Description

BACKGROUND OF THE INVENTION

Field of the invention

This invention relates to certain substituted thiacycloalkeno [3,2-b] pyridines. These compounds are useful as calcium channel antagonists with cardiovascular, antiasthmatic, antibronchospastic, gastric antisecretory, cytoprotective and platelet aggregation inhibitory activity. In addition, the compounds are useful in treating hypermotility of the G-I tract and in the treatment of diarrhea. This invention also relates to a process for preparing these compounds, compositions thereof, methods of use and novel intermediates.

Related Disclosure

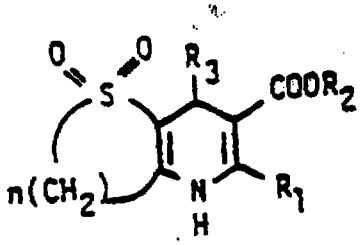
U.S. Patent No. 4,285,955 and U.S. Patent No. 4,483,985 (which is a divisional of the aforementioned patent) disclose acyclic sulfone substitution on simple dihydropyridines which possess calcium channel antagonist activity. However, the compounds in question are chemically distinct from the compounds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

10-Phenyl-2H-thiopyrano[3,2-b]quinolines are disclosed in G.P.A. Pagani, J.Chem.Soc., Perkin Trans.2,1392-7(1974).

However, these compounds are not calcium channel antagonists.

U.S. Patent No. 4532248 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 U.S. Patent No. 4532248.

The substituted thiacycloalkeno [3,2-b] pyridines which are the subject of this invention have the following general formula:



wherein:

n is an integer from 1 to 12;

R_1 is hydrogen, C_1-C_8 alkyl or C_1-C_8 haloalkyl;

R_2 is C_1-C_8 alkyl, C_3-C_7 cycloalkyl or alkylene-X having at least 2 carbon atoms, wherein X = alkoxy having up to 4 carbon atoms, hydroxy, halo, p-tosyloxy, mesyloxy, amino, pyridyl or $-NR_4R_5$, wherein R_4 and R_5 are the same or different, and are selected from hydrogen, C_1-C_8 alkyl, phenyl, benzyl, phenethyl, or R_4/R_5 and the nitrogen atom to which they are attached form a 5, 6 or 7-membered heterocyclic ring which optionally contains an oxygen or sulfur or an additional nitrogen atom, or said heterocyclic ring may be fused to a benzene ring as in indoline, isoindoline, tetrahydroquinoline or tetrahydroisoquinoline, and in the instance wherein said heterocyclic ring is piperazino, said piperazino may optionally be substituted in the 4-position with the substituent R_6, which is selected from C_1-C_8 alkyl, benzyl, phenyl or phenyl substituted by alkoxy having up to 4 carbon atoms, halo, C_1-C_8 alkyl, nitro or trifluoromethyl;

R_3 is 2-pyridyl, 3-pyridyl, 3-pyridyl substituted at positions 2, 4, 5 or 6 with one or more groups selected from halogen, nitro, alkoxy or alkylthio having up to 4 carbon atoms, cyano, difluoromethoxy, difluoromethylthio or C_1-C_8 alkylsulfonyl; 2-thienyl, 3-thienyl, 2,1,3-benzoxadiazolyl, 2,1,3-benzthiadiazolyl or phenyl optionally substituted at positions 2 through 6 with one or more groups selected from hydrogen, C_1-C_8 alkyl, alkoxy having up to 4 carbon atoms, cyano, difluoromethoxy, difluoromethylthio, C_1-C_8 alkylsulfonyl, halo, nitro or trifluoromethyl, their optical antipodes or the pharmaceutically acceptable acid and base addition salts thereof.

The compounds of this invention are assymetric in the pyridine ring at the R_3 point of attachment and thus exist as optical antipodes and as such are part of this invention. The antipodes can be separated by

methods known to those skilled in the art such as, for example, fractional recrystallization of diastereomeric salts of enantiomerically pure acids. Alternatively, the antipodes can be separated by chromatography in a Pirkle column.

Also included in this invention is a process for preparing the compounds of formula I, said process being disclosed in detail hereinafter.

Also part of the present invention are certain intermediates and the process for the preparation thereof.

Preferred compounds of the present invention are:

1. Ethyl 2,3,4,7-tetrahydro-5-methyl-7-(3-nitrophenyl)-1,1-dioxothieno[3,2-b]pyridine-6-carboxylate.
2. N,N-Dimethylaminoethyl 2,3,4,7-tetrahydro-5-methyl-7-(3-nitrophenyl)-1,1-dioxothieno[3,2-b]pyridine-6-carboxylate.
3. N-Benzyl-N-methylaminoethyl 2,3,4,7-tetrahydro-5-methyl-7-(3-nitrophenyl)-1,1-dioxothieno [3,2-b]-pyridine-6-carboxylate.
4. Ethyl 3,4,5,8-tetrahydro-6-methyl-8-(3-nitrophenyl)-1,1-dioxo-2H-thio-pyrano [3,2-b]pyridine-7-carboxylate.
5. N,N-Dimethylaminoethyl 3,4,5,8-tetrahydro-6-methyl-8-(3-nitrophenyl)-1,1-dioxo-2H-thiopyrano[3,2-b]-pyridine-7-carboxylate.
6. N-Benzyl-N-methylaminoethyl 3,4,5,8-tetrahydro-6-methyl-8-(3-nitrophenyl)-1,1-dioxo-2H-thiopyrano-[3,2-b]pyridine-7-carboxylate.
7. N-Benzyl-N-methylaminoethyl 3,4,5,8-tetrahydro-6-methyl-8-(2,3,4,5,6-pentafluorophenyl)-1,1-dioxo-2H-thiopyrano[3,2-b]pyridine-7-carboxylate.
8. Ethyl 9-(2,3,4,5,6-pentafluorophenyl)-2,3,4,5,6,9-hexahydro-7-methyl-1,1-dioxothiacycloheptenо[3,2-b] pyridine-8-carboxylate.
9. N-Benzyl-N-methylaminoethyl 2,4,5,6,9-hexahydro-7-methyl-9-(3-nitrophenyl)-1,1-dioxothiacyclohepteno [3,2-b]pyridine-8-carboxylate.
10. N.N-Dimethylaminoethyl 2,3,4,5,6,9-hexahydro-7-methyl-9-(3-nitrophenyl)-1,1-dioxothiacycloheptenо-[3,2-b] pyridine-8-carboxylate.
11. 2-Methoxyethyl 2,3,4,5,6,9-hexahydro-7-methyl-9-(3-nitrophenyl)-1,1-dioxo-thiacycloheptenо[3,2-b] pyridine-8-carboxylate.
12. N-Benzyl-N-methylaminoethyl 9-(2,3,4,5,6-pentafluorophenyl)-2,3,4,5,6,9-hexahydro-7-methyl-1,1-dioxothiacycloheptenо[3,2-b]pyridine-8-carboxylate.
13. Ethyl 10-(2,3,4,5,6-pentafluorophenyl)-3,4,5,6,7,10-hexahydro-8-methyl-1,1-dioxo-2H-thiacyclooctenо-[3,2-b]pyridine-9-carboxylate.
14. N-Benzyl-N-methylaminoethyl 10-(2,3,4,5,6-pentafluorophenyl)-3,4,5,6,7,10-hexahydro-8-methyl-1,1-dioxo-2H-thiacyclooctenо[3,2-b]pyridine-9-carboxylate.
15. N-Benzyl-N-methylaminoethyl 3,4,5,6,7,10-hexahydro-8-methyl-10-(3-nitrophenyl)-1,1-dioxo-2H-thiacyclooctenо [3,2-b]pyridine-9-carboxylate.
16. N-Benzyl-N-methylaminoethyl 11-(3-nitrophenyl) 2,3,4,6,7,8,11-octahydro-9-methyl-1,1-dioxothiacyclononenо[3,2-b]pyridine-10-carboxylate.
17. N-Benzyl-N-methylaminoethyl 2,4,5,6,9-hexahydro-6-methyl-9-(3-nitrophenyl)-1,1-dioxothiacyclohepteno [3,2-b]pyridine-8-carboxylate.
18. N-Benzyl-N-methylaminoethyl 9-(2-chlorophenyl)-2,4,5,6,9-hexahydro-7-methyl-1,1-dioxothiacyclohepteno [3,2-b]pyridine-8-carboxylate.
19. N-Benzyl-N-methylaminoethyl 9-(2,3-dichlorophenyl)-2,4,5,6,9-hexahydro-7-methyl-1,1-dioxothiacycloheptenо[3,2-b]pyridine-8-carboxylate.
20. N-Benzyl-N-methylaminoethyl 9-(2-chloro-6-fluorophenyl)-2,4,5,6,9-hexahydro-7-methyl-1,1-dioxothiacycloheptenо[3,2-b]pyridine-8-carboxylate.
21. N-Benzyl-N-methylaminoethyl 9-(2-cifluoromethoxyphenyl)-2,4,5,6,9-hexahydro-7-methyl-1,1-dioxothiacycloheptenо[3,2-b]pyridine-8-carboxylate.
22. N-Benzyl-N-methylaminoethyl 2,4,5,6,9-hexahydro-7-methyl-9-(2-trifluoromethylphenyl)-1,1-dioxothiacycloheptenо[3,2-b]pyridine-8-carboxylate.
23. N-Benzyl-N-methylaminoethyl 10-(2-chlorophenyl)-3,4,5,6,7,10-hexahydro-8-methyl-1,1-dioxocyclooctenо [3,2-b]pyridine-9-carboxylate.
24. N-Benzyl-N-methylaminoethyl 10-(2,3-dichlorophenyl-3,4,5,6,7,10-hexahydro-8-methyl-1,1-dioxothiacyclooctenо[3,2-b]pyridine-9-carboxylate.
25. N-Benzyl-N-methylaminoethyl 10-(2-difluoromethoxyphenyl)-3,4,5,6,7,10-hexahydro-8-methyl-1,1-dioxothiacyclooctenо[3,2-b]pyridine-9-carboxylate.
26. N-Benzyl-N-methylaminoethyl 10-(2-chloro-6-fluorophenyl)-3,4,5,6,7,10-hexahydro-8-methyl-1,1-dioxothiacyclooctenо[3,2-b]pyridine-9-carboxylate.

