridyl group; a 3,4-dimethoxyphenyl group; a cyclopropyl group which is optionally substituted with one or two alkyl groups; a group COR where R is a C₁₄ alkyl group, a phenyl group or a piperidyl group; a benzyl group, the phenyl ring of which is substituted with one or more halogen atoms and/or linear or branched C₄ alkyl groups, linear or branched C₁₄ alkoxy groups or groups CO₂R' where R' is a linear or branched C₁₄ alkyl group; or a
naphthylmethyl group; or a pharmaceutically acceptable acid addition salt thereof; process for their production; their use in the treatment of diabetes, obesity, hypotension, post-operative ileus, asthma and urinary incontinence and a synthetic intermediate.

**CLAIM**

1. A 5,6-dihydro-4H-thieno[3,4-c]pyrrole derivative of formula (I)

![Chemical Structure](image)

in which $R_1$ represents a cyano group; a $C_4$ alkoxy group; a $C_4$ alkylthio group; a $C_4$ alkylsulphonyl group; a pyridyl group; a 3,4-dimethoxyphenyl group; a cyclopropyl group which is optionally substituted with one or two alkyl groups; a group COR where $R$ is a $C_4$ alkyl group, a phenyl group or a piperidyl group; a benzyl group, the phenyl ring of which is substituted with one or more halogen atoms and/or linear or branched $C_4$ alkyl groups, linear or branched $C_4$ alkoxy groups or groups $CO_2R'$ where $R'$ is a linear or branched $C_4$ alkyl group; or a naphthylmethyl group; or a pharmaceutically acceptable acid addition salt thereof.

5. A process for the preparation of a compound of formula (I) as defined in any one of claims 1 to 3, in which a compound of formula (II)

![Chemical Structure](image)

in which $R_1$, which is as defined as in claim 1 or 3, is reacted with 2-chloromethyl-4,5-dihydro-1H-imidazole, in the presence
of N,N-diisopropylethylamine and, if desired, converting the compound of formula (I) into a pharmaceutically acceptable acid addition salt thereof.

10. A method for treating or preventing diabetes, obesity, hypotension, post-operative paralytic ileus, asthma or urinary incontinence in a subject which comprises administering to that subject a compound as defined in any one of claims 1 to 4 or 7.
NAME OF APPLICANT(S):

Synthelabo

ADDRESS FOR SERVICE:

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

INVENTION TITLE:

5,6-Dihydro-4H-thieno[3,4-c]pyrrole derivatives, their preparation and their therapeutic application

The following statement is a full description of this invention, including the best method of performing it known to me/us:-
The subject of the present invention is 5,6-dihydro-4H-thieno[3,4-c]pyrrole derivatives, their preparation and their therapeutic application.

The present invention provides a 5,6-dihydro-4H-thieno[3,4-c]pyrrole derivative of formula (I)

\[ \text{\textit{(I)}} \]

in which R represents a cyano group; a C\(_1\)-C\(_4\) alkoxy group; a C\(_1\)-C\(_4\) alkylthio group; a C\(_1\)-C\(_4\) alkylsulphonyl group; a pyridyl group; a 3,4-dimethoxyphenyl group; a cyclopropyl group which is optionally substituted with one or two alkyl groups; a group COR where R is a C\(_1\)-C\(_4\) alkyl group, a phenyl group or a piperidyl group; a benzyl group, the phenyl ring of which is substituted with one or more halogen atoms and/or linear or branched C\(_1\)-C\(_4\) alkyl groups, linear or branched C\(_1\)-C\(_4\) alkoxy groups or groups CO\(_2\)R' where R' is a linear or branched C\(_1\)-C\(_4\) alkyl group; or a naphthylmethyl group; or a pharmaceutically acceptable acid addition salt thereof.

Preferred are hydrochloride and methanesulphonate salts.

Preferred compounds are those in which R is methoxy or methylthio. These compounds are particularly preferred when in the form of their dihydrochloride salts.

The compounds of formula (I) can be prepared according to the process of Scheme 1 set out below, which comprises treating a compound of formula (III)
in which R₁ is defined as in formula (I), with trifluoroacetic acid, typically at a temperature in the region of 0°C, and then reacting the compound obtained, of formula (II)

with 2-chloromethyl-4,5-dihydro-1H-imidazole, in a solvent such as dimethylformamide, in the presence of N,N-diisopropylethylamine.

The compounds of formula (III) can be prepared from 1,1-dimethylethyl 5,6-dihydro-4H-thieno[3,4-c]pyrrole-5-carboxylate of formula (IV)

according to processes which depend on the nature of the substituent R₁. These processes are represented in Scheme 2 and set out below.

The processes represented in Scheme 2 relate to the preparation of the compounds of formula (III) in which R₁ is a C₃₋₄ alkoxy group (compounds VI), a pyridyl group or a 3,4-dimethoxyphenyl group (compounds VII).

