Description

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to novel pyrido[2,3-f][1,4]-thiazepines and novel pyrido[3,2-b][1,5]-benzothiazepines. These compounds are inhibitors of calcium ion uptake into smooth muscle tissue, and act to relax or prevent contraction of the tissue mediated by calcium mechanisms. The compounds are active antihypertensives and bronchodilators.

These compounds are useful for the treatment of cardiovascular disorders, including hypertension, ischemia, angina, congestive heart failure, migraine, myocardial infarction and stroke. The compounds are also useful for the treatment of other disorders such as hypersensitivity, allergy, asthma, dysmenorrhea, esophageal spasm, gastrointestinal motility disorders, glaucoma, premature labor and urinary tract disorders. The present invention also relates to a process for preparing these compounds, compositions thereof, methods of use and novel intermediates.

2. Related Disclosure

United States Patent No. 4,285,955 and United States Patent No. 4,483,985 (which is a divisional of the aforementioned patent) disclose acyclic sulfone substitution on simple dihydropyridines which possess calcium channel antagonist activity. However, the compounds in question are chemically distinct from the compounds of the present invention.

DE-A-2815088 describes pyrido-[3,2-b][1,5]benzothiazepines which are substituted with a 1-piperazinyl group at the 5 position of the thiazepine ring. The compounds are stated to be useful as antihistamines, orexigenics and antianaphylactics.

FR-A-2511683 describes pyrido-[3,2-b][1,5]benzothiazepines similar to those of DE-A-2815088, wherein the 1-piperazinyl group is substituted at its 4 position with a carbonyl group or a thiocarbonyl group. Preferred carbonyl groups are alkoxycarbonyl groups. The compounds are stated to be non-orexigenic antihistamines and antianaphylactics.

Mannhold *et al.* in Pharmazie Heute vol. 3 (104), pages 139-147 (1983) describe a study of structure-activity relationships in calcium antagonists, including 1,4-dihydropyridine derivatives. They determined that the following features are essential for calcium antagonist activity in 1,4-dihydropyridine derivatives:(1) a dihydropyridine ring, (2) a secondary nitrogen at the 1 position of the dihydropyridine ring, and (3) a bulky substituent at the 4 position of the dihydropyridine ring. They also determined that the presence of ester groups at the 3 and 5 positions of the dihydropyridine ring in calcium antagonists such as Nifedipine is not essential for the calcium antagonist activity.

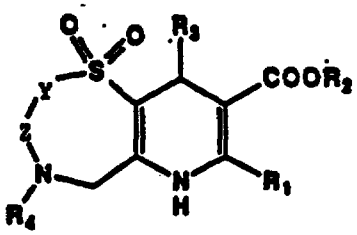
EP-A-0225175 describes 1,4-dihydropyridine derivatives useful as calcium antagonists. The principal characterising feature of these derivatives is the presence of a 5 or 6 membered unsaturated nitrogen containing ring which is optionally substituted and/or optionally fused to a phenyl ring, and which is coupled to the 2 position of the 1,4-dihydropyridine ring through a methyleneoxy, methylene amino, methyleneimino, methylenethio or methylenesulfoxy group.

10-Phenyl-2H-thiopyranol[3,2-b]quinolines are disclosed in Pagani, G.P.A., J. Chem. Soc., Perkin Trans. 2, 1392 (1974). However, these compounds are not calcium channel antagonists.

United States Patent No. 4,532,248 discloses a broad genus of dihydropyridines, including cyclic sulfones fused to a dihydropyridine nucleus. Cardiotonic activity is claimed for the entire genus. The compounds of the present invention, on the other hand, are potent calcium antagonists with pharmacologic activity opposite to that claimed in United States Patent No. 4,532,248.

SUMMARY OF THE INVENTION

The present invention is directed to pyrido[2,3-f][1,4]thiazepines and pyrido[3,2-b][1,5]benzothiazepines of the general formula



where

Y and Z may be CH_2, or together Y and Z may form a fused phenyl ring;

R_1 may be hydrogen, amino, C_1-C_8 straight or branched chain alkyl, trifluoromethyl or alkoxymethyl;

R_2 may be C_1-C_8 straight or branched chain alkyl, benzyl, 3-piperidyl, N-substituted 3-piperidyl, N-substituted 2-pyrrolidinyl methylene or substituted alkyl;

wherein said N-substituted 3-piperidyl and said N-substituted 2-pyrrolidinyl methylene may be substituted with C_1-C_8 straight or branched chain alkyl or benzyl, and said substituted alkyl may be substituted with C_1-C_8 alkoxy, C_2-C_8 alkanoyloxy, phenylacetyloxy, benzoyloxy, hydroxy, halogen, p-tosyloxy, mesyloxy, amino, carboalkoxy or NR_5R_6;

R_3 may be 2-pyridyl, 3-pyridyl, 2-thienyl, 3-thienyl, 2,1,3-benzoxadiazolyl, 2,1,3-benzthiadiazolyl or substituted phenyl;

wherein said substituted phenyl may be substituted at any of positions 2-6 with hydrogen, C_1-C_8 straight or branched chain alkyl, C_1-C_8 alkoxy, cyano, C_1-C_4 carboalkoxy, C_1-C_8 alkylthio, difluoromethoxy, difluoromethylthio, C_1-C_8 alkylsulfonyl, halogen, nitro or trifluoromethyl;

R_4 may be hydrogen, C_1-C_8 straight or branched chain alkyl, C_3-C_7 cycloalkyl, phenyl, benzyl, substituted benzyl, formyl, acetyl, t-butyloxy carbonyl, propionyl, substituted alkyl or $R_7CH_2C=O$;

wherein said substituted benzyl may be substituted with halogen, trifluoromethyl, C_1-C_8 straight or branched chain alkyl or C_1-C_8 alkoxy, and said substituted alkyl may be substituted with amino, C_1-C_4 dialkyl amino, C_1-C_8 alkoxy, hydroxy or halogen;

R_5 and R_6 may be the same or different and may be hydrogen, C_1-C_8 straight or branched chain alkyl, C_3-C_7 cycloalkyl, phenyl, benzyl, phenethyl or R_5 and R_6 together may form a heterocyclic ring selected from the group consisting of piperidino, pyrrolidino, morpholino, thiomorpholino, piperazino or an N_4-substituted derivative of piperidine;

wherein said N-substituted heterocyclic ring may be substituted with hydrogen, C_1-C_8 straight or branched chain alkyl, benzyl, benzhydryl, phenyl or substituted phenyl;

wherein said substituted phenyl may be substituted with hydrogen, C_1-C_8 alkoxy, halogen, C_1-C_8 straight or branched chain alkyl, nitro or trifluoromethyl;

R_7 may be amino, C_1-C_4 dialkyl amino, C_1-C_8 alkoxy, hydroxy or halogen; and

optical antipodes (enantiomers or diasteriomers) or pharmaceutically acceptable salts thereof such as salts of organic and inorganic acids such as hydrochloric, hydrobromic, fumaric, maleic, p-toluene sulfonic, methyl sulfonic acid and the like.

Also included in this invention is a process for preparing the compounds described above, said process disclosed in detail hereinafter. A further part of the present invention are certain intermediates and the process for the preparation thereof.

The compounds of the above formula inhibit the uptake of calcium ions into smooth muscle, and therefore act to relax or prevent calcium ion-mediated contraction of smooth muscle tissue. These compounds are useful for the treatment of cardiovascular disorders, including hypertension, ischemia, angina, congestive heart failure, myocardial infarction and stroke. The compounds are also useful for the treatment of other disorders such as hypersensitivity, allergy, asthma, bronchospasm, dysmenorrhea, esophageal spasm, gastrointestinal motility disorders, glaucoma, premature labor and urinary tract disorders.

DETAILED DESCRIPTION OF THE INVENTION

The invention in its broadest aspects relates to pyrido[2,3-f][1,4]thiazepines and pyrido[3,2-b][1,5]-benzothiazepines which inhibit the uptake of calcium ions into smooth muscle tissue. The compounds which possess this activity are shown in the formula above.

The preferred compounds of the present invention are those in which

R_1 is methyl:

R_2 is ethyl or substituted C_1-C_8 alkyl wherein the substituent is acetoxy, amino or NR_5R_6 wherein R_5 and R_6 are as previously defined;

R_3 is substituted phenyl;

R_4 is hydrogen, C_1-C_8 straight or branched chain alkyl, benzyl, formyl, $R_7CH_2C=O$ or t-butyloxy carbonyl;

R_7 is amino;

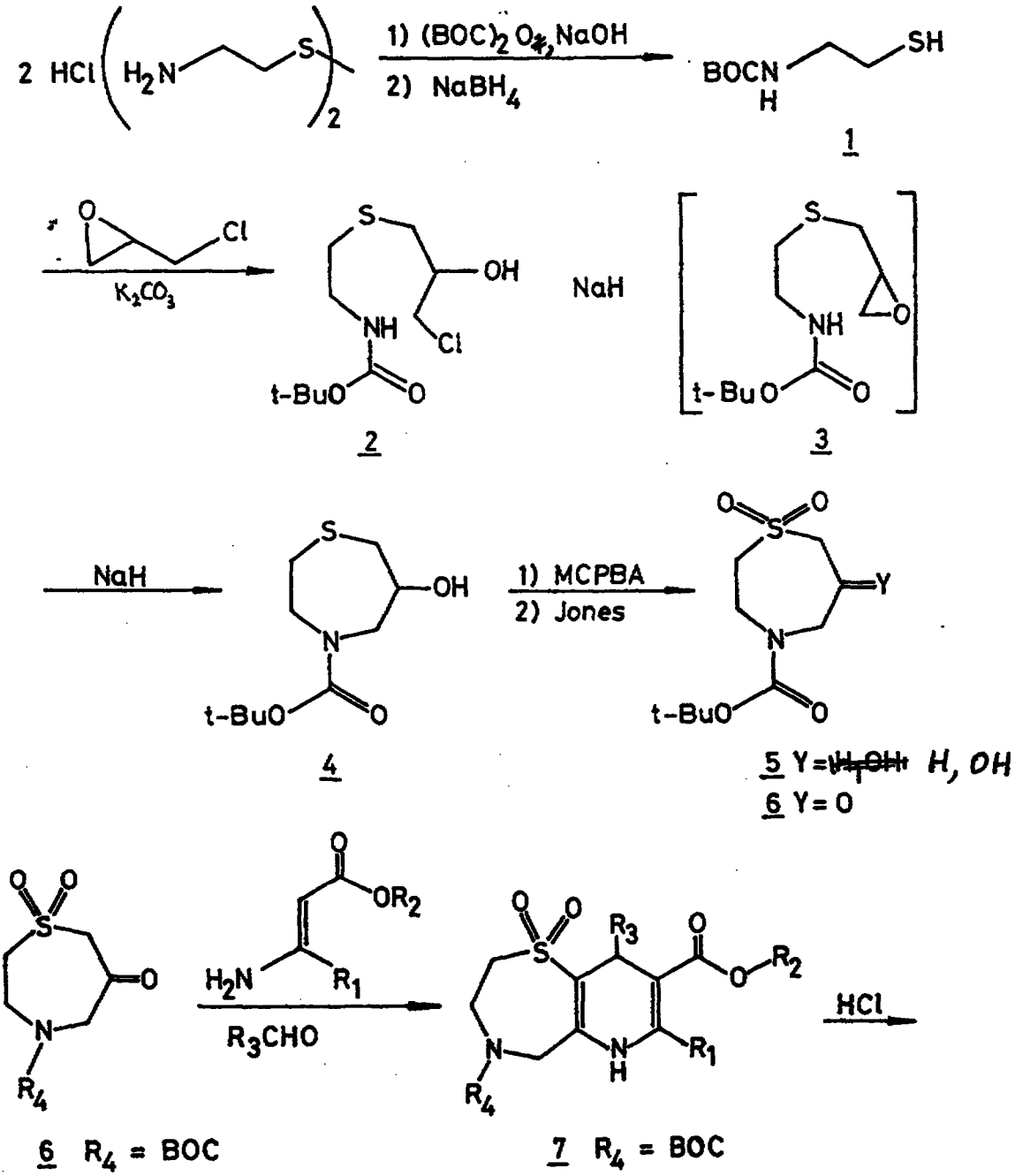
and the optical antipodes (enantiomers or diastereoisomers) or the pharmaceutically acceptable salts thereof.