27. N-Benzyl-N-methylaminoethyl 10-(2-chloro-3-trifluoromethylphenyl)-3,4,5,6,7,10-hexahydro-8-methyl-1,1-dioxothiacyclooctено[3,2-b]pyridine-9-carboxylate.

28. N-Benzyl-N-methylaminoethyl 12-(2-chloro-3-trifluoromethylphenyl)-2,3,4,5,6,7,8,11-octahydro-9-methyl-1,1-dioxothiacyclononeno[3,2-b]pyridine-10-carboxylate.

29. N-Methyl-N-phenylaminoethyl 10-(2,3,4,5,6-pentafluorophenyl)-3,4,5,6,7,10-hexahydro-8-methyl-1,1-dioxothiacyclooctено[3,2-b]pyridine-9-carboxylate.

The compounds of this invention are potent inhibitors of calcium ion uptake into smooth muscle tissue and act to relax or prevent contraction of tissue mediated by calcium mechanisms. The compounds of this invention have therapeutic utility in the treatment of cardiovascular disorders including hypertension, ischemia, angina, arrhythmias, congestive heart failure, peripheral vascular disorders such as intermittant claudication, migraines, myocardial infarction, platelet aggregation and stroke.

In addition, the compounds of the invention possess utility with respect to other disorders such as hypersensitivity, allergy, asthma, dysmenorrhea, bronchoconstriction, esophageal spasm, premature labor and urinary tract, gastric hypersecretory and membrane integrity disorders. The compounds, compositions and methods for making the various aspects of the present invention will become more readily apparent from the following description.

Description and Preferred Embodiments

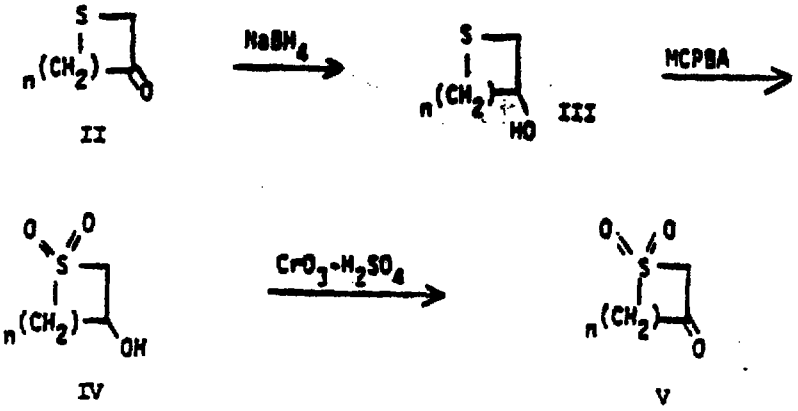
Various terms used herein should be understood to signify the following:
Unless specified otherwise, the term "halo" means fluoro, chloro, bromo and iodo.

The phrase "pharmaceutically acceptable salts" denotes salts of the free base which possess the desired pharmacological activity of the free base and which are neither biologically nor otherwise undesirable. These salts may be derived from inorganic or organic acids. Examples of inorganic acids are hydrochloric acid, nitric acid, hydrobromic acid, sulfuric acid or phosphoric acid. Examples of organic acids are acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

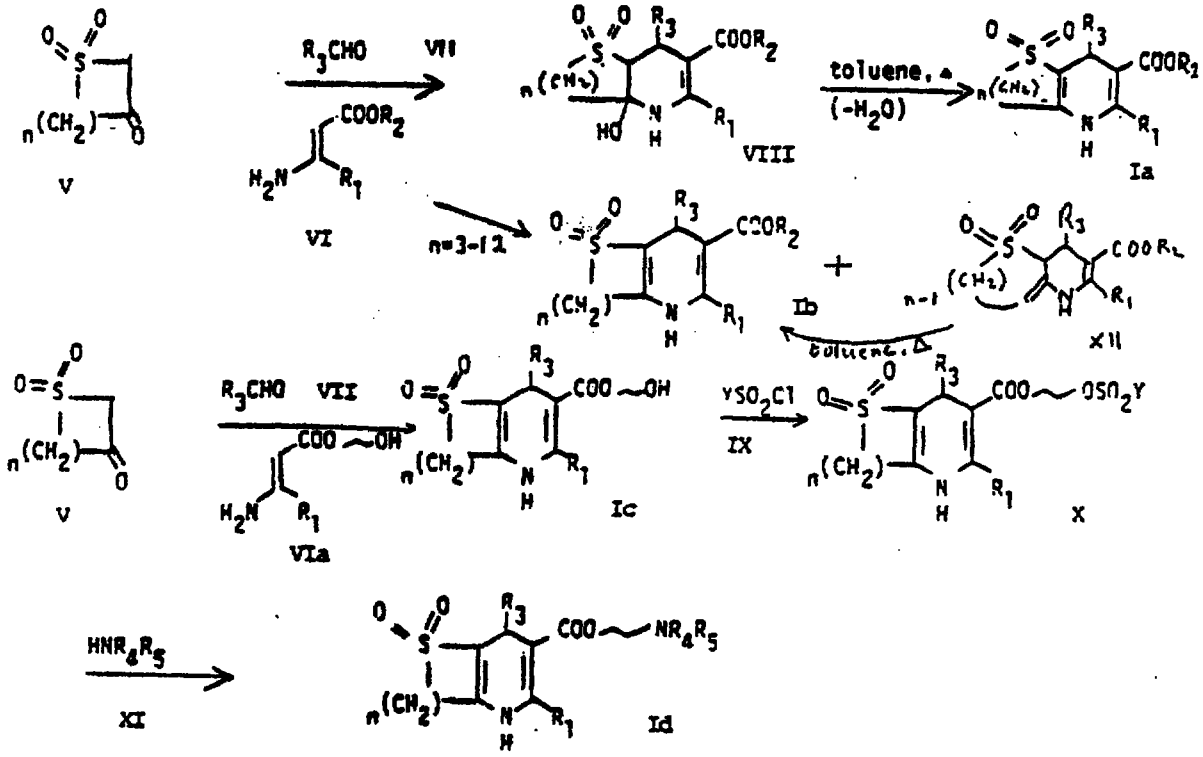
Pharmaceutical compositions containing a compound of the present invention as the active ingredient in intimate admixture with a pharmaceutical carrier can be prepared according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., aerosol, intravenous, sublingual, oral or topical. 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, binders, disintegrating agents and the like in the case or 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. For aerosol use, suspensions or solutions may be employed. 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 novel compounds of the present invention may be synthesized according to the following reaction scheme wherein R_1, R_2, R_3, R_4, R_5, are as defined above, MCPBA signifies m-chloroperoxybenzoic acid, and Y is p-methylphenyl or alkyl.