According to these processes, a compound of formula (IV) is treated with a strong base, for example a compound of
formula R₃Li in which R₃ represents an alkyl group, in particular n-butyl, in a solvent such as tetrahydrofuran, typically at a temperature in the region of -70°C, is then treated with a trialkyl or triaryl borate, for example trimethyl borate, generally at room temperature, and is finally treated with hydrochloric acid, typically at a temperature in the region of -40°C, to give 1,1-dimethylethyl 1-borono-5,6-dihydro-4H-thieno[3,4-c]pyrrole-5-carboxylate of formula (V), which is either treated with hydrogen peroxide generally at a temperature in the region of 45°C and then with a dialkyl sulphate of formula (R₅O)₂SO₂ in which R₅ represents a linear or branched C₁₋₄ alkyl group, generally at room temperature, to give the compound of formula (VI) in which R₅ is defined as above, or treated with a halide of formula ArX in which Ar represents a pyridyl group or a 3,4-dimethoxyphenyl group and X represents a halogen atom, in the presence of palladium (0) and a base such as butyltrimethylammonium hydroxide, in a solvent such as methanol, typically at the reflux temperature, to give the compound of formula (VII) in which Ar is defined as above.

The processes represented in Scheme 3 relate to the preparation of the compounds of formula (III) in which R₁ is a cyano group (compounds IX), a C₁₋₄ alkylthio group (compounds X), a C₁₋₄ alkylsulphonyl group (compounds XI), a group COR in which R is a C₁₋₄ alkyl group or a phenyl group (compounds XIII), or a substituted or unsubstituted cyclopropyl group (compounds XV).

According to these processes, the compound of formula (IV) is treated with a strong base, for example a compound of
formula $R_3Li$ in which $R_3$ represents an alkyl group, in particular n-butyl, in a solvent such as tetrahydrofuran, typically at a temperature in the region of -70°C, and then the compound obtained is reacted, either with dimethylformamide generally at room temperature to give the compound of formula (VIII) which is treated with hydroxylamine and then with carbonyldiimidazole, generally at room temperature, to give a compound of formula (IX), or with a compound of formula $R_6S_2$ in which $R_6$ represents a C$_{1-4}$ alkyl group, generally at room temperature, to give a compound of formula (X), which may then be oxidized, for example using potassium peroxymonosulphate, generally at room temperature, to give a compound of formula (XI), or with a compound of formula $R_7(R_8)C=O$ in which $R_7$ represents a hydrogen atom or an alkyl group and $R_8$ represents a hydrogen atom or an alkyl group, in a solvent such as tetrahydrofuran, typically at room temperature, to give a compound of formula (XII) in which $R_7$ and $R_8$ are defined as above, which compound, in the case where $R_8$ is a hydrogen atom, is treated with pyridinium dichromate in the presence of acetic acid, typically at room temperature, to give a compound of formula (XIII), and, in the case where $R_8$ is an alkyl group, is treated with acetic acid in the presence of calcium chloride to give a compound of formula (XIV) in which $R_7$ is defined as above and $R_8$ represents a hydrogen atom or an alkyl group, which compound is then treated with diiodomethane, to give a compound of formula (XV) in which $R_7$ and $R_8$ are defined as above.

The compounds of formula (III) in which $R_1$ represents a
substituted benzyl group can be prepared according to a process similar to the process described in European Patent Application No. 93 402785.5 for the preparation of compounds of formula (III) containing an unsubstituted benzyl group. This process comprises treating the compound of formula (IV) with a compound of formula R₃Li in which R₃ is defined as above, in a solvent such as tetrahydrofuran, typically at a temperature in the region of -70°C, and then with a suitably substituted benzyl halide.

The compounds of formula (III) in which R₁ represents a naphthylmethyl group can be prepared by a similar process, by replacing the benzyl halide by a naphthylmethyl halide.

The compound of formula (III) in which R₁ represents the piperidylcarbonyl group can be prepared according to a process similar to the process described in French Patent Application FR 93 07538 for the preparation of the compounds of formula (III) containing a carbamoyl group. This process comprises treating the compound of formula (III), in which R₁ represents a carboxyl group, with piperidine in the presence of a condensing agent.

A preparation of the compound of formula (IV) is described in European Patent Application No. 93 402785.5.

The examples which follow illustrate the invention. Examples 2 to 11 relate to the preparation of the compounds of formula (III) according to the processes represented in Schemes 2 and 3 and to the preparation of the corresponding compounds of formula (II).

The analyses confirm the structure of the compounds.
Example 1: 1-Methoxy-5-[(4,5-dihydro-1H-imidazol-2-yl)methyl]-5,6-dihydro-4H-thieno[3,4-c]pyrrole dihydrochloride

1.1. 1,1-Dimethylethyl 1-borono-5,6-dihydro-4H-thieno[3,4-c]pyrrole-5-carboxylate.