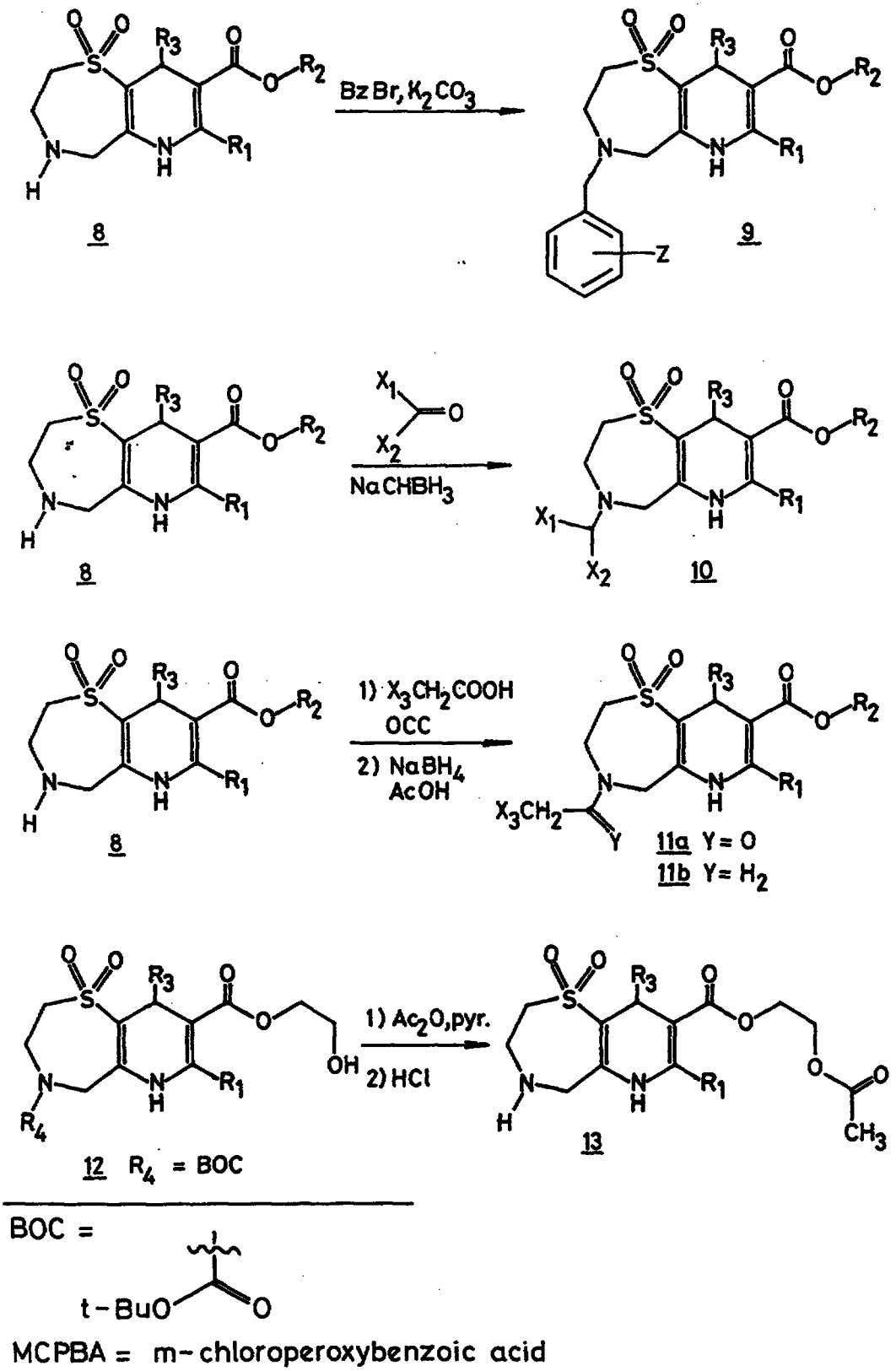
Particularly, the preferred compounds of the present invention are:

1. 2-(N-benzyl-N-methylamino)ethyl 9-(2,3-dichlorophenyl)-1,1-dioxo-2,3,4,5,6,9-hexahydro-7-methyl-pyrido[2,3-f][1,4]thiazepine-8-carboxylate;
2. 2-(N-benzyl-N-methylamino)ethyl 9-(2,3-dichlorophenyl)-4,7-dimethyl-1,1-dioxo-2,3,4,5,6,9-hexahydro-pyrido[2,3-f][1,4]thiazepine-8-carboxylate;
3. Ethyl 9-(2,3-dichlorophenyl)-1,1-dioxo-2,3,4,5,6,9-hexahydro-7-methyl-pyrido[2,3-f][1,4]thiazepine-8-carboxylate;
4. Ethyl 9-(2,3-dichlorophenyl)-1,1-dioxo-4-ethyl-2,3,4,5,6,9-hexahydro-7-methyl-pyrido[2,3-f][1,4]-thiazepine-8-carboxylate;
5. Ethyl 9-(2,3-dichlorophenyl)-4,7-dimethy-1,1-dioxo-2,3,4,5,6,9-hexahydropyrido[2,3-f][1,4]thiazepine-8-carboxylate;
6. Ethyl 4,7-dimethyl-1,1-dioxo-2,3,4,5,6,9-hexahydro-9-(2,3,4,5,6-pentafluorophenyl)-pyrido[2,3-f][1,4]-thiazepine-8-carboxylate;
7. Ethyl 1,1-dioxo-2,3,4,5,6,9-hexahydro-7-methyl-9-(2,3,4,5,6-pentafluorophenyl)-pyrido[2,3-f][1,4]-thiazepine-8-carboxylate;
8. Ethyl 1,1-dioxo-4-ethyl-2,3,4,5,6,9-hexahydro-7-methyl-9-(3-nitrophenyl)-pyrido[2,3-f][1,4]-thiazepine-8-carboxylate;
9. Ethyl 4-(2,3-dichlorophemyl)-5,5-dioxo-10-formyl-2-methyl-1,4,10,11-tetrahydropyrido[3,2-b][1,5]-benzothiazepine-3-carboxylate;
10. 2-Acetoxyethyl 9-(2,3-dichlorophenyl)-4,7-dimethyl-1,1-dioxo-2,3,4,5,6,9-hexahydropyrido[2,3-f][1,4]-thiazepine-8-carboxylate;
11. 2-Pivaloyloxyethyl 9-(2,3-dichlorophenyl)-4,7-dimethyl-1,1-dioxo-2,3,4,5,6,9-hexahydropyrido[2,3-f]-[1,4]thiazepine-8-carboxylate;
12. Ethyl 4-(2,3-dichlorophenyl)-2,10-dimethyl-5,5-di oxo-1,4,10,11-tetrahydropyrido[3,2-b][1,5]-benzothiazepine-3-carboxylate;
13. 2-(N-benzyl-N-methylamino)ethyl 4-(2,3-dichlorophenyl)-2,10-dimethyl-5,5-dioxo-1,4,10,11-tetrahydro-pyrido[3,2-b][1,5]benzothiazepine-3-carboxylate;
14. 2-(N,N-dibenzylamino)ethyl 4-(2,3-dichlorophenyl)-4,7-dimethyl-1,1-dioxo-2,3,4,5,6,9-hexahydro-pyrido[2,3-f][1,4]thiazepine-8-carboxylate;
15. 2-(N-benzyl-N-methylamino)ethyl 4-(2,3-dichlorophenyl)-4-ethyl-1,1-dioxo-2,3,4,5,6,9-hexahydro-7-methyl-pyrido[2,3-f][1,4]thiazepine-8-carboxylate; and
16. (N-benzyl-2-pyrolidinyl)methyl 9-(2,3-dichlorophenyl)-4,7-dimethyl-1,1-dioxo-2,3,4,5,6,9-hexahydropyrido[2,3-f][1,4]thiazepine-8-carboxylate.

The compounds of the present invention in which Y and Z are CH_2 (i.e. pyrido[2,3-f][1,4]thiazepines) are prepared as shown in Scheme I below.

SCHEME 1


2 HCl
1) (BOC)2O, NaOH
2) NaBH4
BOCN H
SH
1
K2CO3
Cl
OH
NH
Cl
t-BuO
O
2
NaH
3
NaH
1) MCPBA
2) Jones
Y
5 Y = H, OH
6 Y = O
4
R4
R1
R2
R3
HCl
6 R4 = BOC
7 R4 = BOC



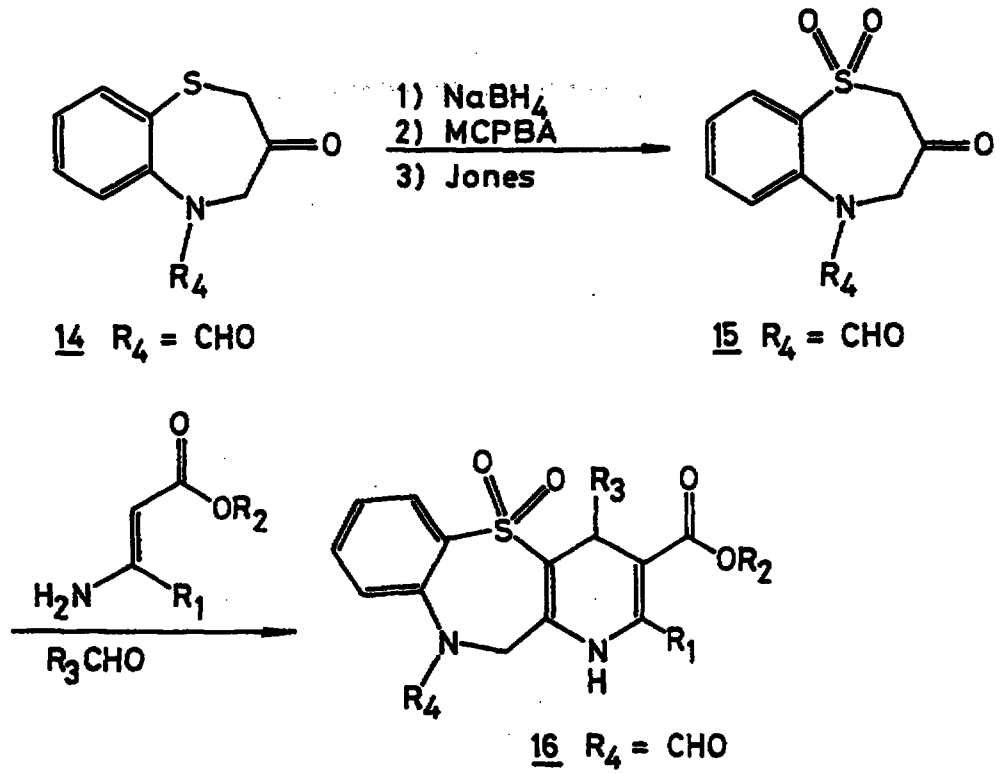
The thiazepinone (6) is a key intermediate in the synthesis of some dihydropyridines and was prepared in the following manner. Reaction of the BOC protected cystamine (1) (available in two steps as shown above, and described in Examples 1 and 2) with epichlorohydrin followed by cyclization of the intermediate chlorohydrin (2) resulted in thiazepinol (4). Cyclization of chlorohydrin (2) proceeds through epoxide (3). Nucleophilic attack by the carbamate anion opens the epoxide from the less hindered side resulting in

formation of the thiazepinol (4). The intermediate epoxide (3) can be isolated if only 1 equivalent of base is used, or the chlorohydrin (2) can be cyclized directly to (4) by the addition of 2 equivalents of base. Thiazepinol (4) was oxidized first with m-chloroperoxybenzoic acid to obtain 1,1-dioxo-thiazepinol (5) which was then oxidized with Jones reagent to obtain the 1,1-dioxothiazepinone (6).

The ketosulfone (6) was then reacted with an appropriately substituted aldehyde and substituted 3-aminoacrylate derivatives to obtain the dihydropyridines (7). The t-butyloxy protecting group was removed by exposure of the dihydropyridine (7) to acidic conditions to yield (8). The free amino functionality of (8) can then be alkylated by benzyl bromide or substituted benzyl bromides to give (9) (where Z=halo, alkyl alkyloxy, alkoxy, nitro, or trifluoromethyl), or reductively aminated with aldehydes or ketones to give (10) (where X_1 and X_2 are hydrogen, alkyl, cycloalkyl or together form a homocyclic or heterocylic ring). Additionally, the amine (8) can be acylated using various carboxylic acids (where X_3 is hydrogen, alkyl, amino, disubstituted amino, alkoxy, hydroxy or halogen) to give the amides (11a) which can then be reduced to the corresponding amines (11b). In the case where an alkoxy group is present on the ester side chain as in (12), it can be acylated and the t-BOC protecting group can be removed to give the compound (13) which can be benzylated, alkylated or acylated in a manner analogous to (8).

The compounds of the present invention in which Y and Z together form a phenyl ring (i.e. pyrido[3,2-b][1,5]benzothiazepines) are prepared as shown in Scheme 2 below.

SCHEME 2



1,1-Dioxo-benzothiazepenone (15) is prepared in three steps from known benzothiazepinone (14) as shown and as described by Federsel, H.J. et al., Tetrahedron Letters 21, 2429 (1980). The dihydropyridine (16) is prepared by reacting (15) with the appropriate aldehyde and substituted 3-aminoacrylate.