Sulfones Synthesis



Synthetic Routes to Dioxothiacycloalkeno[3,2-b]pyridines



With reference to the above Reaction Scheme, the synthesis of the compounds of this invention is accomplished as follows:

The 3-keto cyclic sulfones of formula V (in the instance wherein n is 1-4) can be prepared in accordance with the procedure disclosed in B. Listert, P. Küffner, and T.J. Arackel, Chem. Ber. 110, 1069-1085 (1977).

However, in the case of 3-oxo-tetrahydrothiophene-1,1-dioxide, that is wherein n is 2, the reference procedure is quite laborious. It has been found, in accordance with the present invention, that the compounds of formula V, in which n is 2 or 3, can be obtained in high yield in a straightforward manner from the respective 3-cyclic sulfides of formula II. Said compound of formula II may be prepared in accordance with the procedure disclosed in E.A. Fehnel, J. Amer. Chem. Soc. 74, 1569-74 (1952).

The 3-keto moiety of compound II is reduced to an alcohol (compound III) preferably with sodium borohydride although a number of other reducing agents such as diborane, lithium aluminum hydride or sodium cyanoborohydride may be used. Thereafter compound III is oxidized to compound IV preferably with m-chloroperoxybenzoic acid. Other suitable oxidizing agents are hydrogen peroxide or sodium periodate. Finally, the hydroxy moiety on compound IV is reoxidized to the corresponding keto moiety in compound V, preferably using Jones reagent (chromic anhydride in dilute sulfuric acid which is added to a solution of the alcohol in acetone). Other suitable oxidizing agents are: potassium dichromatic or Collins reagent (chromic anhydride in pyridine).

The 7, 8 and 9 membered 3-keto cyclic sulfones may be prepared in accordance with the method described in the Listert et al reference, previously mentioned.

Compounds of the formula I, wherein n is 1-12 (designated compound Ia in the following Reaction Scheme) may be prepared by stirring equal molar amounts of for example 3-oxotetrahydrothiophene-1,1-dioxide, the appropriately substituted aldehyde of formula VII and the substituted 3-aminoester of formula VI in ethanol for two to twenty-four hours at room temperature (see example 4). The resultant hydroxy intermediate of formula VIII is a novel compound. Said compound VIII is then heated in refluxing toluene for one to twenty-four hours to effect dehydration, thus producing compound Ia (see example 5).

The 6 to 15 membered cyclic sulfone products of formula I (wherein n is 3-12) may be obtained directly by refluxing a stirred ethanolic mixture of equimolar amounts of the ketosulfone of formula V, the aldehyde of formula VII and the substituted 3-aminoester of formula VI for about 16 hours in accordance with the procedure of example 6. The resultant product wherein n is 3-12, is designated compound Ib and/or XII. Note that compound 1b is actually the same as compound 1a, but obtained by a different route. Where the novel compound XII is formed, it can be converted to Ib by heating with ethanolic hydrogen chloride or toluene.

The preparation of compound I wherein R_2 is alkylene-NR_4R_5 can also be achieved when a compound of the formula V is reacted with an appropriate aldehyde of the formula VII and 2-hydroxyethyl-3-aminocrotonate of formula VIa in order to prepare the intermediate of formula Ic (see example VIII). The latter intermediate of formula Ic is then converted to the sulfonyl ester preferably by refluxing with a compound of the formula IX, wherein Y is p-methylphenyl or alkyl. The sulfonyl ester of formula X is then displaced with an appropriate amine of formula XI in order to produce a compound of the formula Id (see example 9).

In the following examples, both example 6 and example 10 illustrate the preparation of compound Ib, by the direct reaction of compound V, compound VII and compound VI, in the instance wherein n is 3-12.

Various Reaction Schemes discussed above are disclosed in the following additional references:

G.A. Pagani, J. Chem. Soc., Perkin Trans. 2, 1392-7 (1974), K.G. Mason, M.A. Smith, and E.S. Stern, J. Chem. Soc. (C) 2171-76 (1967).

Maruko Seiyaku, Japan No. 58201764 (1984).

The following specific examples are illustrative of the present invention and should not be considered as limitative thereof in any manner.

EXAMPLES:

Example 1

Tetrahydrothiopyran-3-ol.

To a solution of tetrahydrothiopyran-3-one (ref 4) (10.0g, 0.086 moles) in ethanol was added sodium borohydride (3.25 g, 0.086 moles) over a 5 minute period. After stirring for 30 minutes, a 1 N. solution of hydrochloric acid was added until a pH of 5 was reached. The reaction mixture was diluted with water and extracted with dichloromethane (6 x 50 mL). The organic phase was dried over magnesium sulfate, filtered, concentrated in vacuo, and distilled (approx. 100 torr, 158°C) to give 6.8 g product. H' NMR $CDCl_3$ 3.9 (broad singlet, 1H) 2.2-2.9 (multiplet, 5H) 1.4-2.2 (multiplet, 4H).

Example 2

Tetrahydrothiopyran-3-ol-1,1-dioxide.

A solution of tetrahydrothiopyran-3-ol (6.8 g, 0.58 moles) and chloroform (250 mL) was cooled to 0°C and treated with m-chloroperoxybenzoic acid (23.4 g, 0.135 moles) at a rate which did not cause the

temperature to rise above 10 °C. After addition was complete, the thickened mixture was stirred at 0 °C for 1 hour and then at room temperature for 30 minutes. The resulting solid was removed by filtration and the filtrate evaporated in vacuo. The resulting solid was diluted with ethanol and evaporated in vacuo to remove remaining chloroform. The resulting solid was diluted with water (150 mL) and filtered. The filtrate was evaporated in vacuo and residual water was removed by repeated evaporation with toluene. This afforded 7.5 g of product as a colorless oil. H' NMR D_6-DMSO 4.3 (broad singlet, 1H) 3.4-4.0 (multiplet, 1H) 2.7-3.3 (multiplet, 4H) 1.2-2.1 (multiplet, 4H).

Example 3

Tetrahydrothiopyran-3-one-1,1-dioxide.

To a solution of tetrahydrothiopyran-3-ol-1,1-dioxide (7.5 g, 0.05 moles) and acetone (150 mL) was slowly added enough Jones reagent to maintain a brown color for at least 10 minutes without need for additional reagent. The excess reagent was reduced by addition of isopropanol (5 mL). The mixture was filtered through anhydrous magnesium sulfate and the chromium salts were washed 3x with acetone. The solvent was removed in vacuo to give a solid which was triturated with ethanol. The resulting crystals were isolated by filtration and rinsed 3x with diethyl ether. After drying, 5.0 g of product was obtained. H' NMR $CDCl_3$ 4.0 (singlet, 2H) 3.3 (triplet, 2H) 2.6 (triplet, 2H) 2.3 (multiplet, 2H).

Example 4

Methyl 2,3,3a,4,7,7a-hexahydro-3a-hydroxy-5-methyl-7-(2-nitrophenyl)-1,1-dioxo-thieno[3,2-b]pyridine-6-carboxylate

A solution of tetrahydrothiophene-3-oxo-1,1-dioxide (1.3 g, 0.01 moles), 2-nitrobenzaldehyde (1.5 g, 0.01 moles) and methyl 3-aminocrotonate (1.1 g, 0.01 moles) in ethanol (20 mL) was stirred overnight. The resulting crystals were isolated by filtration and washed 2x with ethanol and 2x with diethyl ether. After drying under high vacuum for 24 hours 2.54 g of product was obtained, mp 175-179 °C (dec).

Example 5

Methyl 2,3,4,7,-tetrahydro-5-methyl-7-(2-nitrophenyl) -1,1-dioxothieno[3,2-b]pyridine-6-carboxylate.

A mixture of methyl 2,3,3a,4,7,7a-hexahydro-3a-hydroxy-5-methyl-7-(2-nitrophenyl)-1,1-dioxothieno [3,2-b]pyridine-6-carboxylate (2.5 g, 0.0065 moles) and toluene (60 mL) was refluxed for 24 hours. The solvent was removed in vacuo and the resulting solid was recrystallized from ethanol. The crystals were washed with diethyl ether 2x and dried at 65 °C under high vacuum for 48 hours. This gave 1.78 g product; mp 215-217 °C.

Example 6

Methyl 3,4,5,8,-tetrahydro-6-methyl-8-(3-nitrophenyl)-1,1-dioxo-2H-thiopyrano-[3,2-b]pyridine-7-carboxylate.