To a solution of 2.29 ml (16.23 mmol) of N,N-diisopropylamine in 66 ml of dry tetrahydrofuran are added, at 0°C, 10.6 ml (17.03 mmol) of a 1.6 M solution of butyllithium in hexane. The mixture is stirred for 45 min, then cooled to -70°C and a solution of 3g (13.31 mmol) of 1,1-dimethylethyl 5,6-dihydro-4H-thieno[3,4-c]pyrrole-5-carboxylate in 26 ml of dry tetrahydrofuran is added. The mixture is maintained at -70°C for 1 hour and the solution obtained is then poured into a solution of 5 ml of trimethyl borate in 10 ml of tetrahydrofuran, at the same temperature. The reaction mixture is then stirred at room temperature overnight and is then cooled to -40°C and 80 ml of 1N hydrochloric acid and 250 ml of ethyl acetate are added. The organic phase is separated out after settling of the phases has taken place and is washed with twice 60 ml of saturated sodium chloride solution, then dried over sodium sulphate and the solvent is evaporated off. After recrystallization of the residue from ethyl acetate, 2.4 g of product are obtained. Melting point: 160-162°C.

1.2. 1,1-Dimethylethyl 1-methoxy-5,6-dihydro-4H-thieno[3,4-c]pyrrole-5-carboxylate.

To a suspension of 4 g (14.9 mmol) of 1,1-dimethylethyl 1-borono-5,6-dihydro-4H-thieno[3,4-c]pyrrole-5-carboxylate in 600 ml of diethyl ether are added 80 ml of 30% hydrogen peroxide. The mixture is heated at 45°C for 20 min and the organic phase
is then separated out after settling of the phases has taken place and is washed with twice 100 ml of 5% sodium carbonate solution and then with 200 ml of saturated sodium chloride solution and, at 0°C, 600 ml of toluene, 49.94 g (147 mmol) of tetrabutylammonium hydrosulphide, 67.8 ml (710 mmol) of dimethyl sulphate and 400 ml (800 mmol) of 2N sodium hydroxide solution are added. The mixture is maintained at room temperature for 1.5 hours and the organic phase is then separated out after settling of the phases has taken place and is washed with twice 400 ml of 7% sodium hydrogen carbonate solution and dried over sodium sulphate, and the solvent is evaporated off. The residue is chromatographed on a column of silica gel with a 1/9 mixture of ethyl acetate and hexane. 0.95 g of product is obtained.

Melting point: 62.8-64.7°C.

1.3 1-Methoxy-5-[(4,5-dihydro-1H-imidazol-2-yl)methyl]-5,6-dihydro-4H-thieno[3,4-c]pyrrole dihydrochloride.

A mixture of 0.95 g (3.72 mmol) of 1,1-dimethylethyl 1-methoxy-5,6-dihydro-4H-thieno[3,4-c]pyrrole-5-carboxylate and 8.5 ml of trifluoroacetic acid is stirred for 10 min at 0°C, then the solvent is evaporated off and the residue is dissolved in 21 ml of dimethylformamide. 1.27 ml (7.5 mmol) of N,N-diisopropylethylamine are added, followed by a solution of 0.577 g (3.72 mmol) of 2-chloromethyl-4,5-dihydro-1H-imidazole hydrochloride and 0.53 ml (3.1 mmol) of N,N-diisopropylethylamine in 21 ml of dimethylformamide. The mixture is left overnight at room temperature, then the solvent is evaporated off and 35 ml of water and 35 ml of 7% sodium hydrogen carbonate solution are added. The mixture is extracted
with 6 times 60 ml of dichloromethane, the organic phases are dried over sodium sulphate and the solvent is evaporated off. The residue is chromatographed on a column of silica gel with a 1/9 mixture of methanol and dichloromethane. 0.49 g of an oily product is obtained, which is converted into the hydrochloride by addition of a saturated solution of hydrochloric acid in isopropanol. 0.31 g of product is obtained. Melting point: 243-245°C (with decomposition).

Example 2: 1-(3,4-Dimethoxyphenyl)-5,6-dihydro-4H-thieno[3,4-c]pyrrole trifluoroacetate.

2.1. 1,1-Dimethylethyl 1-(3,4-dimethoxyphenyl)-5,6-dihydro-4H-thieno[3,4-c]pyrrole-5-carboxylate.

3 g (11.14 mmol) of 1,1-dimethylethyl 1-borono-5,6-dihydro-4H-thieno[3,4-c]pyrrole-5-carboxylate, 1.53 ml (12.03 mmol) of 1-bromo-3,4-dimethoxybenzene, 0.9 g (0.78 mmol) of tetrakis(triphenylphosphine)palladium (0), 10 ml (22.8 mmol) of a 40% solution of butyltrimethylammonium hydroxide in methanol and 60 ml of methanol are introduced into a 250 ml round-bottomed flask. The mixture is heated at reflux for 6 hours and the solvent is evaporated off. The residue is then taken up in 150 ml of dichloromethane, washed with twice 100 ml of saturated sodium hydrogen carbonate solution and dried over sodium sulphate, and the solvent is evaporated off. The residue is chromatographed on a column of silica gel with a 1/5 mixture of ethyl acetate and hexane. 1.32 g of product are obtained. Melting point: 130-132°C.

2.2. 1-(3,4-Dimethoxyphenyl)-5,6-dihydro-4H-thieno[3,4-c]pyrrole trifluoroacetate.
A solution of 1.32 g (3.65 mmol) of 1,1-dimethylethyl 1-(3,4-dimethoxyphenyl)-5,6-dihydro-4H-thieno[3,4-c]pyrrole-5-carboxylate in 12 ml of trifluoroacetic acid is stirred for 10 min at 0°C. After evaporation of the solvent, 1.37 g of an oily product are obtained.