Pharmaceutical compositions containing a compound of the present invention as the active ingredient in intimate admixture with a pharmaceutical carrier can be prepared according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., intravenous, oral or parenteral. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid

preparations (such as, for example, suspensions, elixirs and solutions); or carriers such as starches, sugars, diluents, granulating agents, lubricants, hinders, disintegrating agents and the like in the case of oral solid preparations (such as, for example, powders, capsules and tablets). Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar-coated or enteric-coated by standard techniques. For parenterals, the carrier will usually comprise sterile water, though other ingredients, for example, to aid solubility or for preservative purposes, may be included. Injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like may be employed. The compounds may also be administered in the form of an aerosol. The pharmaceutical compositions will generally contain per dosage unit, e.g., tablet, capsule, powder, injection, teaspoonful and the like, from about 0.001 to about 100 mg/kg, and preferably from about 0.001 to about 20 mg/kg of the active ingredient.

The following examples describe the invention in greater particularity and are intended to illustrate but not limit the invention.

Example 1

Bis-N-(t-Butyloxycarbonyl)-cystamine

A mixture of cystamine dihydrochloride (46.95 g, 0.285 moles) in 1 L THF and sodium hydroxide (33.33 g, 0.833 mole) in 500 mL of water was treated with di-t-butyldicarbonate (100.0 g, 0.458 mole) and stirred at room temperature for 2 hours. The aqueous phase was separated and extracted with 2 X 500 mL of ether. The combined organic phases were dried with brine and $MgSO_4$ and evaporated under reduced pressure to afford the product as a white solid (78.2 g, 78% yield) D.C.I.M.S. (M+H) 325.

Example 2

N-(t-Butyloxycarbonyl)-2-aminoethanethiol

A solution of his N-(t-butyloxycarbonyl)-cystamine (77.37 g, 0.220 mole) from Example 1, in 1 L of ethanol was treated with $NaBH_4$ (32.5 g, 0.859 mmole). Vigorous gas evolution ensued and subsided in 40 minutes. The reaction was stirred for an additional half hour and was poured into 2.5 L of a cold dilute solution of citric acid (pH 6). The mixture was then extracted with 3 x 1L of chloroform. The combined organic extracts were dried with $MgSO_4$ and the solvents were removed under reduced pressure. The resulting residue was distilled (66°-73°C 0.25 torr) to obtain the product (41.5 g, 53% yield).

Example 3

(2-(t-Butyloxycarbonyl-amino)-ethyl)-(3-chloro-2-hydroxypropyl)-thioether

N-(t-butyloxycarbonyl)-aminoethanethiol (40 g, 225 mmole) from Example 2, and epichlorohydrin (35.4 g, 383 mmole) in 300 mL of ethanol were cooled to 0°C and treated with potassium carbonate (35.4 g). The reaction was warmed to room temperature over 90 minutes and filtered through celite. The volatiles were removed under reduced pressure to give a clear oil (62.09 g, 100% yield) D.C.I.M.S. 270(M+H).

Example 4

4-N-(t-Butyloxycarbonyl)-6-hydroxy-2,3,4,5,6,7-hexahydro-1,4-thiazepine

(2-(t-Butyloxycarbonyl-amino)-ethyl)-(3-chloro-2-hydroxypropyl)-thioether (30 g, 111.52 mmole) from Example 3, was dissolved in dimethylformamide (500 mL) at 0°C and treated with sodium hydride (9.81 g, 245 mmole) in 3 portions over 15 minutes. The reaction was allowed to warm to room temperature over 1 hour and 15 minutes, poured into 2.5 L ice water and extracted with 3 x 1 L chloroform. The combined organic extracts were dried with brine and Na_2SO_4, evaporated, and the resulting residue chromatographed (3:1 hexane:ethyl acetate, silica gel) to obtain the product as a white solid (12.47 g, 48% yield) D.C.I.M.S. 234(M+H) M.P. 80-82°C.

Example 5

4-N-(t-Butyloxycarbonyl)-1,1-dioxo-6-hydroxy-2,3,4,5,6,7-hexahydro-1,4-thiazepine

A solution of 4-N-(t-butyloxycarbonyl)-6-hydroxy-2,3,4,5,6,7-hexahydro-1,4-thiazepine (11.7 g, 50.6 mmole) from Example 4, in 100 mL of chloroform was added in a dropwise manner to a solution of m-chloroperbenzoic acid (19.2 g, 111 mmole) in chloroform (130 mL) over 1 hour. After the addition was complete, the reaction was stirred at ambient temperature for 2 hours. The reaction mixture was filtered and the filtrate concentrated under reduced pressure. The resulting residue was recrystallized from ethyl acetate-hexane to give the product (11.37 g, 85%) D.C.I.M.S. 266(M+H) M.P. 123-124°C.

Example 6

4-N-(t-Butyloxycarbonyl)-1,1-dioxo-2,3,4,5,6,7-hexahydro-1,4-thiazepin-6-one

4-N-(t-Butyloxycarbonyl)-1,1-dioxo-6-hydroxy-2,3,4,5,6,7-hexahydro-1,4-thiazepine (10.0 g, 37.7 mmole) from Example 5, was dissolved in 110 mL of acetone, cooled to 0°C and treated with 18.8 mL of freshly prepared Jones reagent. The reaction was stirred at ambient temperature for three hours and then treated with 5 mL of methanol. After 15 minutes, the reaction was filtered through magnesium sulfate and the filtrate immediately concentrated. The residue was filtered through a pad of silica gel using 3:1 chloroform-ethyl acetate to obtain the product (9.67 g, 87%) D.C.I.M.S. 264(M+H) M.P. 172-173°C.

Example 7

Ethyl 9-(2,3-Dichlorophenyl)-4-(t-butyloxycarbonyl)-1,1-dioxo-2,3,4,5,6,9-hexahydro-7-methylpyrido[2,3-f][1,4]thiazepine-8-carboxylate

A mixture of 4-N-(t-butyloxycarbonyl)-1,1-dioxo-2,3,4,5,6,7-hexahydro-1,4-thiazepin-6-one (2.00 g, 7.60 mmole) from Example 6, 2,3-dichlorobenzaldehyde (1.33 g, 7.60 mmole) and ethyl 3-aminocrotonate (0.98 g, 7.60 mmole) was heated to reflux in 40 mL of ethanol for 24 hours. The ethanol was removed under reduced pressure and replaced with 85 mL of toluene. The mixture was heated to reflux for 2 hours, cooled to room temperature and filtered to obtain the product (2.45 g, 61%).

Example 8

Ethyl 9-(2,3-Dichlorophenyl)-1,1-dioxo-2,3,4,5,6,9-hexahydro-7-methylpyrido-[2,3-f][1,4]thiazepine-8-carboxylate

A mixture of ethyl 9-(2,3-dichlorophenyl)-4-(t-butyloxycarbonyl)-1,1-dioxo-2,3,4,5,6,9-hexahydro-7-methylpyrido[2,3-f][1,4]thiazepine-8-carboxylate (2.45 g, 4.6 mmole) from Example 7, in ethyl acetate (150 mL) was cooled to 0°C and saturated with gaseous hydrogen chloride. The mixture was warmed to room temperature. The reaction was then again chilled to 0°C and shaken with 200 mL of cold 4 N NaOH. The aqueous layer was separated and extracted with 2 x 100 mL of chloroform. The ethyl acetate layer was dried with brine and the combined organic extracts were dried over Na_2SO_4. The solvents were evaporated under reduced pressure and the residue triturated with ether to give the product (1.86 g, 94% yield).

Example 9

Ethyl 9-(2,3-Dichlorophenyl)-4,7-dimethyl-1,1-dioxo-2,3,4,5,6,9-hexahydropyrido-[2,3-f][1,4]thiazepine-8-carboxylate

A mixture of ethyl 9-(2,3-dichlorophenyl)-1,1-dioxo-2,3,4,5,6,9-hexahydro-7-methylpyrido-[2,3-f][1,4]-thiazepine-8-carboxylate (0.500 g, 1.16 mmole) from Example 8, in acetonitrile (10 mL) was treated with formaldehyde (0.240 g, 37% aqueous solution) and sodium cyanoborohydride (0.062 g, 1.16 mmole). After 15 minutes, 6 drops of AcOH were added and the reaction was stirred for 1 hour. Then, 30 mL of water were added and the reaction mixture was extracted with 3 x 40 mL of chloroform. The pH was adjusted to 8 after the first extract. The combined organic extracts were dried with brine and Na_2SO_4 and then treated with 3 mL of triethylamine. After standing for 1.5 hours, the volatiles were removed under reduced pressure and the residue chromatographed (silica gel, 1.5% MeOH, 0.1% NH_3 in $CHCl_3$) to obtain the product as an oil which solidified on triturating with ether (0.479 g, 92% yield).

Example 10

Ethyl 4-N-Benzyl-9-(2,3-dichlorophenyl)-1,1-dioxo-2,3,4,5,6,9-hexahydro-7-methylpyrido[2,3-f][1,4]thiazepine-8-carboxylate

A mixture of ethyl 9-(2,3-dichlorophenyl)-1,1-dioxo-2,3,4,5,6,9-hexahydro-7-methylpyrido[2,3-f][1,4]-thiazepine-8-carboxylate (0.400 g, 0.92 mmole), benzyl bromide (0.190 g, 1.11 mmole), and potassium carbonate (0.213 g, 1.55 mmole) was heated in acetonitrile (10 mL) for 3 hours. The reaction was cooled, the solids filtered, and the solvent was evaporated under reduced pressure. The residue was then chromatographed (silica gel 2:1 hexane:ethyl acetate) to give the product which was crystallized from ether (0.313 g, 65% yield).

Example 11

2-(N-benzyl-N-methylamino)ethyl 4-t-butyloxycarbonyl-9-(2,3-dichlorophenyl)-1,1-dioxo-5a-hydroxy-2,3,4,5,5a,6,9,9a-octahydro-7-methyl-pyrido[2,3-f][1,4]thiazepine-8-carboxylate

A mixture of 4-N-(t-butyloxycarbonyl)-1,1-dioxo-2,3,4,5,6,7-hexahydro-1,4-thiazepin-6-one (8.39 g, 31.9 mmole) from Example 6, 2,3-dichlorobenzaldehyde (5.58 g, 31.9 mmole) and 2-(N-benzyl-N-methylamino)-ethyl 3-aminocrotonate (7.91 g, 31.9 mmole) were heated to reflux in 40 mL of ethanol for 17 hours. The reaction was cooled to room temperature, filtered, and the solid washed with 50 mL of ether to obtain the title compound (10.72 g, 50% yield) D.C.I.M.S. (M + H) 668.

Example 12

2-(N-Benzyl-N-methylamino)ethyl 9-(2,3-dichlorophenyl)-4,7-dimethyl-1,1-dioxo-5a-hydroxy-2,3,4,5,6,9-hexahydro-7-pyrido-[2,3-f][1,4]thiazepine-8-carboxylate

4-N-(t-Butyloxycarbonyl)-1,1-dioxo-2,3,4,5,6,7-hexahydro-1,4-thiazepin-6-one (2.10 g, 3.2 mmole) from Example 6, was treated as in Examples 8 and 9 to obtain the product which was recrystallized from isopropanol (1.23 g, 70% yield).

Example 13

Optical Resolution of Ethyl 9-(2,3-dichlorophenyl)-1,1-dioxo-2,3,4,5,6,9-hexahydro-7-methylpyrido[2,3-f][1,4]-thiazepine-8-carboxylate

Racemic ethyl 9-(2,3-dichlorophenyl)-1,1-dioxo-2,3,4,5,6,9-hexahydro-7-methylpyrido[2,3-f][1,4]-thiazepine-8-carboxylate (2.41 g, 5.59 mmole) from Example 8, was dissolved in 100 ml of hot methanol.

This solution was combined with D-dibenzoyl tartrate (2.10 g, 5.59 mmole), and the solvent was removed under reduced pressure. The residue was crystallized 3 times from ethyl acetate. The salt was converted to the free base by extraction of a chloroform solution of the salt with aqueous ammonia. $[\alpha]^D$ = +7.7° (C, 0.41, $CHCl_3$). The (-) isomer was obtained in a similar fashion using L-dibenzoyl tartaric acid; $[\alpha]^D$ = -8.0 (C, 0.40, $CHCl_3$).

Example 14

5-N-Formyl-3-hydroxy-2,3,4,5-tetrahydro-[1,5]-benzothiazepine

To a solution of 5-N-formyl-3-hydroxy-2,3,4,5-tetrahydro-[1,5]-benzothiazepin-3-one (0.480 g, 2.31 mmole) prepared as described by Federsel, H. J. et al., Tetrahedron Letters 21, 2229 (1986), in 10 mL of ethanol was added $NaBH_4$ (0.090 g, 2.38 mmole). The reaction was stirred at room temperature for 1 hour. The reaction was partitioned between a saturated NH_4Cl solution and chloroform. The organic layer was washed with water, brine and dried over $MgSO_4$. The solvents were removed under reduced pressure to give the product as an oil (0.452 g, 94% yield) D.C.I.M.S. 210 [M+H].