A mixture of tetrahydrothiopyran-3-one-1,1-dioxide (0.830 g, 0.0056 moles), 3-nitrobenzaldehyde (0.846 g, 0.0056 moles) and methyl 3-aminocrotonate (0.644 g, 0.0056 moles) in methanol (20 mL) was refluxed for 16 hours. After cooling, the resulting solid was isolated by filtration and washed with diethyl ether. This solid was dried at 40 °C for 4 hours under vacuum to give 0.620 g product; mp 236-238 °C.

Example 7

2-Hydroxyethyl 3-Aminocrotonate

Anhydrous ammonia gas was bubbled through a solution of 2-hydroxyethyl 3-oxo-butyrate (25 g, 0.17 moles) (ref 5) and ethanol (250 mL) for 20 minutes. This solution was stirred for 16 hours at room temperature. The solvent was removed in vacuo and the resulting oil was chromatographed on silica gel (250 g) using ethyl acetate-hexane 60:40 as eluant. The enriched fractions were combined and the solvent removed in vacuo to give the product: H' NMR $CDCl_3$ 4.33 (t, 2H) 3.85 (t, 2H) 3.55 (s, 1H) 2.85 (broad

singlet, 1H) 2.31 (s, 3H).

Example 8

2-Hydroxyethyl 3,4,5,8-tetrahydro-6-methyl-8-(3-nitrophenyl)-1,1-dioxo-2H-thiopyrano [3,2-b]pyridine-7-carboxylate.

A mixture of tetrahydrothiopyran-3-one-1,1-dioxide (2.80 g, 0.0189 moles), 3-nitrobenzaldehyde (2.85 g, 0.0189 moles), 2-hydroxyethyl-3-aminocrotonate (3.28 g, 0.0226 moles), ammonium acetate (0.291 g, 0.0038 moles) and ethanol (35 mL) was refluxed for 16 hours. After cooling to room temperature the resulting solid was isolated by filtration, washed with ethanol and diethyl ether. The product was dried under vacuum for 16 hours at room temperature affording the product: mp 233-235 °C.

Example 9

N-Benzyl-N-methyl-2-aminoethyl 2,3,4,8-tetrahydro-6-methyl-8-(3-nitrophenyl)-1,1-dioxo-5H-thiopyrano[3,2-b] pyridine-7-carboxylate Hemioxalate.

A mixture of 2-hydroxyethyl 3,4,5,8-tetrahydro-6-methyl-8-(3-nitrophenyl)- 1,1-dioxo-2H-thiopyrano[3,2-b] pyridine-7-carboxylate (2.5 g, 0.0061 moles), p-toluenesulfonyl chloride (4.65 g, 0.0244 moles), triethylamine (2.46 g, 0.0244 moles) and dichloromethane (25 mL) was refluxed for 4.5 hours. The reaction mixture was cooled and the solvent removed in vacuo. The resulting oil was chromatographed on silica gel (170 g) using ethyl acetate - methanol 95:5 as eluant. The enriched fractions containing the tosylate (H' NMR $CDCl_3$ 7.3-8.2 (multiplet, 8H) 6.9 (singlet, 1H) 5.2 (singlet, 1H)) were combined and N-benzyl-N-methylamine (4.69 g, 0.0387 moles) was added to the solution. The solvent was removed in vacuo and the resulting residue was allowed to stand for 72 hours at room temperature. Chromatography of the mixture was accomplished on silica gel (170 g) using a mixture of ethyl acetate and methanol 97:3 as eluant. The isolated product was dissolved in ether and treated with a saturated solution of oxalic acid in diethyl ether. The resulting solid was collected by filtration, washed with diethyl ether and dried at 60 °C for 16 hours under vacuum affording the product (2.07 g) mp 220-222 °C.

Example 10

Ethyl 2,3,4,5,6,9-hexahydro-7-methyl-9-(3-nitrophenyl)-1,1-dioxothiacycloheptено[3,2-b]pyridine-8-carboxylate.

A solution of thiacycloheptane -3-one-1,1-dioxide (1.3 g, 0.0080 moles), 3-nitrobenzaldehyde (1.2 g, 0.0080 moles), ethyl 3-aminocrotonate (1.04 g, 0.0080 moles) and ethanol (20 mL) was refluxed 16 hours. After removal of the solvent in vacuo the residue was chromatographed on silica gel (170 g) using a mixture of ethyl acetate and hexane (4:1) as eluant. The enriched fractions were combined and the solvent removed in vacuo. The solid was triturated with diethyl ether, filtered and dried under vacuum overnight to give 1.52 g of product; mp 211-213 °C.

Example 11

Ethyl 3,4,5,7,10,10a-hexahydro-8-methyl-10-(3-nitrophenyl) -1, 1-dioxo-2H-thiacyclooctено[3,2-b] pyridine-9-carboxylate.

A solution of thiacyclooctane -3-one-1,1-dioxide (0.35g, 0.002 moles), 3-nitrobenzaldehyde (0.30g, 0.002 moles), ethyl 3-aminocrotonate (0.26g, 0.002 moles) and ethanol (30mL) was refluxed 16 hours. After cooling to room temperature a yellow precipitate formed which was isolated by filtration, washed with diethyl ether and dried in vacuo to afford the product (0.56g) mp 211-214 °C.

Example 12

Ethyl 3,4,5,6,7,10-hexahydro-8-methyl-10-(3-nitrophenyl-1, 1-dioxo-2H-thiacyclooctено[3,2-b] pyridine-9-carboxylate.

A mixture of ethyl 3,4,5,7,10,10a-hexahydro-8-methyl-10-(3-nitrophenyl)-1,1-dioxo-2H-thiacyclooctено-[3,2-b] pyridine-9-carboxylate (0.45g,0.0011 moles) and toluene (30mL) was refluxed for 24 hours. The resulting solid was isolated by filtration, washed with diethyl ether and dried in vacuo to afford the product mp 234-235 °C.

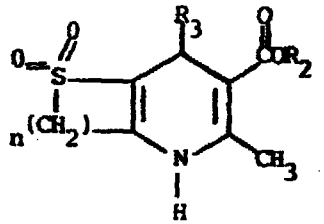
The compounds of the present invention were evaluated for their biological properties. The present compounds have shown the ability to influence calcium mediated events including inhibition of smooth muscle contraction of trachea and vascular tissues. The model screening regimen used to evaluate these compounds has shown:

1) Inhibition of nitrendipine binding to calcium channels.
2) Ability to modulate the activity of tissues which are dependent on calcium utilization as in trachea and vascular tissue,
3) Their use as antihypertensives and/or bronchodilating agents in mammals.

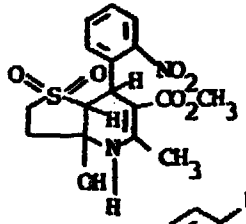
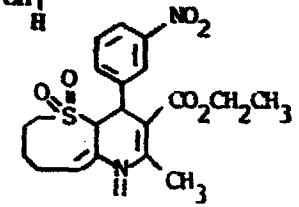
Based on the above results, it is believed that these compounds will be useful in hypertension, myocardial, ischemia, angina, congestive heart failure, migraine, myocardial infarction, platelet aggregation, stroke, hypersensitivity, allergy, asthma, gastric secretory dysmenorrhea, esophageal spasm, premature labor and urinary tract disorders.