**Example 3**: 1-pyrid-2-yl-5,6-dihydro-4H-thieno[3,4-c]pyrrole trifluoroacetate.

This compound is obtained by a process similar to that of Example 2, starting with 2-bromopyridine.

**Example 4**: 1-Cyano-5,6-dihydro-4H-thieno[3,4-c]pyrrole trifluoroacetate.

4.1. 1,1-Dimethylethyl 1-formyl-5,6-dihydro-4H-thieno[3,4-c]pyrrole-5-carboxylate.

To a solution of 3.2 ml (22.7 mmol) of diisopropylamine in 84 ml of dry tetrahydrofuran are added, at 0°C, 15.55 ml (24.88 mmol) of a 1.6 M solution of butyllithium in hexane. After 30 min, the mixture is cooled to -70°C and a solution of 5 g (22.2 mmol) of 1,1-dimethylethyl 5,6-dihydro-4H-thieno[3,4-c]pyrrole-5-carboxylate in 34 ml of tetrahydrofuran, cooled to -70°C, is added. The mixture is then stirred for 30 min at 0°C, followed by addition at -70°C of 10 ml of dimethylformamide. The mixture is stirred at room temperature for 30 min, followed by addition of 34 ml of saturated ammonium chloride solution. The organic phase is separated out after settling of the phases has taken place and the aqueous phase is extracted with twice 50 ml of ethyl acetate, then the organic phases are combined and washed with saturated sodium chloride solution, and the solvent is
I. II

evaporated off. The residue is chromatographed on a column of silica gel with a 1/10 mixture of ethyl acetate and hexane. 4.6 g of product are obtained.

Melting point: 84.3-86.6°C.

4.2. 1,1-Dimethylethyl 1-[(hydroxyimino)methyl]-5,6-dihydro-4H-thieno[3,4-c]pyrrole-5-carboxylate.

3.59 g (14.17 mmol) of 1,1-dimethylethyl 1-formyl-5,6-dihydro-4H-thieno[3,4-c]pyrrole-5-carboxylate, 11.56 g (85 mmol) of sodium acetate trihydrate, 4.91 g (70.85 mmol) of hydroxylamine hydrochloride and 180 ml of methanol are introduced into a 500 ml round-bottomed flask. The mixture is stirred at room temperature for 3 hours, then the solvent is evaporated off and 200 ml of saturated sodium chloride solution and 200 ml of dichloromethane are added. The organic phase is separated out after settling of the phases has taken place and the aqueous phase is extracted with twice 150 ml of dichloromethane. The organic phases are combined and dried over sodium sulphate, and the solvent is evaporated off. 1.76 g of product are obtained.

Melting point: 193.8-194.9°C.

4.3. 1,1-Dimethylethyl 1-cyano-5,6-dihydro-4H-thieno[3,4-c]pyrrole-5-carboxylate.

To a suspension of 1.73 g (6.44 mmol) of 1,1-dimethylethyl 1-[(hydroxyimino)methyl]-5,6-dihydro-4H-thieno[3,4-c]pyrrole-5-carboxylate in 41 ml of chloroform are added, at 0°C, 3.12 g (19.34 mmol) of carbonyldiimidazole. The mixture is stirred at room temperature for 24 hours and is then poured into a mixture, cooled to 0°C, of 200 ml of 1N hydrochloric acid and 200 ml of dichloromethane. The organic phase is separated out
after settling of the phases has taken place and is dried over sodium sulphate, then the solvent is evaporated off. 1.58 g of product are obtained. Melting point: 106.2-107.3°C.

4.4. 1-Cyano-5,6-dihydro-4H-thieno[3,4-c]pyrrole trifluoroacetate.

A solution of 1.3 g (5.19 mmol) of 1,1-dimethylethyl 1-cyano-5,6-dihydro-4H-thieno[3,4-c]pyrrole-5-carboxylate in 11 ml of trifluoroacetic acid is stirred for 10 min at 0°C, and the solvent is then evaporated off. 1.37 g of product are obtained. Melting point: 87.5-89.7°C.

Example 5: 1-(1-Methylcyclopropyl)-5,6-dihydro-4H-thieno[3,4-c]pyrrole trifluoroacetate.

5.1. 1,1-Dimethylethyl 1-(1-methylcyclopropyl)-5,6-dihydro-4H-thieno[3,4-c]pyrrole-5-carboxylate.

To a suspension of 1.45 g (5.46 mmol) of 1,1-dimethylethyl 1-(1-propen-2-yl)-5,6-dihydro-4H-thieno[3,4-c]pyrrole-5-carboxylate in 80 ml of n-hexane, cooled to -23°C, are added 7.05 ml (7.05 mmol) of a 1M solution of diethylzinc in hexane, followed by 21.96 g (82 mmol) of diiodomethane. The mixture is stirred at -23°C for 6 hours and then at 4°C for 19 hours, followed by addition of 200 ml of diethyl ether and 50 ml of saturated ammonium chloride solution. The organic phase is separated out after settling of the phases has taken place and is dried over sodium sulphate, and the solvent is evaporated off. The residue is chromatographed on a column of silica gel with a 1/15 mixture of ethyl acetate and hexane. 0.46 g of an
oily product is obtained.