Example 15

1,1-Dioxo-5-N-formyl-3-hydroxy-2,3,4,5-tetrahydro-[1,5]-benzothiazepine

A solution of m-chloroperoxybenzoic acid (0.946 g, 5.5 mmole) in 20 ml of chloroform was treated with 5-N-formyl-3-hydroxy-2,3,4,5-tetrahydro-[1,5]-benzothiazepine (0.450 g, 1.93 mmole) from Example 14, in 10 mL of chloroform. The reaction was stirred for 16 hours at room temperature and the solvents were removed under reduced pressure. The residue was triturated with 2 x 10 mL water and the water was evaporated to obtain the product (0.443 g, 95% yield) D.C.I.M.S. 242 [M+H].

Example 16

1,1-Dioxo-5-N-formyl-2,3,4,5-tetrahydro-[1,5]-benzothiazepine-3-one

A solution of 1,1-dioxo-5-N-formyl-3-hydroxy-2,3,4,5-tetrahydro-[1,5]-benzothiazepine (0.443 g, 1.83 mmole) from Example 15, in 5 mL of acetone was treated with Jones reagent (0.54 mL, 1.40 mmole), and the solution was heated to reflux for 15 minutes. An additional 0.15 mL of Jones reagent was added and the reaction was heated for 20 minutes longer. The cooled solution was filtered through $MgSO_4$, and the solvents were removed under reduced pressure. The residue was triturated with chloroform and filtered. Evaporation of the filtrate afforded the product (0.418 g, 95% yield) D.C.I.M.S. 240 [M+H].

Example 17

Ethyl 4-(2,3-Dichlorophenyl)-5,5-dioxo-10-formyl-2-methyl-1,4,10,11-tetrahydropyrido[3,2-b][1,5]-benzothiazepine-3-carboxylate

A solution of 1,1-dioxo-5-N-formyl-2,3,4,5-tetrahydro-[1,5]-benzothiazepin-3-one (0.410 g, 1.71 mmole) from Example 16, 2,3-dichlorobenzaldehyde (0.297 g, 1.71 mmole) and ethyl 3-aminocrotonate (0.219 g, 1.71 mmole) in 7 mL of ethanol was heated to reflux for 18 hours. The solvent was removed under reduced pressure and the residue was chromatographed (silica gel, 1:1 hexane:ethyl acetate) to obtain the product as an oil (0.75 g, 86% yield). The product was recrystallized from chloroform-ether.

Example 18

2-Hydroxyethyl 4-t-Butyloxycarbonyl-9-(2,3-dichlorophenyl)-1,1-dioxo-5a-hydroxy-2,3,4,5,5a,6,9,9a-octahydro-7-methylpyrido-[2,3-f][1,4]thiazepine-8-carboxylate

A mixture of 4-N-(t-butyloxycarbonyl)-1,1-dioxo-2,3,4,5,6,7-hexahydro-1,4-thiazepine-6-one (9.06g, 34.5 mmole) from Example 6, 2,3-dichlorobenzaldehyde (6.03 g, 34.5 mmole) and 2-hydroxyethyl 3-aminocrotonate (5.00 g, 34.5 mmole) was heated to reflux in 200 mL of ethanol for 24 hours. The ethanol was removed under reduced pressure and the residue was heated in refluxing toluene for 2 hours. After cooling a precipitate was filtered to give 6.75 g of the title compound. Evaporation of the filtrate and chromatography (2.5:1, ethyl acetate:hexane) produced 3.78 g of product.

Example 19

2-Acetoxyethyl 9-(2,3-Dichlorophenyl)-1,1-dioxo-2,3,4,5,6,9-hexahydro-7-methylpyrido[2,3-f][1,4]thiazepine-8-carboxylate

2-Hydroxyethyl 4-t-butyloxycarbonyl-9-(2,3-dichlorophenyl)-1,1-dioxo-5a-hydroxy-2,3,4,5,5a,6,9,9a-octahydro-7-methylpyrido[2,3-f][1,4]thiazepine-8-carboxylate (0.500 g, 0.97 mmole) from Example 18, was dissolved in 5 mL of pyridine and 5mL of acetic anhydride, and stirred for 2 hours. The solvents were removed under reduced pressure, and the residue was slurried in 25 mL of ethyl acetate and cooled to 0°C, after which the mixture was saturated with gaseous HCl. After 90 minutes, the reaction was poured into 30 mL of 4H NaOH. The ethyl acetate layer was separated and dried with brine, and the aqueous layer was extracted with 2 x 30 mL of chloroform. The combined organic extracts were dried with sodium sulfate and evaporated, and the residue was chromatographed (2% methanol, 0.1% ammonia in chloroform, silica gel) to give the product as a white solid (0.351 g, 89% yield).

Example 20

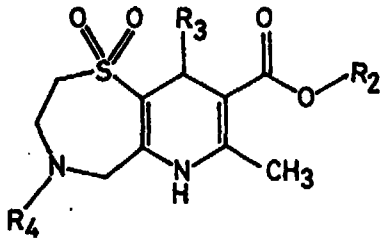
2-Acetoxyethyl 9-(2,3-Dichlorophenyl)-4,7-dimethyl-1,1-dioxo-2,3,4,5,6,9-hexahydro-pyrido[2,3-f][1,4]-thiazepine-8-carboxylate

A mixture of 2-acetoxyethyl 9-(2,3-dichlorophenyl)-1,1-dioxo-2,3,4,5,6,9-hexahydro-7-methyl-pyrido[2,3-f][1,4]thiazepine-8-carboxylate (0.880 g, 1.69 mmole) from Example 19, and 1 mL of 38% aqueous formaldehyde solution in 20 mL of acetonitrile was treated with sodium cyanoborohydride (0.070 g, 1.69 mmole). After stirring for 1 hour, 0.5 mL of acetic acid was added, and the reaction was stirred for another 2 hours. After the addition of 40 mL of water and adjustment of the pH to 9 with 6N sodium hydroxide, the reaction was extracted with 3 x 30 mL of chloroform. The combined organic extracts were dried with sodium sulfate, the solvent was removed under reduced pressure, and the residue was chromatographed (2% methanol, 0.1% ammonia in chloroform on silica gel) to obtain the title compound (0.743 g, 82%).

The physical constants for these dihydropyridine examples as well as a number of additional representative compounds of the present invention are presented below in Table 1.

TABLE 1

Additional Representative Compounds



R_3 = Phenyl Substitution	R_4	R_2	Molecular Formula	D.C.I.M.S. [M+H]	M.P. °C
2,3-dichloro	H	ethyl	$C_{18}H_{20}C_{12}N_2O_4S.HCl.3/2\ H_2O$	431	145-7
2,3-dichloro	BOC	ethyl	$C_{23}H_{28}C_{12}N_2O_4S$	531	228-30
pentafluoro	BOC	ethyl	$C_{23}H_{25}F_5N_2O_4S$	553	224-6
2,3-dichloro	Bz	ethyl	$C_{25}H_{26}C_{12}N_2O_4S$	521	219(d)
pentafluoro	H	ethyl	$C_{18}H_{17}F_5N_2O_4S$	453	211-3
2,3-dichloro	Me	ethyl	$C_{19}H_{22}C_{12}N_2O_4S$	445	206-8
2-CF_3	BOC	ethyl	$C_{25}H_{29}F_3N_2O_6S$	531	213-5
2-CF_3	H	ethyl	$C_{19}H_{21}F_3N_2O_4S$	431	125(d)
pentafluoro	Me	ethyl	$C_{19}H_{19}F_5N_2O_4S$	467	212-5
2,3-dichloro	CHO	ethyl	$C_{23}H_{20}Cl_2N_2O_5S$*	507	185-7
2,3-dichloro	Et	ethyl	$C_{20}H_{24}Cl_2N_2O_4S.HCl.3/2\ H_2O$	459	185-8
2-Cl, 6-F	H	ethyl	$C_{18}H_{20}ClFN_2O_4S$	415	118-20
3-nitro	H	ethyl	$C_{18}H_{21}N_3O_6S$	408	186-8
2,3-dichloro	Pr	ethyl	$C_{21}H_{26}Cl_2N_2O_4S$	473	196-8
2-nitro	H	ethyl	$C_{18}H_{21}N_3O_6S$	408	171-3

* Benzothiazepine ring system

TABLE 1 - cont'd

Additional Representative Compounds

R_3 = Phenyl Substitution	R_4	R_2	Molecular Formula	D.C.I.M.S. [M+H]	M.P. °C
2,3-dichloro	iPr	ethyl	$C_{21}H_{28}Cl_2N_2O_4S$	473	217-8
2,3,-dichloro	heptyl	ethyl	$C_{25}H_{34}Cl_2N_2O_4S$	529	142-4
2,3-(213 oxadialzolyl)	H	ethyl	$C_{18}H_{20}N_4O_5S \cdot HCl$	405	216-9
3-nitro	Et	ethyl	$C_{20}H_{23}N_3O_6S \cdot HCl \cdot 3/2\ H_2O$	436	195(d)
2,3-dichloro	H	ethyl	$C_{18}H_{20}Cl_2N_2O_4S$ (-)	431	190(d)
2,3-dichloro	H	ethyl	$C_{18}H_{20}Cl_2N_2O_4S$ (+)	431	193(d)
2,3-dichloro	NH_2CH_2CO	ethyl	$C_{20}H_{23}Cl_2N_3O_5S$	488	166(d)
2,3-dichloro	H	N-Bz-N-Me-ethyl	$C_{26}H_{29}N_3O_4Cl_2S$	550	132-5
2,3-dichloro	Me	N-Bz-N-Me-ethyl	$C_{27}H_{31}N_3O_4Cl_2S$	564	166-8
2,3-dichloro	Me	N-Bz-N-Me-ethyl	$C_{27}H_{31}N_3O_4Cl_2S \cdot 2HCl \cdot H_2O$	564	173(d)
2,3-dichloro	Me	2-acetoxy-ethyl	$C_{21}H_{24}Cl_2N_2O_6S$	503	168-70
2,3-dichloro	Me	2-hydroxy-ethyl	$C_{19}H_{22}Cl_2N_2O_5S$	461	203-4
2,3-dichloro	H	2-acetoxy-ethyl	$C_{20}H_{24}Cl_2N_2O_6S$	489	179-81
2,3-dichloro	H	2-hydroxy-ethyl	$C_{18}H_{20}Cl_2N_2O_5S$	447	197-9
2,3-dichloro	H	cyclopropylmethyl	$C_{20}H_{22}Cl_2N_2O_4S$	457	199-200
2,3-dichloro	H	cyclopropylmethyl	$C_{21}H_{24}Cl_2N_2O_4S$	471	177-9
2,3-dichloro	H	2-i-butryloxy ethyl	$C_{23}H_{28}Cl_2N_2O_6S$	531	185-5
2,3-dichloro	Me	2-benzoyloxy-ethyl	$C_{26}H_{26}Cl_2N_2O_6S$	565	108-10
2,3-dichloro	Et	2-NBz(Me)-ethyl	$C_{28}H_{33}Cl_2N_3O_4S \cdot 2HCl \cdot H_2O$	578	171-3
3-nitro	Me	2-NBz(Me)-ethyl	$C_{27}H_{32}Cl_2N_4O_6S \cdot 2HCl \cdot H_2O$	541	148(d)
2,3-dichloro	Me	2-NBz_2-ethyl	$C_{33}H_{33}Cl_2N_3O_4S \cdot 2HCl \cdot H_2O$	640	175(d)
2,3-dichloro	Me	3-Ph-propyl	$C_{33}H_{33}Cl_2N_3O_4S \cdot HCl$	535	173(d)
2-chloro-3-NO_2	Me	ethyl	$C_{19}H_{23}ClN_2O_4S$	456	199-201

TABLE 1 - cont'd

Additional Representative Compounds

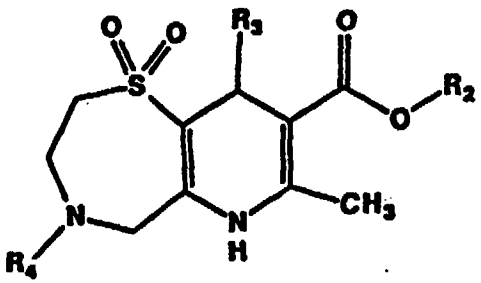
R_3 = Phenyl Substitution	R_4	R_2	Molecular Formula	D.C.I.M.S. [M+H]	M.P. °C
2,3-dichloro	i-Pr	2-acetoxyethyl	$C_{23}H_{28}Cl_2N_2O_6S$	531	181-3
2,3-dichloro	Et	2-acetoxyethyl	$C_{22}H_{26}Cl_2N_2O_6S$	517	187-9
2,3-dichloro	Bz*	2-acetoxyethyl	$C_{27}H_{28}Cl_2N_2O_6S$	579	102-4
2-chloro	Me	ethyl	$C_{15}H_{23}ClN_2O_4S$	411	223-4

* Bz = benzyl

Table 2, below, sets forth inhibition of nitrendipine binding as well as inhibition of calcium dependent smooth muscle contraction in terms of percent inhibition, for a number of representative compounds of the present invention.