The following Table 1 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 I



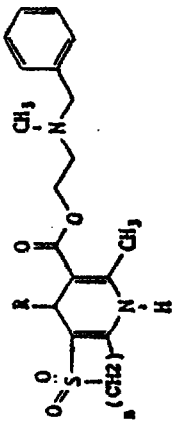
N	R_2	R_3	mp °C	Inhibition of Nitrendipine binding IC_{50} (μM)	Inhibition of Ca^{2+} dependent smooth muscle contraction % Inhibition	(μM) concentration
2	CH_3	C_6F_5	228–231	0.15	47	2.0
2	CH_3	3-NO_2-C_6H_4	198–201	0.70	76	10.0
2	CH_3	3-Cl-C_6H_4	196–199	0.93	–	–
2	CH_3	3-CN-C_6H_4	204–205	2.0	–	–
2	CH_3	2-NO_2-C_6H_4	215–217	1.35	63	2.0
2	$CH_2CH_2NCH_3CH_2C_6H_5$	3-NO_2-C_6H_4	117–123	1.0	65	5.0
3	CH_2CH_3	2-NO_2-C_6H_4	215–217	1.5	75	10.0
3	CH_2CH_3	3-NO_2-C_6H_4	207–209	0.17	69	10.0
3	CH_3	3-NO_2-C_6H_4	236–238	0.16	57	10.0
3	CH_3	2-NO_2-C_6H_4	291–292	0.89	84	10.0

N	R_2	R_3	mp °C	Inhibition of Nitrendipine binding IC_{50} (μM)	Inhibition of Ca^{2+} dependent smooth muscle contraction % Inhibition	(μM) concentration
3	$CH_2C_6H_5$	$2\text{-}NO_2\text{-}C_6H_4$	123-126 dec	3.4	69	10.0
3	CH_3	C_6F_5	242-244	0.40	46	0.5
3	$CH_2CH_2NCH_3CH_2C_6H_5$	$3\text{-}NO_2\text{-}C_6H_4$	220-222	1.85	46	2.0
4	CH_3	$3\text{-}NO_2\text{-}C_6H_4$	217-219	0.027, 0.039	94	2.0
2	CH_2CH_3	C_6F_5	223-226	0.56	48	2.0
4	CH_2CH_3	C_6F_5	202-205	0.028	95	0.5
4	$CH_2CH_2NCH_3CH_2C_6H_5$	C_6F_5	160-165	0.035	74	0.2
4	CH_2CH_3	$3\text{-}NO_2\text{-}C_6H_4$	211-213	0.044	96	2.0
4	$CH_2CH_2NCH_3CH_2C_6H_5$	$3\text{-}NO_2\text{-}C_6H_4$	123-127	0.13	68	0.2
			175-179 dec	56% @ 8.0	26	2.0
			211-214	0.27	53%	2.0
5	$-CH_2CH_3$	$3\text{-}NO_2\text{-}C_6H_4$	234-235	0.0055	71%	0.1

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TABLE II

n	R	X	MP	Mass Spectra MH+	Inhibition of Nitrendipine binding IC^{50}(μM)	Inhibition of Trachea Muscle Contraction % Inhibition	Concentration (μM)	Inhibition of Aorta Muscle Contraction % Inhibition	Concentration (μM)
4	3-$NO_2C_6H_4$	$CH_2CH_2CH_2NCH_2CH_2C_6H_5$	190-194	540	0.29	50	2.0	25	0.1
4	3-NO_2-C_6H_4		131-134	552	0.860	17	2.0	12	0.1
4	3-NO_2-C_6H_4	CH_2CH_2OH	185-187	423	2.40	23	2.0	41	3.0
5		CH_2CH_3	180-185	423	0.108	79	0.3	42	0.1
4	3-NO_2-C_6H_4	$CH_2CH_2NHC_6H_5$	147-150	498	0.016	72	1.0	48	0.1
4	3-NO_2-C_6H_4		202-204	524	0.100	56	1.0	80	0.1
5	3-NO_2-C_6H_4		159-165	498	0.065	53	0.1	48	0.1
4	2-CF_3-C_6H_4	$CH_2CH_2NCH_3C_6H_5$	135-137	535	0.046	59	0.1	57	0.1
5	2,3-Cl_2-C_6H_3	$CH_2CH_2NCH_3CH_2C_6H_5$	162-166	577	0.149	57	1.0	67	0.1
4	2-NO_2-C_6H_4	$CH_2CH_2NCH_3C_6H_5$	137-140	512	0.086	57	0.1	43	0.1
5	2-NO_2-C_6H_4	$CH_2CH_2NCH_3CH_2C_6H_5$	144-147	540	0.105	69	0.1	73	0.1
4	3-NO_2-C_6H_4		141-145	538	0.200	45	0.2	53	0.1
5	3-NO_2-C_6H_4		184-185	548	0.070	29	0.1	48	0.1
4	2-NO_2-C_6H_4	$CH_2CH_2CH_2NCH_3CH_2C_6H_5$	127-130	540	1.0	41	1.0	7.7	0.1
4	3-NO_2-C_6H_4	$CH_2CH_2NCH_3C_6H_5$	186-187	512	0.045	65	1.0	53	0.1
5	C_6F_5	$CH_2CH_2NCH_3C_6H_5$	124-126	571	0.018	47	0.1	63	0.1
4	C_6F_5		243-245	524		53	2.0		
4	2,3-Cl_2-C_6H_3		195-197	503		51	2.0		



N	R	MP	Mass Spectra MH+	Inhibition Nitrendipine binding IC^{50}(μM)	Inhibition Contraction Trachea % Inhibition	Inhibition Contraction Trachea Concentration (μM)	Inhibition Contraction Aorta % Inhibition	Inhibition Contraction Aorta Concentration (μM)
4	2-CF_3-C_6H_4	101-104	549	0.16	64	0.1	85	0.1
4	2-Cl,6-F-C_6H_3	156-162	533	0.029	50	0.1	66	0.1
4	2,5-F_2-C_6H_3	152-160	517	0.12	43	0.1	47	0.1
4	2,3-Cl_2-C_6H_3	150-157	549	0.10	62	0.1	83	0.1
4	3-CF_3-C_6H_4	117-120	549	2.8	37	0.2	44	0.1
4	2-F-C_6H_4	137-140	499	0.44	84	2.0	32	0.1
4	2-NO_2-C_6H_4	144-147	526	0.44	49	0.1	44	0.1
5	C_6F_5	181-184	585	0.087	50	0.1	70	0.1
4	2-Cl,5-NO_2-C_6H_3	170-173	560	0.26	38	0.1	63	0.1
4	2-Cl-C_6H_4	128-134	515	0.22	57	0.1	54	0.1
4	2-Cl,3-CF_3-C_6H_3	168-172	583	0.39	50	0.2	66	0.1
5	2-Cl,3-CF_3-C_6H_3	165-175	597	0.20	57	0.1	78	0.1
5	3-NO_2-C_6H_4	150-154	540	0.045	43	0.1	67	0.1
5	2,3-Cl_2-C_6H_3	155-160	563	0.075	26	0.1	58	0.1
5	2-NO_2-C_6H_4	144-147	540	0.11	48	0.1	73	0.1
6	2-Cl,3-CF_3-C_6H_3	150-155	611	0.47	46	2.0	30	0.1
4	2,6-Cl_2-C_6H_3	160-165	549	0.086	55	0.1	50	0.1
5	2-$OCHF_2$-C_6H_4	88-91	561	0.095	76	0.1	80	0.01
4	2-$OCHF_2$-C_6H_4	130-134	547	0.072	54	0.1		

The assay for inhibition of nitrendipine binding follows 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 5X volume of 0.05M Hepes buffer, pH 7.4. The homogenate is centrifuged at 4000 xg for 10 minutes; the supernatant is recentrifuged at 42,000 xg 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 fibers. 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:

Trachea 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. After cutting the cartilage, the trachealis muscle tissue is suspended in oxygenated Krebs-Henseleit buffer at 37°C in a 25 ml tissue bath. After a 60 minutes equilibration period, the tissues are challenged with 10 uM 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 mMKcl. After 30 minutes, the contraction is recorded and used to determine the % inhibition of control.

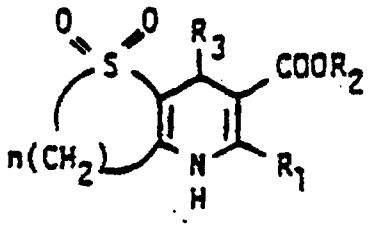
The percent inhibition of smooth muscle contraction is calculated from response data before and after drug treatment.

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

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

Claims

1. A compound of the formula I



(I)

wherein:

n is an integer from 1 to 12;

R_1 is hydrogen, C_1-C_8 alkyl or C_1-C_8 haloalkyl;

R_2 is C_1-C_8 alkyl, C_3-C_7 cycloalkyl or alkylene-X having at least 2 carbon atoms, wherein X = alkoxy having up to 4 carbon atoms, hydroxy, halo, p-tosyloxy, mesyloxy, amino, pyridyl or -NR_4R_5, wherein R_4 and R_5 are the same or different, and are selected from hydrogen, C_1-C_8 alkyl, phenyl, benzyl, phenethyl, or R_4/R_5 and the nitrogen atom to which they are attached form a 5, 6 or 7-membered heterocyclic ring which optionally contains an oxygen or sulfur or an additional nitrogen atom, or said heterocyclic ring may be fused to a benzene ring as in indoline, isoindoline, tetrahydroquinoline or tetrahydroisoquinoline, and in the instance wherein said heterocyclic ring is piperazino, said piperazino may optionally be substituted in the 4-position with the substituent R_6, which is selected from C_1-C_8 alkyl, benzyl, phenyl or phenyl substituted by alkoxy having up to 4 carbon atoms, halo, C_1-C_8 alkyl, nitro or trifluoromethyl;

R_3 is 2-pyridyl, 3-pyridyl, 3-pyridyl substituted at positions 2, 4, 5 or 6 with one or more groups selected from halogen, nitro, alkoxy or alkylthio having up to 4 carbon atoms, cyano, difluoromethoxy,

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 fibers. After rinsing, the filters are dried and counted in a liquid scintillation counter.