5.2. 1-(1-Methylcyclopropyl)-5,6-dihydro-4H-thieno[3,4-c]pyrrole trifluoroacetate.

A solution of 0.905 g (3.24 mmol) of 1,1-dimethylethyl 1-(1-methylcyclopropyl)-5,6-dihydro-4H-thieno[3,4-c]pyrrole-5-carboxylate in 6 ml of trifluoroacetic acid is stirred for 10 min at 0°C, and the solvent is then evaporated off. 0.95 g of an oily product is obtained.


6.1. 1,1-Dimethylethyl 1-methylthio-5,6-dihydro-4H-thieno[3,4-c]pyrrole-5-carboxylate.

To a solution of 6.5 ml (46.3 mmol) of N,N-diisopropylamine in 130 ml of dry tetrahydrofuran are added, at 0°C, 30 ml (48 mmol) of a 1.6 M solution of butyllithium in hexane. After 30 min, the mixture is cooled to -70°C and a solution of 8.7 g (38.59 mmol) of 1,1-dimethylethyl 5,6-dihydro-4H-thieno[3,4-c]pyrrole-5-carboxylate in 30 ml of dry tetrahydrofuran is added. After 1 hour at -70°C, 4.86 ml (54 mmol) of dimethyl disulphide are added, followed by stirring at room temperature for 1 hour. The reaction mixture is then poured into 100 ml of saturated ammonium chloride solution and then extracted with twice 100 ml of dichloromethane. The organic phases are dried over sodium sulphate and the solvent is evaporated off. After recrystallization from hexane, 10 g of product are obtained. Melting point: 51-53°C.

6.2. 1-Methylthio-5,6-dihydro-4H-thieno[3,4-c]pyrrole
trifluoroacetate.

A solution of 4.88 g (17.9 mmol) of 1,1-dimethylethyl 1-methylthio-5,6-dihydro-4H-thieno[3,4-c]pyrrole-5-carboxylate in 10 ml of trifluoroacetic acid is stirred for 1 hour at a temperature in the region of 0°C, and the solvent is then evaporated off. The residue is chromatographed on a column of silica gel with a 1/9 mixture of methanol and dichloromethane. The product obtained is dissolved in 1 ml of trifluoroacetic acid and the solvent is then evaporated off. 5 g of an oily product are obtained.

Example 7: l-Methylsulphonyl-5,6-dihydro-4H-thieno[3,4-c]pyrrole trifluoroacetate.

7.1. 1,1-Dimethylethyl l-methylsulphonyl-5,6-dihydro-4H-thieno[3,4-c]pyrrole-5-carboxylate.

To a solution of 2.1 g (7.8 mmol) of 1,1-dimethylethyl 1-methylthio-5,6-dihydro-4H-thieno[3,4-c]pyrrole-5-carboxylate in 50 ml of ethanol is added, at a temperature in the region of -20°C, a solution of 9.5 g (15.5 mmol) of potassium peroxymonosulphate in 50 ml of water. The mixture is stirred for 3 hours at room temperature and then filtered, and the ethanol is removed. The aqueous phase is extracted with 4 times 50 ml of ethyl acetate, then the organic phases are dried over sodium sulphate and the solvent is evaporated off. The residue is chromatographed on a column of silica gel with a 3/7 mixture of ethyl acetate and hexane. 1.1 g of product are obtained.

Melting point: 122-125°C.

7.2. 1-Methylsulphonyl-5,6-dihydro-4H-thieno[3,4-c]pyrrole trifluoroacetate.
A solution of 1 g (3.3 mmol) of 1,1-dimethylethyl 1-methylsulphonyl-5,6-dihydro-4H-thieno[3,4-c]pyrrole-5-carboxylate in 8 ml of trifluoroacetic acid is stirred for 1 hour at a temperature in the region of 0°C, and the solvent is then evaporated off. 10 ml of diethyl ether are added and the precipitate formed is filtered off. 1 g of product is obtained. Melting point: 172-176°C.

Example 8: 1-(Piperid-1-ylcarbonyl)-5,6-dihydro-4H-thieno[3,4-c]pyrrole trifluoroacetate.

8.1. 1,1-Dimethylethyl 1-(piperid-1-ylcarbonyl)-5,6-dihydro-4H-thieno[3,4-c]pyrrole-5-carboxylate.

To a solution of 1.95 g (7.2 mmol) of 1,1-dimethylethyl 1-carboxy-5,6-dihydro-4H-thieno[3,4-c]pyrrole-5-carboxylate in 50 ml of dry tetrahydrofuran is added a solution of 1.29 g (7.9 mmol) of carbonyldiimidazole in 12 ml of tetrahydrofuran. After one hour at room temperature, 5 ml of piperidine are added and the mixture is stirred for 30 min at room temperature. The solvent is evaporated off, 40 ml of water are added and the mixture is extracted with twice 50 ml of ethyl acetate. The organic phases are dried over sodium sulphate and the solvent is evaporated off. 1.89 g of an oily product are obtained.