TABLE 2

Calcium Channel Antagonist Activity



R_3 = Phenyl Substitution	R_4	R_2	P#166 Nit. Binding	P#176 Trach %INHB/μM	P#176 Aorta %INHB/μM
2,3-dichloro	H	ethyl	99, 105nM	73/1.0; 43/0.1	96/1.0; 85/0.1; 21/0.01
2,3-dichloro	BOC	ethyl	32% @ 1.0μM	0/2.0	18/1.0; 4/0.3
pentafluoro	BOC	ethyl	24% @ 1μM	7/2.0	37/1.0; 0/0.1
2,3-dichloro	Bz	ethyl	210nM	32/2.0; 10/0.1	79/1.0
pentafluoro	H	ethyl	90nM	98/2.0; 63/0.1; 13/0.01	95/1.0; 89/0.1; 61/0.01
2,3-dichloro	Me	ethyl	120nM	98/2.0; 80/0.1; 55/0.01	97/1.0; 96/0.1; 67/0.01
2-CF_3	BOC	ethyl	7% @ 1.0μM	50/2.0; 24/0.3	47/1.0; 37/0.1
2-CF_3	H	ethyl	360nM	73/2.0; 35/0.3; 38/0.1	83/1.0; 68/0.1; 37/0.01

TABLE 2 - cont'd

Calcium Channel Antagonist Activity

R_3 = Phenyl Substitution	R_4	R_2	P#166 Nit. Binding	P#176 Trach #INHB/μM	P#176 Aorta %INHB/μM
pentafluoro	Me	ethyl	53nM	95/1.0; 73/0.1; 35/0.01	97/1.0; 50/0.01
2,3-dichloro	Et	ethyl	60nM	90/1.0; 70/0.3; 33/0.01	96/1.0; 76/0.1; 19/0.01
2-Cl, 6-F	H	ethyl	870nM	88/2.0; 56/0.3	86/1.0; 4.8/0.01
3-nitro	H	ethyl	240nM	93/2.0; 58/0.03	100/1.0; 24/0.01
2,3-dichloro	Pr	ethyl	145nM	68/2.0; 53/0.3; 44/0.1; 30/0.03	100/1.0; 88/0.1; 53/0.01
2-nitro	H	ethyl		75/2.0; 45/0.3; 12/0.10	77/1.0; 47/0.1; 27/0.01
2,3-dichloro	iPr	ethyl	72nM	86/2.0; 61/0.3; 37/0.1	95/1.0; 83/0.1; 38/0.01
2,3-dichloro	hept	ethyl		27/2.0	44.1.0; 4/0.1
2,3-(2,1,3 oxadiazolyl)	H	ethyl	660nM	68/2.0; 22/0.3	83/1.0; 22/0.1
3-nitro	Et	ethyl		92/0.3; 73/0.1; 50/0.03	73/0.10; 5/0.01
2,3-dichloro	H	ethyl		54/2.0; 24/0.3; 2/0.1	69/1.0; 0/0.1; 0/.01
2,3-dichloro	H	ethyl		96/2.0; 47/0.1; 25/0.03	97/1.0; 67/0.1; 14/0.01
2,3-dichloro	NH_2CH_2CO	ethyl		36/2.0; 6/0.3	20/1.0

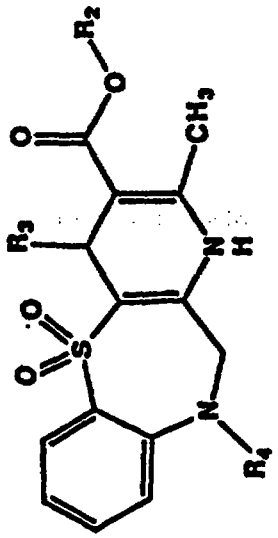
TABLE 2 - cont'd

Calcium Channel Antagonist Activity

R_3 = Phenyl Substitution	R_4	R_2	P#166 Nit. Binding	P#176 Trach #INHB/μM	P#176 Aorta %INHB/μM
2,3-dichloro	H	N-Bz-N-Me-ethyl	380nM	86/2.0; 62/0.3; 23/0.1	93/1.0; 48/0.1; 20/0.03
2,3-dichloro	Me	N-Bz-N-Me-ethyl	150nM	88/2.0; 71/0.3; 54/0.1; 28/0.03	
2,3-dichloro	Me	2-acetoxyethyl			89/1.0;26/0.1; 0/0.01
2,3-dichloro	Me	2-hydroxyethyl			95/10; 77/3.0; 62/1.0; 14/0.1
2,3-dichloro	H	2-acetoxyethyl			72/1.0; 62/0.3; 18/0.1
2,3-dichloro	H	2-hydroxyethyl			56/10; 0/1.0
2,3-dichloro	H	cyclopropylmethyl			
2,3-dichloro	H	cyclopropylmethyl			93/10; 86/3.0; 17/0.01

TABLE 2 - cont'd

Calcium Channel Antagonist Activity



R_3 = Phenyl Substitution	R_4	R_2	P#176 Trach %INHB/μM	P#176 Aorta %INHB/μM
2,3-dichloro	CHO	ethyl	73/2.0; 35/0.3; 38/0.01	74/1.0; 50/0.1; 33/0.01

The assay for inhibition of nitrendipine binding is performed using the following procedure:

Female, New Zealand white rabbits (1-2 kg) are sacrificed by cervical dislocation, and the heart is immediately removed, cleaned and chopped into small pieces. The tissue is homogenized in 5 x volume of 0.05M Hepes buffer, pH 7.4. The homogenate is centrifuged at 4000 x g for 10 minutes, and the supernatant is recentrifuged at 42,000 x g for 90 minutes. The resulting membrane pellet is resuspended (0.7 ml/g weight) in 0. 05M Hepes, pH 7.4 and stored at - 70 °C until used. Each tube of the binding assay contains ^{3}H-nitrendipine (0.05-0.50nM), buffer, membranes (0.10 ml), and test compound in a total volume of 1.0 ml. After 90 minutes at 4 °C, the bound nitrendipine is separated from the unbound by filtration on Whatman GF/C filters. After rinsing, the filters are dried and counted in a liquid scintillation counter.

Non-specific binding of ^{3}H-nitrendipine (that amount bound in the presence of excess unlabelled nitrendipine) is subtracted from the total bound to obtain specifically bound radiolabeled nitrendipine. The

amount of specifically bound nitrendipine in the presence of a test compound is compared to that amount bound in the absence of a compound. A percent displacement (or inhibition) can then be obtained.

The test for inhibition of calcium dependent smooth muscle contraction is determined according to the following procedure:

The trachea and the aorta from dogs sacrificed by excess KCl injection are stored overnight at 4°C in oxygenated Krebs-Henseleit buffer. Tracheal rings, one cartilage segment wide (5-10 mm), are cut starting from the bronchial end. Rings of aorta tissue of the same width are also prepared. After cutting the cartilage, the trachealis muscle tissue and the aorta tissue are suspended in oxygenated Krebs-Henseleit buffer at 37°C in a 25 ml tissue bath. After a 60-minute equilibration period, the tissues are challenged with 10 µM carbachol. After 5 minutes, the tissues are rinsed and allowed to rest 50 minutes. The tissues are then challenged with 50 mM KCl and, after 30 minutes, the contractions are quantitated. The tissues are then rinsed and reequilibrated for 50 minutes. Test compounds are then added for 10 minutes, and the tissue is rechallenged with 50 mM KCl. After 30 minutes, the contraction is recorded and used to determine the % inhibition of control.

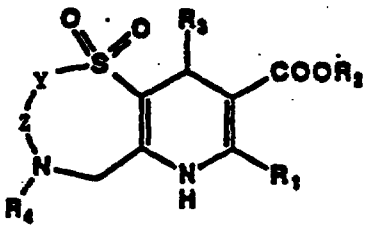
The percent inhibition of smooth muscle contraction is calculated from response data before and after drug treatment.

$$\% \text{ inhibition} = 100 - 100 \left[\frac{\text{peak response after drug treatment}}{\text{peak response before drug treatment}} \right]$$

A rating is assigned to the compound depending upon the percent inhibition obtained.

Claims

1. A compound of the formula



where

Y and Z are CH_2 or together Y and Z form a phenyl ring;

R_1 is hydrogen, amino, C_1-C_8 straight or branched chain alkyl, trifluoromethyl or alkoxymethyl;

R_2 is C_1-C_8 straight or branched chain alkyl, substituted alkyl, benzyl, 3-piperidyl, N-substituted 3-piperidyl or N-substituted 2-pyrrolidinyl methylene;

wherein said N-substituted 3-piperidyl and said N-substituted 2-pyrrolidinyl methylene are substituted with C_1-C_8 straight or branched chain alkyl or benzyl, and said substituted alkyl is substituted with C_1-C_8 alkoxy, alkanoyloxy, aralkanoyloxy, aroyloxy, hydroxy, halogen, p-tosyloxy, mesyloxy, amino, carboalkoxy or NR_5R_6;

R_3 is 2-pyridyl, 3-pyridyl, 2-thienyl, 3-thienyl, 2,1,3-benzoxadiazolyl, 2,1,3 benzthiadiazolyl or substituted phenyl;

wherein said substituted phenyl is substituted at any of positions 2-6 with hydrogen, C_1-C_8 straight or branched chain alkyl, C_1-C_8 alkoxy, cyano, carboalkoxy, C_1-C_8 alkylthio, difluoromethoxy, difluoromethylthio, C_1-C_8 alkylsulfonyl, halogen, nitro or trifluoromethyl;

R_4 is hydrogen, C_1-C_8 straight or branched chain alkyl, C_3-C_7 cycloalkyl, aryl, benzyl, substituted benzyl, formyl, acetyl, t-butyloxy carbonyl, propionyl, substituted alkyl or $R_7CH_2C=O$;

wherein said substituted benzyl is substituted with halogen, trifluoromethyl, C_1-C_8 straight or branched chain alkyl or C_1-C_8 alkoxy, and said substituted alkyl is substituted with amino, dialkyl

amount of specifically bound nitrendipine in the presence of a test compound is compared to that amount bound in the absence of a compound. A percent displacement (or inhibition) can then be obtained.

The test for inhibition of calcium dependent smooth muscle contraction is determined according to the following procedure:

The trachea and the aorta from dogs sacrificed by excess KCl injection are stored overnight at 4 °C in oxygenated Krebs-Henseleit buffer. Tracheal rings, one cartilage segment wide (5-10 mm), are cut starting from the bronchial end. Rings of aorta tissue of the same width are also prepared. After cutting the cartilage, the trachealis muscle tissue and the aorta tissue are suspended in oxygenated Krebs-Henseleit buffer at 37 °C in a 25 ml tissue bath. After a 60-minute equilibration period, the tissues are challenged with 10 μM carbachol. After 5 minutes, the tissues are rinsed and allowed to rest 50 minutes. The tissues are then challenged with 50 mM KCl and, after 30 minutes, the contractions are quantitated. The tissues are then rinsed and reequilibrated for 50 minutes. Test compounds are then added for 10 minutes, and the tissue is rechallenged with 50 mM KCl. After 30 minutes, the contraction is recorded and used to determine the % inhibition of control.

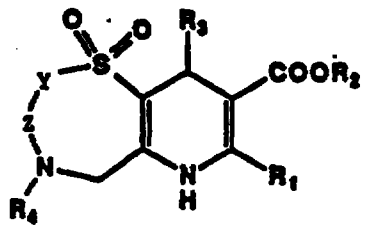
The percent inhibition of smooth muscle contraction is calculated from response data before and after drug treatment.

$$\% \text{ inhibition} = 100 - 100 \left[\frac{\text{peak response after drug treatment}}{\text{peak response before drug treatment}} \right]$$

A rating is assigned to the compound depending upon the percent inhibition obtained.