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

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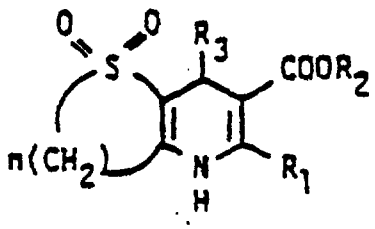
The percent inhibition of smooth muscle contraction is calculated from response data before and after drug treatment.

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

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

Claims

1. A compound of the formula I



(I)

wherein:

n is an integer from 1 to 12;

R_1 is hydrogen, C_1-C_8 alkyl or C_1-C_8 haloalkyl;

R_2 is C_1-C_8 alkyl, C_3-C_7 cycloalkyl or alkylene-X having at least 2 carbon atoms, wherein X = alkoxy having up to 4 carbon atoms, hydroxy, halo, p-tosyloxy, mesyloxy, amino, pyridyl or -NR_4R_5, wherein R_4 and R_5 are the same or different, and are selected from hydrogen, C_1-C_8 alkyl, phenyl, benzyl, phenethyl, or R_4/R_5 and the nitrogen atom to which they are attached form a 5, 6 or 7-membered heterocyclic ring which optionally contains an oxygen or sulfur or an additional nitrogen atom, or said heterocyclic ring may be fused to a benzene ring as in indoline, isoindoline, tetrahydroquinoline or tetrahydroisoquinoline, and in the instance wherein said heterocyclic ring is piperazino, said piperazino may optionally be substituted in the 4-position with the substituent R_6, which is selected from C_1-C_8 alkyl, benzyl, phenyl or phenyl substituted by alkoxy having up to 4 carbon atoms, halo, C_1-C_8 alkyl, nitro or trifluoromethyl;

R_3 is 2-pyridyl, 3-pyridyl, 3-pyridyl substituted at positions 2, 4, 5 or 6 with one or more groups selected from halogen, nitro, alkoxy or alkylthio having up to 4 carbon atoms, cyano, difluoromethoxy,

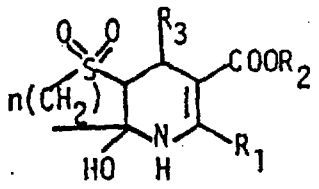
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difluoromethylthio or C_1-C_8alkylsulfonyl; 2-thienyl, 3-thienyl, 2,1,3-benzoxadiazolyl, 2,1,3-benzthiadiazolyl or phenyl optionally substituted at positions 2 through 6 with one or more groups selected from hydrogen, C_1-C_8 alkyl, alkoxy having up to 4 carbon atoms, cyano, difluoromethoxy, difluoromethylthio, C_1-C_8 alkylsulfonyl, halo, nitro or trifluoromethyl,
their optical antipodes or the pharmaceutically acceptable acid and base addition salts thereof.

2. Any one of the compounds 1 to 29 listed below:
1) Ethyl 2,3,4,7-tetrahydro-5-methyl-7-(3-nitrophenyl)-1,1-dioxothieno[3,2-b]pyridine-6-carboxylate.
2) N,N-Dimethylaminoethyl 2,3,4,7-tetrahydro-5-methyl-7-(3-nitrophenyl)-1,1-dioxothieno[3,2-b]-pyridine-6-carboxylate.
3) N-Benzyl-N-methylaminoethyl 2,3,4,7-tetrahydro-5-methyl-7-(3-nitrophenyl)-1,1-dioxothieno [3,2-b]pyridine-6-carboxylate.
4) Ethyl 3,4,5,8-tetrahydro-6-methyl-8-(3-nitrophenyl)-1,1-dioxo-2H-thio-pyrano [3,2-b]pyridine-7-carboxylate.
5) N,N-Dimethylaminoethyl 3,4,5,8-tetrahydro-6-methyl-8-(3-nitrophenyl)-1,1-dioxo-2H-thiopyrano[3,2-b]pyridine-7-carboxylate.
6) N-Benzyl-N-methylaminoethyl 3,4,5,8-tetrahydro-6-methyl-8-(3-nitrophenyl)-1,1-dioxo-2H-thiopyrano[3,2-b]pyridine-7-carboxylate.
7) N-Benzyl-N-methylaminoethyl 3,4,5,8-tetrahydro-6-methyl-8-(2,3,4,5,6-pentafluorophenyl)-1,1-dioxo-2H-thiopyrano[3,2-b]pyridine-7-carboxylate.
8) Ethyl 9-(2,3,4,5,6-pentafluorophenyl)-2,3,4,5,6,9-hexahydro-7-methyl-1,1-dioxothiacycloheptено-[3,2-b] pyridine-8-carboxylate.
9) N-Benzyl-N-methylaminoethyl 2,4,5,6,9-hexahydro-7-methyl-9-(3-nitropnenyl)-1,1-dioxothiacycloheptено [3,2-b]pyridine-8-carboxylate.
10) N,N-Dimethylaminoethyl 2,3,4,5,6,9-hexahydro-7-methyl-9-(3-nitrophenyl)-1,1-dioxothiacycloheptено[3,2-b] pyridine-8-carboxylate.
11) 2-Methoxyethyl 2,3,4,5,6,9-hexahydro-7-methyl-9-(3-nitrophenyl)-1,1-dioxo-thiacycloheptено[3,2-b] pyridine-8-carboxylate.
12) N-Benzyl-N-methylaminoethyl 9-(2,3,4,5,6-pentafluorophenyl)-2,3,4,5,6,9-hexahydro-7-methyl-1,1-dioxothiacycloheptено[3,2-b]pyridine-8-carboxylate.
13) Ethyl 10-(2,3,4,5,6-pentafluorophenyl)-3,4,5,6,7,10-hexahydro-8-methyl-1,1-dioxo-2H-thiacycloocteno[3,2-b]pyridine-9-carboxylate.
14) N-Benzyl-N-methylaminoethyl 10-(2,3,4,5,6-pentafluorophenyl)-3,4,5,6,7,10-hexahydro-8-methyl-1,1-dioxo-2H-thiacycloocteno[3,2-b]pyridine-9-carboxylate.
15) N-Benzyl-N-methylaminoethyl 3,4,5,6,7,10-hexahydro-8-methyl-10-(3-nitrophenyl)-1,1-dioxo-2H-thiacycloocteno [3,2-b]pyridine-9-carboxylate.
16) N-Benzyl-N-methylaminoethyl 11-(3-nitrophenyl) 2,3,4,6,7,8,11-octahydro-9-methyl-1,1-dioxothiacyclononeno[3,2-b]pyridine-10-carboxylate.
17) N-Benzyl-N-methylaminoethyl 2,4,5,6,9-hexahydro-6-methyl-9-(3-nitrophenyl)-1,1-dioxothiacycloheptено [3,2-b]pyridine-8-carboxylate.
18) N-Benzyl-N-methylaminoethyl 9-(2-chlorophenyl)-2,4,5,6,9-hexahydro-7-methy1-1,1-dioxothiacycloheptено [3,2-b]pyridine-8-carboxylate.
19) N-Benzyl-N-methylaminoethyl 9-(2,3-dichlorophenyl)-2,4,5,6,9-hexahydro-7-methyl-1,1-dioxothiacycloheptено[3,2-b]pyridine-8-carboxylate.
20) N-Benzyl-N-methylaminoethyl 9-(2-chloro-6-fluorophenyl)-2,4,5,6,9-hexahydro-7-methyl-1,1-dioxothiacycloheptено[3,2-b]pyridine-8-carboxylate.
21) N-Benzyl-N-methylaminoethyl 9-(2-cifluoromethoxyphenyl)-2,4,5,6,9-hexahydro-7-methyl-1,1-dioxothiacycloheptено[3,2-b]pyridine-8-carboxylate.
22) N-Benzyl-N-methylaminoethyl 2,4,5,6,9-hexahydro-7-methyl-9-(2-trifluoromethylphenyl)-1,1-dioxothiacycloheptено[3,2-b]pyridine-8-carboxylate.
23) N-Benzyl-N-methylaminoethyl 10-(2-chlorophenyl)-3,4,5,6,7,10-hexahydro-8-methyl-1,1-dioxocycloocteno [3,2-b]pyridine-9-carboxylate.
24) N-Benzyl-N-methylaminoethyl 10-(2,3-dichlorophenyl-3,4,5,6,7,10-hexahydro-8-methyl-1,1-dioxothiacycloocteno[3,2-b]pyridine-9-carboxylate.
25) N-Benzyl-N-methylaminoechyl 10-(2-difluoromethoxyphenyl)-3,4,5,6,7,10-hexahydro-8-methyl-1,1-dioxothiacycloocteno[3,2-b]pyridine-9-carboxylate.
26) N-Benzyl-N-methylaminoethyl 10-(2-chloro-6-fluorophenyl)-3,4,5,6,7,10-hexahydro-8-methyl-1,1-dioxothiacycloocteno[3,2-b]pyridine-9-carboxylate.