8.2. 1-(Piperid-1-ylcarbonyl)-5,6-dihydro-4H-thieno[3,4-c]pyrrole trifluoroacetate.

A solution of 1.86 g (5.5 mmol) of 1,1-dimethylethyl 1-(piperid-1-ylcarbonyl)-5,6-dihydro-4H-thieno[3,4-c]pyrrole-5-carboxylate in 10 ml of trifluoroacetic acid is stirred for 30 min at a temperature in the region of 0°C, and the solvent is then evaporated off. 1.96 g of an oily product are obtained.
Example 9: l-Acetyl-5,6-dihydro-4H-thieno[3,4-c]pyrrole trifluoroacetate.

9.1. 1,1-Dimethylethyl 1-(1-hydroxy-1-ethyl)-5,6-dihydro-4H-thieno[3,4-c]pyrrole-5-carboxylate.

To a solution of 0.72 g (7.2 mmol) of N,N-diisopropylamine in 10 ml of dry tetrahydrofuran are added, at 0°C, 4.5 ml (7.2 mmol) of a 1.6 M solution of butyllithium in hexane. After 30 min, the mixture is cooled to -40°C and a solution of 1.35 g (6 mmol) of 1,1-dimethylethyl 5,6-dihydro-4H-thieno[3,4-c]pyrrole-5-carboxylate in 10 ml of tetrahydrofuran is added. After 1 hour at -40°C, the mixture is cooled to -70°C and 1 ml (18 mmol) of acetaldehyde is added, followed by stirring at room temperature for two hours. The reaction mixture is then poured into 30 ml of saturated ammonium chloride solution, followed by extraction with twice 50 ml of ethyl acetate. The organic phases are dried over sodium sulphate and the solvent is then evaporated off. The residue is chromatographed on a column of silica gel with a 1/4 mixture of ethyl acetate and hexane. 1.19 g of an oily product are obtained.

9.2. 1,1-Dimethylethyl l-acetyl-5,6-dihydro-4H-thieno[3,4-c]pyrrole-5-carboxylate.

To a solution of 5.39 g (20 mmol) of 1,1-dimethylethyl 1-(1-hydroxy-1-ethyl)-5,6-dihydro-4H-thieno[3,4-c]pyrrole-5-carboxylate in 100 ml of dichloromethane are added 1.14 ml (20 mmol) of acetic acid followed by 5.64 g (15 mmol) of pyridinium dichromate. The mixture is stirred for 16 hours at room temperature, then 4 g of Celite are added, the mixture is filtered and the solvent is evaporated off.

The residue is chromatographed on a column of silica gel.
with a 35/65 mixture of ethyl acetate and hexane. 2.16 g of product are obtained.
Melting point: 119-121°C.

9.3. 1-Acetyl-5,6-dihydro-4H-thieno[3,4-c]pyrrole trifluoroacetate.
A solution of 1.87 g (7 mmol) of 1,1-dimethylethyl 1-acetyl-5,6-dihydro-4H-thieno[3,4-c]pyrrole-5-carboxylate in 8 ml of trifluoroacetic acid is stirred for 30 min at a temperature in the region of 0°C. The solvent is then evaporated off, 20 ml of diethyl ether are added and the mixture is filtered. 1.76 g of product are obtained.
Melting point: 136-138°C.

Example 10: 1-Benzoyl-5,6-dihydro-4H-thieno[3,4-c]pyrrole trifluoroacetate.
This compound is obtained by a process similar to that of Example 9, by replacing the acetaldehyde by benzaldehyde.

Example 11: 1-Propylcarbonyl-5,6-dihydro-4H-thieno[3,4-c]pyrrole trifluoroacetate.
This compound is obtained by a process similar to that of Example 9, by replacing the acetaldehyde by butyraldehyde.

The compounds of the invention are collated in Table I with their physical characteristics.
Table

![Molecular structure](image)

\( (I) \)

<table>
<thead>
<tr>
<th>Compound</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>salt</th>
<th>m.p. (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H&lt;sub&gt;3&lt;/sub&gt;CO-</td>
<td>dihydrochloride</td>
<td>202-204 (d)</td>
</tr>
<tr>
<td>2</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;CO-</td>
<td>dimethanesulphonate</td>
<td>194-195 (d)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>trimethanesulphonate</td>
<td>161-162 (d)</td>
</tr>
<tr>
<td>4</td>
<td>NC-</td>
<td>dimethanesulphonate</td>
<td>205-206</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>dihydrochloride</td>
<td>224-226 (d)</td>
</tr>
<tr>
<td>6</td>
<td>H&lt;sub&gt;3&lt;/sub&gt;CS-</td>
<td>dihydrochloride</td>
<td>227-229 (d)</td>
</tr>
<tr>
<td>7</td>
<td>H&lt;sub&gt;3&lt;/sub&gt;CSO&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>dimethanesulphonate</td>
<td>192-194 (d)</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>dihydrochloride</td>
<td>206-208 (d)</td>
</tr>
<tr>
<td>9</td>
<td>H&lt;sub&gt;3&lt;/sub&gt;CCO-</td>
<td>dihydrochloride</td>
<td>&gt; 270 (d)</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>dihydrochloride</td>
<td>&gt; 270 (d)</td>
</tr>
<tr>
<td>11</td>
<td>H&lt;sub&gt;3&lt;/sub&gt;C(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;CO-</td>
<td>dihydrochloride</td>
<td>198-200 (d)</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>dihydrochloride</td>
<td>246-248</td>
</tr>
</tbody>
</table>
The compounds of the invention exhibit an $\alpha_2$-antagonist pharmacological activity and were tested in various biological trials.