Claims

1. A compound of the formula



where

Y and Z are CH_2 or together Y and Z form a phenyl ring;

R_1 is hydrogen, amino, C_1-C_8 straight or branched chain alkyl, trifluoromethyl or alkoxymethyl;

R_2 is C_1-C_8 straight or branched chain alkyl, substituted alkyl, benzyl, 3-piperidyl, N-substituted 3-piperidyl or N-substituted 2-pyrrolidinyl methylene;

wherein said N-substituted 3-piperidyl and said N-substituted 2-pyrrolidinyl methylene are substituted with C_1-C_8 straight or branched chain alkyl or benzyl, and said substituted alkyl is substituted with C_1-C_8 alkoxy, alkanoyloxy, aralkanoyloxy, aroyloxy, hydroxy, halogen, p-tosyloxy, mesyloxy, amino, carboalkoxy or NR_5R_6;

R_3 is 2-pyridyl, 3-pyridyl, 2-thienyl, 3-thienyl, 2,1,3-benzoxadiazolyl, 2,1,3 benzthiadiazolyl or substituted phenyl;

wherein said substituted phenyl is substituted at any of positions 2-6 with hydrogen, C_1-C_8 straight or branched chain alkyl, C_1-C_8 alkoxy, cyano, carboalkoxy, C_1-C_8 alkylthio, difluoromethoxy, difluoromethylthio, C_1-C_8 alkylsulfonyl, halogen, nitro or trifluoromethyl;

R_4 is hydrogen, C_1-C_8 straight or branched chain alkyl, C_3-C_7 cycloalkyl, aryl, benzyl, substituted benzyl, formyl, acetyl, t-butyloxy carbonyl, propionyl, substituted alkyl or $R_7CH_2C=O$;

wherein said substituted benzyl is substituted with halogen, trifluoromethyl, C_1-C_8 straight or branched chain alkyl or C_1-C_8 alkoxy, and said substituted alkyl is substituted with amino, dialkyl

* C L M S *

amino, C_1-C_8 alkoxy, hydroxy or halogen;

R_5 and R_6 are the same or different and are hydrogen, C_1-C_8 straight or branched chain alkyl, C_3-C_7 cycloalkyl, phenyl, benzyl, phenethyl or R_5 and R_6 together are a heterocyclic ring selected from the group consisting of piperidino, pyrrolidino, morpholino, thiomorpholino, piperazino or an N-substituted derivative of said heterocyclic rings;

wherein said N-substituted heterocyclic ring is substituted with hydrogen, C_1-C_8 straight or branched chain alkyl, benzyl, benzhydryl, phenyl or substituted phenyl;

wherein said substituted phenyl is substituted with hydrogen, C_1-C_8 straight or branched chain alkyl, C_1-C_8 alkoxy, halogen, nitro or trifluoromethyl;

R_7 is amino, dialkyl amino, C_1-C_8 alkoxy, hydroxy or halogen;

and optical antipodes or pharmaceutically acceptable salts thereof.

2. The compound of claim 1 wherein

R_1 is methyl;

R_2 is ethyl or substituted alkyl;

R_3 is substituted phenyl;

R_4 is hydrogen, C_1-C_8 straight or branched chain alkyl, benzyl, formyl, t-butyloxycarbonyl or $R_7CH_2C=O$; and

R_7 is amino.

3. The compound of claim 1 selected from the group consisting of

a. 2-(N-benzyl-N-methylamino)ethyl 9-(2,3-dichlorophenyl)-1,1-dioxo-2,3,4,5,6,9-hexahydro-7-methyl-pyrido[2,3-f][1,4]-thiazepine-8-carboxylate;

b. 2-(N-benzyl-N-methylamino)ethyl 9-(2,3-dichlorophenyl)-4,7-dimethyl-1,1-dioxo-2,3,4,5,6,9-hexahydropyrido[2,3-f][1,4]-thiazepine-8-carboxylate;

c. Ethyl 9-(2,3-dichlorophenyl)-1,1-dioxo-2,3,4, 5,6,9-hexahydro-7-methyl-pyrido[2,3-f][1,4]thiazepine-8-carboxylate;

d. Ethyl 9-(2,3-dichlorophenyl)-1,1-dioxo-4-ethyl-2,3,4,5,6,9-hexahydro-7-methyl-pyrido-[2,3-f][1,4]-thiazepine-8-carboxylate;

e. Ethyl 9-(2,3-dichlorophenyl)-4,7-dimethyl,1-dioxo-2,3,4,5,6,9-hexahydropyrido[2,3-f]-[1,4]-thiazepine-8-carboxylate;

f. Ethyl 4,7-dimethy-1,1-dioxo-2,3,4,5,6,9-hexahydro-9-(2,3,4,5,6-pentafluorophenyl)-pyrido [2,3-f]-[1,4]thiazepine-8-carboxylate;

g. Ethyl 1,1-dioxo-2,3,4,5,6,9-hexahydro-7-methyl-9-(2,3,4,5,6-pentafluorophenyl)-pyrido[2,3-f] [1,4]-thiazepine-8-carboxylate;

h. Ethyl 1,1-dioxo-4-ethyl-2,3,4,5,6,9-hexahydro-7-methyl-9-(3-nitrophenyl)-pyrido[2,3-f][1,4]-thiazepine-8-carboxylate;

i. 2-Acetoxyethyl 9-(2,3-dichlorophenyl)-4,7-dimethyl-1,1-dioxo-2,3,4,5,6,9-hexahydro-pyrido[2,3-f]-[1,4]thiazepine-8-carboxylate;

j. 2-Pivaloyloxyethyl 9-(2,3-dichlorophenyl)-4,7-dimethyl-1,1-dioxo-2,3,4,5,6,9-hexahydropyrido[2,3-f]-[1,4]thiazepine-8-carboxylate;

k. 2-(N,N-dibenzylamino)ethyl 4-(2,3,dichlorophenyl)-4,7-dimethyl-1,1-dioxo-2,3,4,5,6,9-hexahydropyrido[2,3-f][1,4]thiazepine-8-carboxylate;

l. 2-(N-benzyl-N-methylamino)ethyl 4-(2,3-dichlorophenyl)-4-ethyl- 1,1,-dioxo-2,3,4,5,6,9-hexahydro-7-methyl-pyrido[2,3-f][1,4] thiazepine-8-carboxylate; and

m. (N-benzyl-2-pyrolidinyl)methyl 9-(2,3-dichlorophenyl)-4,7-dimethyl-1,1-dioxo-2,3,4,5,6,9-hexahydropyrido[2,3-f][1,4]-thiazepine-8-carboxylate.

4. The compound of claim 1 selected from the group consisting of

a. Ethyl 4-(2,3-dichlorophenyl)-5,5-dioxo-10-formyl-2-methyl-1,4,10,11-tetrahydropyrido-[3,2-b] [1,5]-benzothiazepine-3-carboxylate;

b. Ethyl 4-(2,3-dichlorophenyl)-2,10-dimethyl-5,5-dioxo-1,4,10,11-tetrahydropyrido[3,2-b] [1,5]-benzothiazepine-3-carboxylate;

c. 2-(N-benzyl-N-methylamino)ethyl 4-(2,3-dichlorophenyl)-2,10-dimethyl-5,5-dioxo-1,4,10,11-tetrahydropyrido[3,2-b] [1,5]-benzothiazepine-3-carboxylate.

5. A pharmaceutical composition comprising as an active ingredient an effective amount of a compound of any one of claims 1 to 4 and a suitable pharmaceutical carrier.

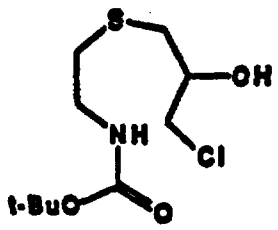
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6. A process for synthesizing the compound of any one of claims 1 to 3 in which Y and Z are CH_2, comprising the steps of:

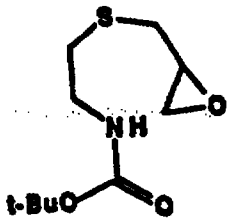
a. treating cystamine dihydrochloride with di-t-butyl dicarbonate to produce bis N-(t-butyloxycarbonyl)-cystamine;

b. treating said bis N-(t-butyloxy-carbonyl)-cystamine with $NaBH_4$ to produce N-(t-butyloxycarbonyl)-2-amino-ethane thiol;

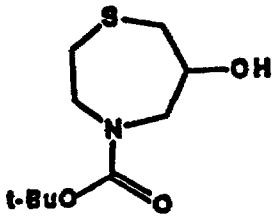
c. reacting said N-(t-butyloxycarbonyl)-2-aminoethane thiol with epichlorohydrin to produce an intermediate chlorohydrin of the formula



d. cyclizing said intermediate chlorohydrin through an epoxide of the formula

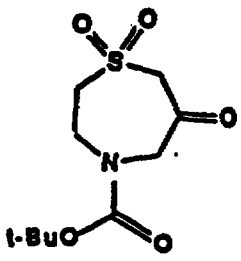


to produce a thiazepinol of the formula



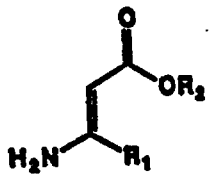
e. oxidizing said thiazepinol with m-chloroperoxybenzoic acid to produce 1,1-dioxo-thiazepinol;

f. further oxidizing said 1,1-dioxo-thiazepinol with Jones reagent to produce a 1,1-dioxo-thiazepinone of the formula

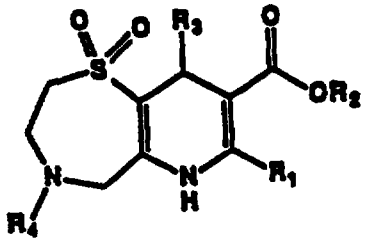


g. reacting said 1,1-dioxothiazepinone with an R_3-substituted aldehyde and a substituted 3-aminoacrylate derivative of the formula

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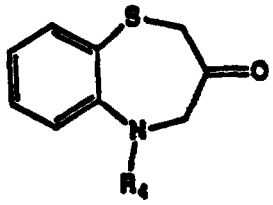
where R_1, R_2 and R_3 are as defined in claim 1, to produce a dihydropyridine of the formula



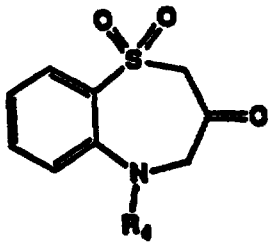
where R_1, R_2, R_3 and R_4 are as defined in claim 1.

7. A process for synthesizing the compound of any one of claims 1, 2 or 4 in which Y and Z together form a phenyl ring, comprising the steps of:

a. reacting a benzothiazepinone of the formula



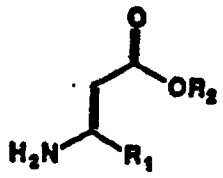
where R_4 is as defined in claim 1, with $NaBH_4$, m-chloroperoxybenzoic acid and Jones reagent to produce a 1,1-dioxo-benzothiazepenone of the formula



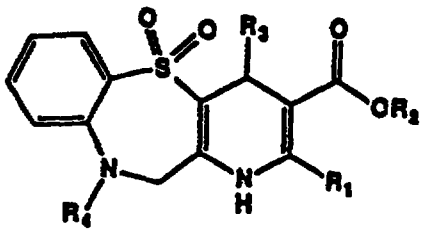
where R_4 is as defined in claim 1; and

b. reacting said 1,1-dioxo-benzothiazepenone with an R_3-substituted aldehyde and a substituted 3-aminoacrylate derivative of the formula

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where R_1, R_2 and R_3 are as defined in claim 1, to produce a dihydropyridine of the formula

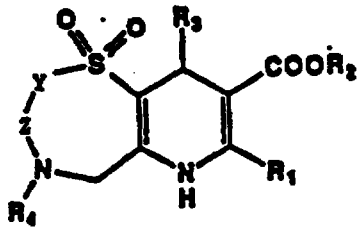


where R_1, R_2, R_3 and R_4 are as defined in claim 1.

8. A compound of any one of claims 1 to 4 or a composition of claim 5, for use in treating cardiovascular disorders, including hypertension, ischemia, angina, congestive heart failure, migraine, myocardial infarction, stroke, hypersensitivity, allergy, asthma, dysmenorrhea, esophageal spasm, gastrointestinal motility disorders, glaucoma, premature labor or urinary tract disorders.

Patentansprüche

1. Verbindung der Formel



wobei

Y und Z gleich CH_2 sind oder Y und Z zusammen einen Phenylring bilden;

R_1 gleich Wasserstoff, Amino, geradkettiges oder verzweigtkettiges C_1 - C_8-Alkyl, Trifluormethyl oder Alkoxymethyl ist;

R_2 geradkettiges oder verzweigtkettiges C_1 -C_8-Alkyl, substituiertes Alkyl, Benzyl, 3-Piperidyl, N-substituiertes 3-Piperidyl oder N-substituiertes 2-Pyrrolidinylmethylen ist;

wobei das N-substituierte 3-Piperidyl und das N-substituierte 2-Pyrrolidinylmethylen mit geradkettigen oder verzweigtkettigem C_1 - C_8-Alkyl oder Benzyl substituiert ist, und das substituierte Alkyl mit C_1 - C_8-Alkoxy, Alkanoyloxy, Aralkanoyloxy, Aroyloxy, Hydroxy, Halogen, p-Tosyloxy, Mesyloxy, Amino, Carboalkoxy oder NR_5R_6 substituiert ist;

R_3 gleich 2-Pyridyl, 3-Pyridyl, 2-Thienyl, 3-Thienyl, 2,1,3-Benzoxadidzolyl, 2,1,3-Benzthiadiazolyl oder substituiertes Phenyl ist;

wobei das substituierte Phenyl an jeder seiner Stellungen 2 bis 6 mit Wasserstoff, gerad- oder verzweigtkettigem C_1 - C_8-Alkyl, C_1 - C_8-Alkoxy, Cyano, Carboalkoxy, C_1-C_8-Alkylthio, Difluormethoxy, Difluormethylthio, C_1 - C_8-Alkylsulfonyl, Halogen, Nitro oder Trifluormethyl substituiert ist;

R_4 gleich Wasserstoff. geradkettiges oder verzweigtkettiges C_1 - C_8-Alkyl, C_3 -C_7-Cycloalkyl, Aryl,

* C L M S *

Benzyl, substituiertes Benzyl, Formyl, Acetyl, t-Butyloxycarbonyl, Propionyl, substituiertes Alkyl oder $R_7CH_2C=O$ ist;

wobei das substituierte Benzyl substituiert ist mit Halogen, Trifluormethyl, geradkettigem oder werzweigtkettigem C_1 - C_8-Alkyl oder C_1 - C_8-Alkoxy und das substituierte Alkyl mit Amino- Dialkylamino, C_1 - C_8-Alkoxy, Hydroxy oder Halogen substituiert ist;

R_5 und R_6 gleich oder verschieden sind und Wasserstoff, gerad- oder verzweigtkettiges C_1 - C_8-Alkyl, C_3 - C_7-Cycloalkyl, Phenyl, Benzyl, Phenethyl sind oder R_5 und R_6 zusammen einen heterocyclischen Ring bilden. ausgewählt aus der Gruppe bestehend aus Piperidino, Pyrrolidino, Morpholino, Thiomorpholino, Piperazino oder einem N-substituierten Derivat des heterocyclischen Ringes;

wobei der N-substituierte heterocyclische Ring mit Wasserstoff, gerad- oder verzweigtkettigem C_1 - C_8-Alkyl, Benzyl, Benzhydryl, Phenyl oder substituiertem Phenyl substituiert ist;

wobei das substituierte Phenyl mit Wasserstoff, gerad- oder verzweigtkettigem C_1 -C_8-Alkyl, C_1 - C_8-Alkoxy, Halogen, Nitro oder Trifluormethyl substituiert ist;

R_7 gleich Amino, Dialkylamino, C_1 -C_8-Alkoxy, Hydroxy oder Halogen ist; und

optische Antipoden oder pharmazeutisch verträgliche Salze davon.