27) N-Benzyl-N-methylaminoethyl 10-(2-chloro-3-trifluoromethylphenyl)-3,4,5,6,7,10-hexahydro-8-methyl-1,1-dioxothiacycloocteno[3,2-b]pyridine-9-carboxylate.
28) N-Benzyl-N-methylaminoethyl 12-(2-chloro-3-trifluoromethylphenyl)-2,3,4,5,6,7,8,11-octahydro-9-methyl-1,1-dioxothiacyclononeno[3,2-b]pyridine-10-carboxylate.
29) N-Methyl-N-phenylaminoethyl 10-(2,3,4,5,6-pentafluorophenyl)-3,4,5,6,7,10-hexahydro-8-methyl-1,1-dioxothiacycloocteno[3,2-b]pyridine-9-carboxylate.

3. A compound of the formula VIII

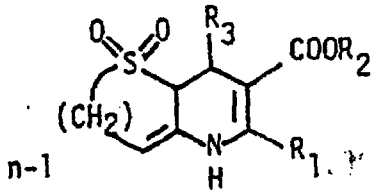


(VIII)

wherein n, R_1, R_2 and R_3 are as defined in claim 1, their optical antipodes or the pharmaceutically acceptable acid and base addition salts thereof.

4. The compound of claim 3, which is methyl 2,3,3a,4,7,7a-hexahydro-3a-hydroxy-5-methyl-7-(2-nitrophenyl)-1,1-dioxothieno [3,2-b] pyridine-6-carboxylate.

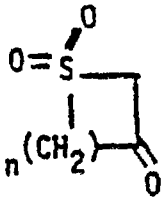
5. A compound of the formula XII



(XII)

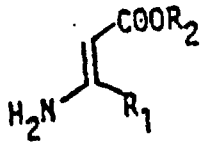
wherein n is an integer from 3 to 12 and R_1, R_2 and R_3 are as defined in claim 1, their optical antipodes or the pharmaceutically acceptable acid and base addition salts thereof.

6. A process for preparing a compound of claim 1 or claim 2 which comprises:
reacting a compound of formula V



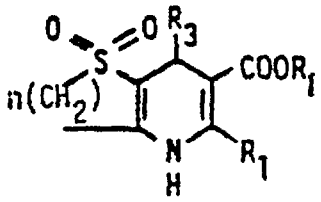
(V)

with a compound of formula VI



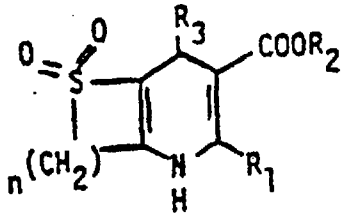
(VI)

and a compound of the formula R_3CHO, to prepare a compound a compound of the formula VIII as defined in claim 3 in the instance wherein n is 2, and thereafter dehydrating said compound VIII in order to prepare compound of the formula Ia



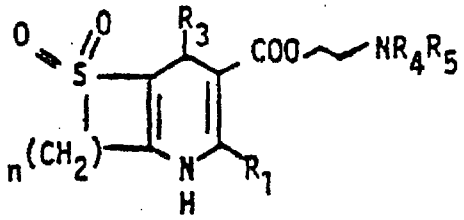
(Ia)

or to prepare a compound of the formula Ib



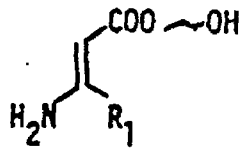
(Ib)

in the instance wherein n is 3, 4, 5 or 6; or to prepare a compound of the formula XII as defined in claim 5, said latter process comprising reacting a compound of the formula V with a compound of the formula VI and a compound of the formula R_3CHO in order to prepare said compound of formula XII and thereafter, if desired, converting compound XII to compound Ib; or, in the instance wherein it is desired to prepare a final compound of the formula Id



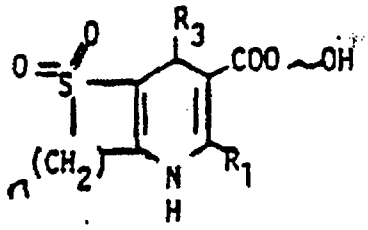
(Id)

reacting a compound of the formula V with a compound of the formula VIa



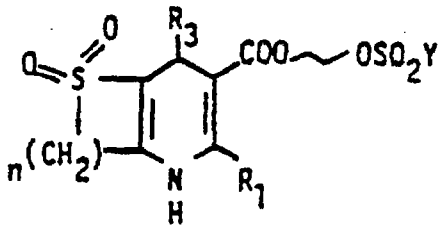
(VIa)

and a compound of the formula R_3CHO in order to prepare a compound of the formula Ic



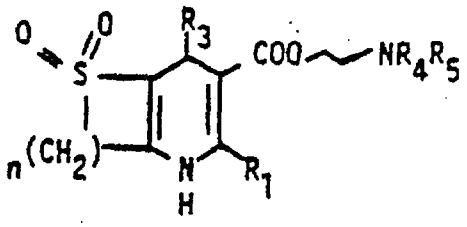
(Ic)

then reacting said compound Ic with a compound of the formula YSO_2Cl, wherein Y is p-methylphenyl or alkyl, in order to prepare compound of the formula X



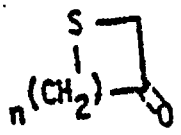
(X)

and thereafter reacting said compound X with a compound of the formula HNR_4R_5 to prepare a compound of the formula Id



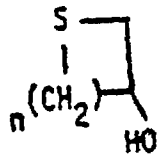
(Id)

7. The process of claim 6, wherein said compound of the formula V, in the instance wherein n is 2 or 3, is initially prepared by reducing a compound of the formula II with $NaBH_4$



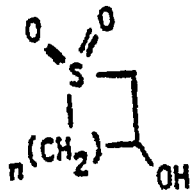
(II)

in order to prepare a compound of the formula III



(III)

followed by oxidizing said compound III with m-chlorobenzoic acid, in order to prepare a compound of the formula IV



(IV)

and then reoxidizing said compound IV with Jones reagent in order to prepare said compound V.

8. A calcium channel antagonist composition comprising an inert carrier and, as an active ingredient, an effective calcium channel antagonist amount of the compound of any one of claims 1 to 5.

9. A pharmaceutical composition useful as a calcium channel antagonist in unit, topical, oral, sublingual, aerosol or intravenous dosage form, comprising from 0.001 mg/kg to 100 mg/kg of the compound of any one of claims 1 to 5 in admixture with a pharmaceutically-acceptable carrier.

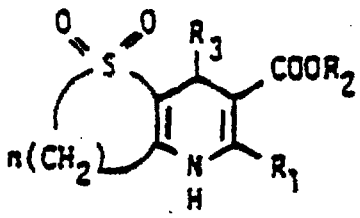
10. The composition of claim 9, comprising from 0.001 mg/kg to 20 mg/kg of the compound in admixture with the pharmaceutically acceptable carrier.

11. A compound of any one of claims 1 to 5 or a composition of any one of claims 8 to 10 for use in treating myocardial insufficiencies, including angina, vasospasm and infarction, cardiovascular disorders, including hypertension, migraine, stroke and platelet aggregation, allergies, hypersensitivities, brochospastic disorders, diarrhea or hypermotility of the G-I tract in a mammal.

12. A method of producing a composition according to any one of claims 8 to 10 comprising mixing the active agent with the pharmaceutically acceptable carrier.