1. **Antagonism of the effects of clonidine on rat vas deferens.**

This determination was carried out on rat vas deferens stimulated at a frequency of 0.1 Hz in the presence of 30 nanomol of prazosin and one micromole of cocaine according to the method described by G.M. Drew in European Journal of Pharmacology, **42**, 123-130, (1977).

The $pA_2$ of the compounds of the invention are between 6.5 and 9.4.
2. **Antagonism of the binding of \(^{3}\text{H}\)-clonidine to \(\alpha_2\)-adrenergic receptors**

The test is performed on a preparation of rat brain membranes, according to the method described by D.A. Greenberg et al. in *Life Sci.* **19**, 69, (1976).

After incubating for 30 min in the presence of tritiated clonidine (0.05 to 7 nmol/l), the mixture is filtered and the radioactivity of the residue is counted according to the method of P.B.M.W.M. Timmermans et al., described in *European Journal of Pharmacology*, **70**, 7, (1981).

The 50% inhibitory concentrations of the compounds of the invention are between 0.02 and 3.02 \(\mu\text{mol/l}\).

The results of the biological trials show that the compounds of the invention exhibit antagonist properties in vitro towards \(\alpha_2\)-type adrenergic receptors. On account of their pharmacological properties, the compounds of the invention may be used for the treatment of diabetes, obesity, hypotension, post-operative paralytic ileus and/or asthma.

The compounds of the invention also exhibit an \(\alpha_1\)-agonist activity, demonstrated by biological trials on pulmonary artery isolated from rabbits.

These trials were performed under the following conditions: rabbits (Fauve de Bourgogne) weighing 2 to 3 kg, were sacrificed and bled, then their pulmonary arteries were removed, dissected and cut into small strips about 1.2 to 2 mm wide and 20 mm long.

These strips of vascular tissue were immersed in physiological saline (composition, expressed in \(\text{mmol/l}\): sodium
- 20 -

chloride 137; potassium chloride 2.7; calcium chloride 1.8; sodium dihydrogen phosphate 0.4; sodium hydrogen carbonate 11.9; magnesium chloride hexahydrate 1.1; dextrose 5.9; ethylenediaminetetraacetic acid disodium salt 0.027 and; ascorbic acid 0.057), oxygenated with a mixture of 95% oxygen and 5% carbon dioxide and maintained at a temperature of 37°C. They were then subjected, for 4 h, to a traction of 4 g, reduced to 2 g just before the start of the experiment. The tissue was then contracted with the compound to be studied and the resulting tension was recorded using a Grass polygraph, model 7D and a force transducer. Two concentration-effect curves were plotted, with cumulative concentrations of compound (from 100 nmol/l to 3 mmol/l), followed by addition to the bath of an α1-antagonist, alfuzosin, at the concentration of 1 μmol/l which was left in contact with the tissue for 30 min. Another concentration-effect curve was then plotted and compared with the second control curve.

The α1-agonist effect is measured by the concentration which induces a contraction equal to 50% of the maximum effect. For the compounds of the invention, this concentration ranges between 1.3 and 2.6 μmol/l.

These results show that the compounds of the invention exhibit agonist properties in vitro towards α1-type adrenergic receptors. The compounds of the invention may thus be used in the treatment of urinary incontinence.

The compounds of the invention may be in any suitable form, in combination with any suitable excipient, for oral or parenteral administration; for example in the form of tablets, dragees, capsules, solutions, etc.
The daily dosage may range from 0.1 to 20 mg/kg via the oral route.

The present invention provides a compound of the invention for use in the treatment of the human or animal body.

The present invention further provides a compound of the present invention for use in the treatment of diabetes, obesity, hypotension, post-operative paralytic ileus, asthma or urinary incontinence.

The present invention provides a compound of the present invention in the manufacture of a medicament for the treatment of diabetes, obesity, hypotension, post-operative paralytic ileus, asthma or urinary incontinence.