2. Verbindung nach Anspruch 1, in der

R_1 gleich Methyl ist;

R_2 gleich Ethyl oder substituiertes Alkyl ist;

R_3 gleich substituiertes Phenyl ist;

R_4 gleich Wasserstoff, geradkettiges oder verzweigtkettiges C_1 - C_8-Alkyl, Benzyl, Formyl, t-Butyloxycarbonyl oder $R_7CH_2C=O$ ist; und

R_7 gleich Amino ist.

3. Verbindung nach Anspruch 1, ausgewählt aus der Gruppe bestehend aus:

a. 2-(N-Benzyl-N-methylamino)ethyl-9-(2,3-dichlorphenyl)-1,1-dioxo-2,3,4,5,6,9-hexahydro-7-methyl-pyrido[2,3-f][1,4]thiazepin-8-carboxylat;

b. 2-(N-Benzyl-N-methylamino)ethyl-9-(2,3-dichlorphenyl)-4,7-dimethyl-1,1-dioxo-2,3,4,5,6,9-hexahydropyrido[2,3-f][1,4]-thiazepin-8-carboxylat

c. Ethyl-9-(2,3-dichlorphenyl)-1,1-dioxo-2,3,4,5,6,9-hexahydro-7-methyl-pyrido[2,3-f][1,4]thiazepin-8-carboxylat;

d. Ethyl-9-(2,3-dichlorphenyl)-1,1-dioxo-4-ethyl-2,3,4,5,6,9-hexahydro-7-methyl-pyrido[2,3-f][1,4]-thiazepin-8-carboxylat;

e. Ethyl-9-(2,3-dichlorphenyl)-4,7-dimethyl-1,1-dioxo-2,3,4,5,6,9-hexahydro-pyrido[2,3-f][1,4]thiazepin-8-carboxylat;

f. Ethyl-4,7-dimethyl-1,1-dioxo-2,3,4,5,6,9-hexahydro-9-(2,3,4,5,6-pentafluorphenyl)-pyrido[2,3-f][1,4]-thiazepin-8-carboxylat;

g. Ethyl-1,1-dioxo-2,3,4,5,6,9-hexahydro-7-methyl-9-(2,3,4,5,6-pentafluorphenyl)-pyrido[2,3-f][1,4]-thiazepin-8-carboxylat;

h. Ethyl-1,1-dioxo-4-ethyl-2,3,4,5,6,9-hexahydro-7-methyl-9-(3-nitrophenyl)-pyrido[2,3-f][1,4]thiazepin-8-carboxylat;

i. 2-Acetoxyethyl-9-(2,3-dichlorphenyl)-4,7-dimethyl-1,1-dioxo-2,3,4,5,6,9-hexahydropyrido[2,3-f][1,4]-thiazepin-8-carboxylat;

j. 2-Pivaloyloxyethyl-9-(2,3-dichlorphenyl)-4,7-dimethyl-1,1-dioxo-2,3,4,5,6,9-hexahydropyrido[2,3-f]-[1,4]thiazepin-8-carboxylat,

k. 2-(N,N-Dibenzylamino)ethyl-4-(2,3-dichlorphenyl)-4,7-dimethyl-1,1-dioxo-2,3,4,5,6,9-hexahydro-pyrido[2,3-f][1,4]thiazepin-8-carboxylat;

l. 2-(N-Benzyl-N-methylamino)ethyl-4-(2,3-dichlorphenyl)-4-ethyl-1,1-dioxo-2,3,4,5,6,9-hexahydro-7-methyl-pyrido[2,3-f][1,4]thiazepin-8-carboxylat; und

m. (N-Benzyl-2-pyrolidinyl)methyl-9-(2,3-dichlorphenyl)-4,7-dimethyl-1,1-dioxo-2,3,4,5,6,9-hexahydropyrido[2,3-f][1,4]thiazepin-8-carboxylat.

4. Verbindung nach Anspruch 1, ausgewählt aus der Gruppe bestehend aus:

a. Ethyl-4-(2,3-dichlorphenyl)-5,5-dioxo-10-formyl-2-methyl-1,4,10,11-tetrahydropyrido-[3,2-b][1,5]-benzothiazepin-3-carboxylat;

b. Ethyl-4-(2,3-dichlorphenyl)-2,10-dimethyl-5,5-dioxo-1,4,10,11-tetrahydropyrido[3,2-b][1,5]-benzothiazepin-3-carboxylat:

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c. 2-(N-Benzyl-N-methylamino)ethyl-4-(2,3-dichlorphenyl)-2,10-dimethyl-5,5-dioxo-1,4,10,11-tetrahydropyrido[3,2-b][1,5]-benzothiazepin-3-carboxylat.

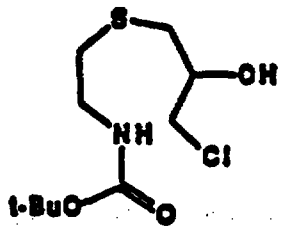
5. Pharmazeutische Zusammensetzung, umfassend als einen Wirkstoff eine wirksame Menge einer Verbindung nach einem der Ansprüche 1 bis 4 und einen geeigneten pharmazeutischen Träger.

6. Verfahren zur Synthese der Verbindung nach einen der Ansprüche 1 bis 3, in der Y und Z gleich CH_2 sind, umfassend die Schritte:

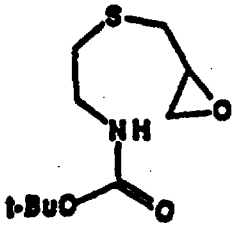
a. Behandeln von Cystamin-dihydrochlorid mit Di-t-Butyldicarbonat, um Bis-N-(t-Butyloxycarbonyl)-cystamin zu bilden;

b. Behandeln des Bis-N-(t-Butyloxy-carbonyl)-cystamins mit $NaBH_4$, um N-(t-Butyloxycarbonyl)-2-aminoethanthiol zu bilden;

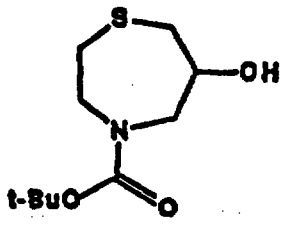
c. Umsetzen des N-(t-Butyloxycarbonyl)-2-Aminoethanthiols mit Epichlorhydrin, um eine Chlorhydrin-Zwischenstufe der Formel zu bilden:



d. Cyclisieren der Chlorhydrin-Zwischenstufe durch ein Epoxid der Formel



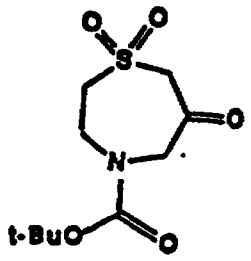
um ein Thiazepinol der Formel zu bilden



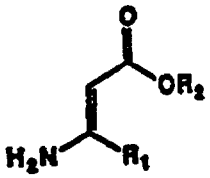
e. Oxidieren des Thiazepinols mit m-Chlorperoxybenzoesäure, um 1,1-Dioxothiazepinol zu bilden;

f. darüber hinaus Oxidieren des 1,1-Dioxothiazepinols mit Jones-Reagens, um ein 1,1-Dioxothiazepinon der Formel zu bilden

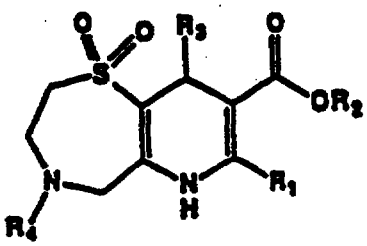
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g. Umsetzen des 1,1-Dioxothiazepinons mit einem R_3 -substituierten Aldehyd und einem substituierten 3-Aminoacrylat-Derivat der Formel

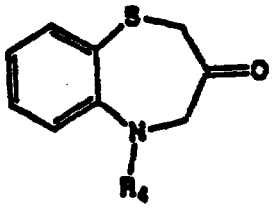


in der R_1, R_2 und R_3 die in Anspruch 1 angegebene Bedeutung aufweisen, um ein Dihydropyridin der Formel zu bilden



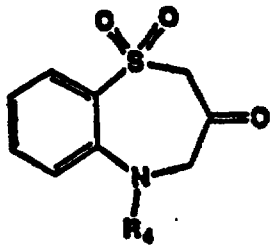
in der R_1, R_2, R_3 und R_4 die in Anspruch 1 angegebene Bedeutung aufweisen.

7. Verfahren zur Synthese der Verbindung nach einem der Ansprüche 1, 2 oder 4, in der Y und Z zusammen einen Phenylring bilden, umfassend die Schritte:
   a. Umsetzen eines Benzothiazepinons der Formel



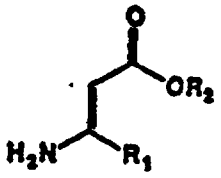
in der R_4 die in Anspruch 1 angegebene Bedeutung aufweist, mit $NaBH_4$, m-Chlorperoxybenzoesäure und Jones-Reagens, um ein 1,1-Dioxobenzothiazepinon der Formel

* C L M S *

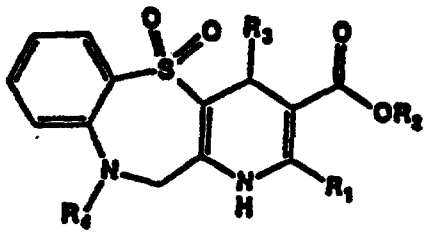


zu bilden, in der R_4 die in Anspruch 1 angegebene Bedeutung aufweist; und

b. Umsetzen des 1,1-Dioxobenzothiazepinons mit einem R_3-substituierten Aldehyd und einem substituierten 3-Aminoacrylat-Derivat der Formel



in der R_1, R_2 und R_3 die in Anspruch 1 angegebene Bedeutung aufweisen, um ein Dihydropyridin der Formel

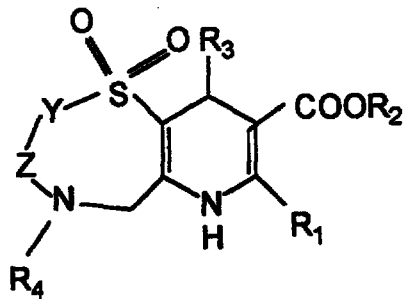


zu bilden, in der R_1, R_2, R_3 und R_4 die in Anspruch 1 angegebene Bedeutung aufweisen.

8. Verbindung nach einem der Ansprüche 1 bis 4, oder Zusammensetzung nach Anspruch 5 zur Verwendung bei der Behandlung kardiovaskulärer Störungen einschließlich Hypertonie, Ischämie, Angina, kongestive Kardiomyopathie, Migräne, Myokardinfarkt, Schlaganfall, Hypersensibilität, Allergien, Asthma, Dysmenorrhoe, Ösophagusspasmen, gastrointestinalen Motilitätsstörungen, Glaukom, vorzeitigen Wehen und Störungen des Harntraktes.

Revendications

1. Composé de la formule



* C L M S *

où

Y et Z sont CH_2 ou bien Y et Z forment ensemble un cycle phényle;

R_1 est hydrogène, amino, alkyle C_1-C_8 à chaîne droite ou ramifiée, trifluorométhyle ou alcoxyméthyle;

R_2 est alkyle C_1-C_8 à chaîne droite ou ramifiée, alkyle substutué, benzyle, 3-pipéridyle, 3-pipéridyle N substitué ou 2-pyrrolidinyl méthylène N-substitué;

où ledit 3-pipéridyle N-substitué et ledit 2-pyrrolidinyl méthylène N-substitué sont substitués par alkyle C_1-C_8 à chaîne droite ou ramifiée ou benzyle et ledit alkyle substitué est substitué par alcoxy C_1-C_8, alcanoyloxy, aralcanoyloxy, aroyloxy, hydroxy, halogène, p-tosyloxy, mésyloxy, amino, carboalcoxy ou NR_5R_6;

R_3 est 2-pyridyle, 3-pyridyle, 2-thiényle, 3-thiényle, 2, 1, 3-benzoxadiazolyle, 2, 1, 3 benzothiadiazolyle ou phényle substitué;

où ledit phényle substitué est substitue en toute positions 2-6 par hydrogène, alkyle C_1-C_8 à chaîne droite ou ramifiée, alcoxy C_1-C_8, cyano, carboalcoxy, alkythio C_1-C_8, difluorométhyle, difluorométhylthio, alkylsulfonyle C_1-C_8,halogène, nitro ou trifluorométhyle;

R_4 est hydrogène, alkyle C_1-C_8 à chaîne droite ou ramifiée, cycloalkyle C_3-C_7, aryle, benzyle, benzyle substitué, formyle, acétyle, t-butyloxy carbonyle, propionyle, alkyle substitué ou $R_7CH_2C=O$;

où ledit benzyle substitué est substitué par halogène, trifluorométhyle, alkyle C_1-C_8 à chaîne droite ou ramifiée ou alcoxy C_1-C_8 et ledit alkyle substitué est substitué par amino, dialkylamino, alcoxy C_1-C_8, hydroxy ou halogène;

R_5 et R_6 sont identiques ou différents et sont hydrogène, alkyle C_1-C_8 à chaîne droite ou ramifiée, cycloalkyle C_3-C_7, phényle, benzyle, phénéthyle ou bien R_5 et R_6 forment ensemble un cycle hétérocyclique sélectionné dans le groupe consistant en pipéridino, pyrrolidino, morpholino, thiomorpholino, pipérazino ou un dérivé N-substitué desdits cycles hétérocycliques;

où ledit cycle hétérocyclique N-substitué est substitué par hydrogène, alkyle C_1-C_8 à chaîne droite ou ramifiée, benzyle, benzhydryle, phényle ou phényle substitué;

où ledit phényle substitué est substitué par hydrogène, alkyle C_1-C_8 à chaîne droite ou ramifiée, alcoxy C_1-C_8, halogène, nitro ou trifluorométhyle;

R_7 est amino, dialkylamino, alcoxy C_1-C_8, hydroxy ou halogène;

et des antipodes optiques ou leurs sels acceptables en pharmacie.

2. Composé de la revendication 1 où

R_1 est méthyle;

R_2 est éthyle ou alkyle substitué;

R_3 est phényle substitué;

R_4 est hydrogène, alkyle C_1-C_8 à chaîne droite ou ramifiée, benzyle, formyle, t-butyloxycarbonyle ou $R_7CH_2C=O$; et

R_7 est amino.

3. Composé de la revendication 1 sélectionné dans le groupe consistant en

a. 9-(2,3-dichlorophényl)-1,1-dioxo-2,3,4,5,6,9-hexahydro-7-méthyl-pyrido[2,3-f] [1,4]-thiazépine-8-carboxylate de 2-(N-benzyl-N-méthylamino)éthyle.

b. 9-(2,3-dichlorophényl)-4,7-diméthyl-1,1-dioxo-2,3,4,5,6,9-hexahydropyrido [2,3-f] [1,4]-thiazépine-8-carboxylate de 2-(N-benzyl-N-méthylamino)éthyle.

c. 9-(2,3-dichlorophényl)-1,1-dioxo-2,3,4,5,6,9-hexahydro-7-méthyl-pyrido [2,3-f] [1,4] thiazépine-8-carboxylate d'éthyle

d. 9-(2,3-dichlorophényl)-1,1-dioxo-4-éthyl-2,3,4,5,6,9-hexahydro-7-méthyl-pyrido-[2,3-f] [1,4] thiazépine-8-carboxylate d'éthyle;

e. 9-(2,3-dichlorophényl)-4,7-diméthyl-1,1-dioxo-2,3,4,5,6,9-hexahydropyrido [2,3-f]-[1,4] thiazépine-8-carboxylate d'éthyle;

f. 4,7-diméthyl-1,1-dioxo-2,3,4,5,6,9-hexahydro-9-(2,3,4,5,6-pentafluorophényl)-pyrido [2,3-f] [1,4] thiazépine-8-carboxylate d'éthyle;

g. 1,1-dioxo-2,3,4,5,6,9-hexahydro-7-méthyl-9-(2,3,4,5,6,9-hexahydro-7-méthyl-9-(2,3,4,5,6-pentafluorophényl)-pyrido [2,3-f] [1,4] thiazépine-8-carboxylate d'éthyle;

h. 1,1-dioxo-4-éthyl-2,3,4,5,6,9-hexahydro-7-méthyl-9-(3-nitrophényl)-pyrido [2,3-f] [1,4] thiazépine-8-carboxylate d'éthyle;

i. 9-(2,3-dichlorophényl)-4,7-diméthyl-1,1-dioxo-2,3,4,5,6,9-hexahydro-pyrido [2,3-f] [1,4] thiazépine-8-carboxylate de 2-acétoxyéthyle.

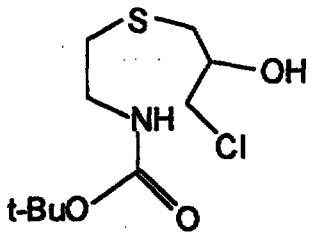
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j. 9-(2,3-dichlorophényl)-4,7-diméthyl-1,1-dioxo-2,3,4,5,6,9-hexahydropyrido [2,3-f] [1,4] thiazépine-8-carboxylate de 2-pivaloyloxyéthyle.
k. 4-(2,3,dichlorophényl)-4,7-diméthyl-1,1-dioxo-2,3,4,5,6,9-hexahydropyrido [2,3-f] [1,4] thiazépine-8-carboxylate de 2-(N,N-dibenzylamino) éthyle;
l. 4-(2,3-dichlorophényl)-4-éthyl-1,1-dioxo-2,3,4,5,6,9-hexahydro-7-méthyl-pyrido [2,3-f] [1,4] thiazépine-8-carboxylate de 2-(N-benzyl-N-méthylamino) éthyle; et
m. 9-(2,3-dichlorophényl)-4,7-diméthyl-1,1-dioxo-2,3,4,5,6,9-hexahydropyrido [2,3-f] [1,4]-thiazépine-8-carboxylate de (N-benzyl-2-pyrolidinyl)méthyle.

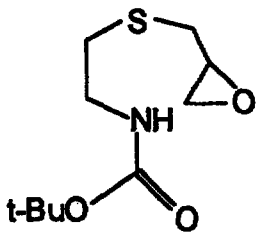
4. Composé de la revendication 1, sélectionné dans le groupe consistant en :
a. 4-(2,3-dichlorophényl)-5,5-dioxo-10-formyl-2-méthyl-1,4,10,11-tétrahydropyrido-[3,2 -b] [1,5] benzothiazépine-3-carboxylate d'éthyle;
b. 4-(2,3-dichlorophényl)-2,10-diméthyl-5,5-dioxo-1,4,10,11-tétrahydropyrido [3,2 -b] [1,5] benzothiazépine-3-carboxylate d'éthyle;
c. 4-(2,3-dichlorophényl)-2,10-diméthyl-5,5-dioxo-1,4,10,11-tétrahydropyrido [3,2 -b] [1,5]-benzothiazépine-3-carboxylate de 2-(N-benzyl-N-méthylamino) éthyle.

5. Composition pharmaceutique comprenant comme ingrédient actif une quantité efficace d'un composé selon l'une quelconque des revendications 1 à 4, et un support pharmaceutique approprié.

6. Procédé pour la synthèse du composé selon l'une quelconque des revendications 1 à 3, où Y et Z sont CH_2, comprenant les étapes de :
a. traiter du dichlorhydrate de cystamine avec du dicarbonate de di-t-butyle tertiaire pour produire la bis N-(t-butyloxycarbonyl)-cystamine;
b. traiter ladite bis N-(t-butyloxy-carbonyl)-cystamine avec $NaBH_4$, pour donner le N-(t-butyloxycarbonyl)-2-amino-éthane thiol;
c. *faire réagir ledit* N-(t-butyloxycarbonyl)-2-aminoéthane thiol avec de l'épichlorohydrine pour donner une chlorhydrine intermédiaire de la formule

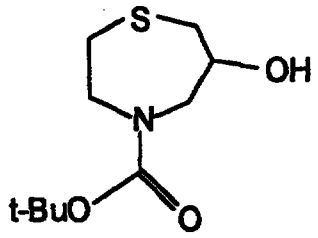


d. cycliser ladite chlorhydrine intermédiaire par un époxyde de la formule

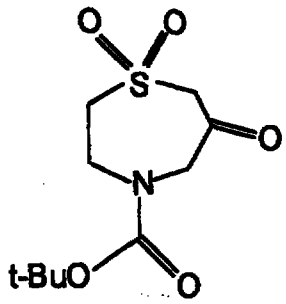


pour produire un thiazépinol de la formule

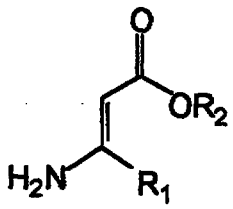
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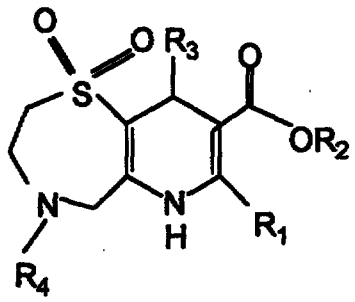
e. oxyder ledit thiazépinol avec de l'acide m-chloroperoxybenzoïque pour donner le 1,1-dioxo-thiazépinol;
f. oxyder encore ledit 1,1-dioxo-thiazépinol avec un réactif de Jones pour donner une 1,1-dioxo-thiazépinone de la formule



g. faire réagir ladite 1,1-dioxothiazépinone avec un aldéhyde R_3-substitué et un dérivé substitué de 3-aminoacrylate de la formule :



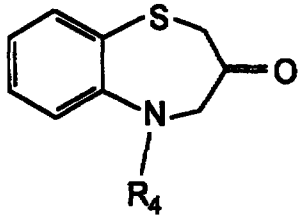
où R_1, R_2 et R_3 sont tels que définis à la revendication 1, pour produire une dihydropyridine de la formule



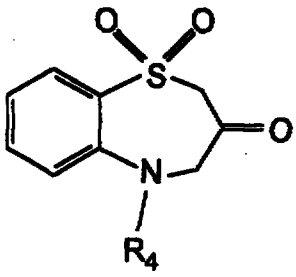
où R_1, R_2, R_3 et R_4 sont tels que définis à la revendication 1.

7. Procédé pour la synthèse du composé selon l'une quelconque des revendications 1, 2 ou 4, où Y et Z forment ensemble un cycle phényle, comprenant les étapes de :

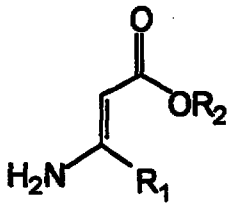
a. faire réagir une benzothiazépinone de la formule



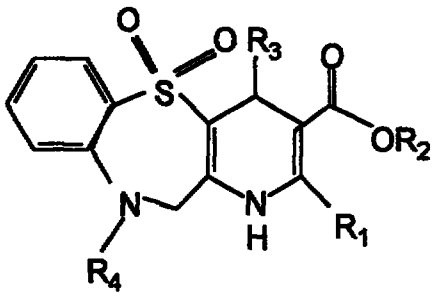
où R_4 est tel que défini à la revendication 1, avec $NaBH_4$, de l'acide m-chloroperoxybenzoïque et un réactif de Jones pour donner une 1,1-dioxo-benzothiazépinone de la formule



où R4 est tel que défini à la revendication 1; et
b. faire réagir ladite 1,1-dioxo-benzothiazépinone avec un aldéhyde R_3-substitué et un dérivé substitué de 3-aminoacrylate de la formule



où R1, R2 et R3 sont tels que définis à la revendication 1, pour produire une dihydropyridine de la formule



où R_1, R_2, R_3 et R_4 sont tels que définis à la revendication 1.

8. Composé selon l'une quelconque des revendications 1 à 4 ou composition de la revendication 5 à utiliser pour le traitement des troubles cardiovasculaires comprenant l'hypertension, l'ischémie, l'angine, l'asystolie congestive, la migraine, l'infarctus du myocarde, la congestion cérébrale, l'hypersensibilité, l'allergie, l'asthme, la dysmenorrhée, les spasmes de l'oesophage, les troubles de motilité gastrointestinale, le glaucome, le travail prématuré ou des troubles des voies urinaires.

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