The compounds of the present invention can be used in a method of treating or preventing diabetes, obesity, hypotension, post-operative paralytic ileus, asthma or urinary incontinence in a subject which comprises administering to that subject an effective amount of a compound of the present invention.
Scheme 1

\[
\begin{array}{c}
\text{Scheme 1} \\
\begin{align*}
&\text{\( \text{R}_1 \text{N-\(\text{CO}_2\text{t-Bu}\)} \)} \\
\text{F}_3\text{CCO}_2\text{H} \\
&\text{\( \text{N-H} \)} \\
&\text{Cl} \\
&\text{\( \text{R}_1 \text{N-\(\text{N-H}\)} \)}
\end{align*}
\end{array}
\]
Scheme 2

1) R₂I₄
2) (R₄O)₃P₈
3) H₂O₄⁺

1) H₂O₂
2) (R₅O)₂SO₂

R₅ = alkyl
ArX, Pd(0)

Ar = 2-pyridyl,
3,4-dimethoxyphenyl
Scheme 3

1) R$_3$Li
2) HOCNMe$_2$

R$_g$ = alkyl, aryl

1) KH$_4$OH
2) CDI

oxidn.

R$_g$ = H, alkyl

1) KH$_4$OH
2) CDI

oxidn.

R$_g$ = H, alkyl
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A 5,6-dihydro-4H-thieno[3,4-c]pyrrole derivative of formula (I)

![Chemical Structure](image)

in which R₁ represents a cyano group; a C₁₋₄ alkoxy group; a C₁₋₄ alkylthio group; a C₁₋₄ alkylsulphonyl group; a pyridyl group; a 3,4-dimethoxyphenyl group; a cyclopropyl group which is optionally substituted with one or two alkyl groups; a group COR where R is a C₁₋₄ alkyl group, a phenyl group or a piperidyl group; a benzyl group, the phenyl ring of which is substituted with one or more halogen atoms and/or linear or branched C₁₋₄ alkyl groups, linear or branched C₁₋₄ alkoxy groups or groups CO₂R' where R' is a linear or branched C₁₋₄ alkyl group; or a naphthylmethyl group; or a pharmaceutically acceptable acid addition salt thereof.

2. A salt according to claim 1 which is a hydrochloride or a methanesulphonate salt.

3. A compound according to claim 1 or 2 in which R₁ is methoxy or methylthio.

4. 1-Methoxy-5-[(4,5-dihydro-1H-imidazol-2-yl)methyl]-5,6-dihydro-4H-thieno[3,4-c]pyrrole dihydrochloride or 1-Methylthio-5-[(4,5-dihydro-1H-imidazol-2-yl)methyl]-5,6-dihydro-4H-thieno[3,4-c]pyrrole dihydrochloride.

5. A process for the preparation of a compound of formula (I) as defined in any one of claims 1 to 3, in which a
compound of formula (II)

in which \( R_1 \), which is as defined as in claim 1 or 3, is reacted with 2-chloromethyl-4,5-dihydro-1H-imidazole, in the presence of N,N-diisopropylethylamine and, if desired, converting the compound of formula (I) into a pharmaceutically acceptable acid addition salt thereof.

6. A process according to claim 4 substantially as described in Example 1.

7. A compound as defined in any one of claims 1 to 4 when obtained by a process as defined in claim 5 or 6.

8. 1,1-Dimethylethyl 1-borono-5,6-dihydro-4H-thieno[3,4-c]pyrrole-5-carboxylate or an ester thereof.

9. Pharmaceutical composition, which comprises a compound of formula (I) as defined in any one of claims 1 to 4 or 7, in combination with an excipient.

10. A method for treating or preventing diabetes, obesity, hypotension, post-operative paralytic ileus, asthma or urinary incontinence in a subject which comprises administering to that subject a compound as defined in any one of claims 1 to 4 or 7.
11. The steps, features, compositions and compounds disclosed herein or referred to or indicated in the specification and/or claims of this application, individually or collectively, and any and all combinations of any two or more of said steps or features.

DATED this NINTH day of MAY 1995

Synthelabo

by DAVIES COLLISON CAVE
Patent Attorneys for the applicant(s)
Abstract

5,6-DIHYDRO-4H-THIENO[3,4-c]PYRROLE DERIVATIVES,
THEIR PREPARATION AND THEIR THERAPEUTIC APPLICATION.

A 5,6-dihydro-4H-thieno[3,4-c]pyrrole derivative of
formula (I)

\[
\begin{array}{c}
\text{R} \\
\text{N} \\
\text{R}_1 \\
\end{array}
\]

in which \( R_1 \) represents a cyano group; a \( C_{1-4} \) alkoxy group; a \( C_{1-4} \) alkylthio group; a \( C_{1-4} \) alkylsulphonyl group; a pyridyl group; a 3,4-dimethoxyphenyl group; a cyclopropyl group which is optionally substituted with one or two alkyl groups; a group \( \text{COR} \) where \( R \) is a \( C_{1-4} \) alkyl group, a phenyl group or a piperidyl group; a benzyl group, the phenyl ring of which is substituted with one or more halogen atoms and/or linear or branched \( C_{1-4} \) alkyl groups, linear or branched \( C_{1-4} \) alkoxy groups or groups \( \text{CO}_2R' \) where \( R' \) is a linear or branched \( C_{1-4} \) alkyl group; or a naphthylmethyl group; or a pharmaceutically acceptable acid addition salt thereof; process for their production; their use in the treatment of diabetes, obesity, hypotension, post-operative ileus, asthma and urinary incontinence and a synthetic intermediate.
END