Patentansprüche

1. Verbindung der Formel I



(I)

worin:

n eine ganze Zahl von 1 bis 12 ist;

R_1 gleich Wasserstoff, eine C_1 - C_8-Alkylgruppe oder eine halogenierte C_1 - C_8-Alkylgruppe ist;

R_2 eine C_1 - C_8-Alkylgruppe, eine C_3 - C_7-Cycloalkylgruppe oder eine Alkylen-X-Gruppe mit mindestens 2 Kohlenstoffatomen ist, wobei X = eine Alkoxygruppe mit bis zu 4 Kohlenstoffatomen,

* C L M S *

eine Hydroxygruppe, ein Halogenatom, eine p-Tosyloxygruppe, eine Mesyloxygruppe, eine Aminogruppe, eine Pyridylgruppe oder -NR_4R_5 ist, wobei R_4 und R_5 gleich oder verschieden sein können und ausgewählt sind aus Wasserstoff, einer C_1 - C_8-Alkylgruppe, einer Phenylgruppe, einer Benzylgruppe, einer Phenethylgruppe oder R_4/R_5 und das Stickstoffatom, an das sie gebunden sind, einen 5-, 6- oder 7-gliedrigen heterocyclischen Ring bilden, der gegebenenfalls Sauerstoff oder Schwefel oder ein weiteres Stickstoffatom enthält, oder der heterocyclische Ring an einen Benzolring kondensiert sein kann, wie in Indolin, Isoindolin, Tetrahydrochinolin oder Tetrahydroisochinolin, und in dem Fall, in dem der heterocyclische Ring Piperazin ist, das Piperazin gegebenenfalls in der 4-Stellung mit dem Substituenten R_6 substituiert sein kann, der ausgewählt ist aus einer C_1 - C_8-Alkylgruppe, einer Benzylgruppe, einer Phenylgruppe, oder einer Phenylgruppe, die mit einer Alkoxygruppe mit bis zu 4 Kohlenstoffatomen, einem Halogenatom, einer C_1 - C_8-Alkylgruppe, einer Nitrogruppe oder einer Trifluormethylgruppe substituiert ist;

R_3 eine 2-Pyridylgruppe, eine 3-Pyridylgruppe, eine 3-Pyridylgruppe, die in den Stellungen 2, 4, 5 oder 6 mit einer oder mehreren Gruppen, ausgewählt aus Halogen, Nitro, Alkoxy oder Alkylthio mit bis zu 4 Kohlenstoffatomen, Cyan, Difluormethoxy, Difluormethylthio oder C_1 - C_8-Alkylsulfonyl substituiert ist; eine 2-Thienylgruppe, eine 3-Thienylgruppe, 2,1,3-Benzoxadiazolylgruppe, eine 2,1,3-Benzthiadiazolylgruppe oder eine Phenylgruppe, die gegebenenfalls an den Stellungen 2 bis 6 mit einer oder mehreren Gruppen, ausgewählt aus Wasserstoff, C_1 - C_8-Alkyl, Alkoxy mit bis zu 4 Kohlenstoffatomen, Cyan, Difluormethoxy, Difluormethylthio, C_1 - C_8-Alkylsulfonyl, Halogen, Nitro oder Trifluormethyl, substituiert ist, deren optischen Antipoden oder deren pharmazeutisch verträglichen Säure- und Base-Additionssalzen.

2. Eine der im folgenden aufgelisteten Verbindungen 1 bis 29:

1) Ethyl-2,3,4,7-tetrahydro-5-methyl-7-(3-nitrophenyl)-1,1-dioxothieno[3,2-b]pyridin-6-carboxylat.

2) N,N-Dimethylaminoethyl-2,3,4,7-tetrahydro-5-methyl-7-(3-nitrophenyl)-1,1-dioxothieno[3,2-b]-pyridin-6-carboxylat.

3) N-Benzyl-N-methylaminoethyl-2,3,4,7-tetrahydro-5-methyl-7-(3-nitrophenyl)-1,1-dioxothieno-[3,2-b]pyridin-6-carboxylat.

4) Ethyl-3,4,5,8-tetrahydro-6-methyl-8-(3-nitrophenyl)-1,1-dioxo-2H-thio-pyrano-[3,2-b]pyridin-7-carboxylat.

5) N,N-Dimethylaminoethyl-3,4,5,8-tetrahydro-6-methyl-8-(3-nitrophenyl)-1,1-dioxo-2H-thiopyrano[3,2-b]pyridin-7-carboxylat.

6) N-Benzyl-N-methylaminoethyl-3,4,5,8-tetrahydro-6-methyl-8-(3-nitrophenyl)-1,1-dioxo-2H-thiopyrano[3,2-b]pyridin-7-carboxylat.

7) N-Benzyl-N-methylaminoethyl-3,4,5,8-tetrahydro-6-methyl-8-(2,3,4,5,6,-pentafluorphenyl)-1,1-dioxo-2H-thiopyrano[3,2-b]pyridin-7-carboxylat.

8) Ethyl-9-(2,3,4,5,6-pentafluorphenyl)-2,3,4,5,6,9-hexahydro-7-methyl-1,1-dioxothiacycloheptено[3,2-b]pyridin-8-carboxylat.

9) N-Benzyl-N-methylaminoethyl-2,3,4,5,6,9-hexahydro-7-methyl-9-(3-nitrophenyl)-1,1-dioxothiacycloheptено-[3,2-b]pyridin-8-carboxylat.

10) N,N-Dimethylaminoethyl-2,3,4,5,6,9-hexahydro-7-methyl-9-(3-nitrophenyl)-1,1-dioxothiacycloheptено[3,2-b]pyridin-8-carboxylat.

11) 2-Methoxyethyl-2,3,4,5,6,9-hexahydro-7-methyl-9-(3-nitrophenyl)-1,1-dioxo-thiacycloheptено[3,2-b]pyridin-8-carboxylat.

12) N-Benzyl-N-methylaminoethyl-9-(2,3,4,5,6-pentafluorphenyl)-2,3,4,5,6,9-hexahydro-7-methyl-1,1-dioxothiacycloheptено[3,2-b]pyridin-8-carboxylat.

13) Ethyl-10-(2,3,4,5,6-pentafluorphenyl)-3,4,5,6,7,10-hexahydro-8-methyl-1,1-dioxo-2H-thiacyclooctено[3,2-b]-pyridin-9-carboxylat.

14) N-Benzyl-N-methylaminoethyl-10-(2,3,4,5,6-pentafluorphenyl)-3,4,5,6,7,10-hexahydro-8-methyl-1,1-dioxo-2H-thiacyclooctено[3,2-b]-pyridin-9-carboxylat.

15) N-Benzyl-N-methylaminoethyl-3,4,5,6,7,10-hexahydro-8-methyl-10-(3-nitrophenyl)-1,1-dioxo-2H-thiacyclooctено-[3,2-b]pyridin-9-carboxylat.

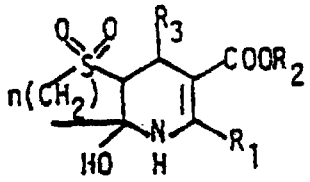
16) N-Benzyl-N-methylaminoethyl-11-(3-nitrophenyl)-2,3,4,6,7,8,11-octahydro-9-methyl-1,1-dioxothiacyclononeno[3,2-b]pyridin-10-carboxylat.

17) N-Benzyl-N-methylaminoethyl-2,4,5,6,9-hexahydro-6-methyl-9-(3-nitrophenyl)-1,1-dioxothiacycloheptено-[3,2-b]pyridin-8-carboxylat.

18) N-Benzyl-N-methylaminoethyl-9-(2-chlorphenyl)-2,4,5,6,9-hexahydro-7-methyl-1,1-dioxothiacycloheptено-[3,2-b]pyridin-8-carboxylat.

19) N-Benzyl-N-methylaminoethyl-9-(2,3-dichlorphenyl)-2,4,5,6,9-hexahydro-7-methyl-1,1-dioxothiacycloheptenо[3,2-b]pyridin-8-carboxylat.
20) N-Benzyl-N-methylaminoethyl-9-(2-chlor-6-fluorphenyl)-2,4,5,6,9-hexahydro-7-methyl-1,1-dioxothiacycloheptenо[3,2-b]pyridin-8-carboxylat.
21) N-Benzyl-N-methylaminoethyl-9-(2-cifluormethoxyphenyl)-2,4,5,6,9-hexahydro-7-methyl-1,1-dioxothiacycloheptenо[3,2-b]pyridin-8-carboxylat.
22) N-Benzyl-N-methylaminoethyl-2,4,5,6,9-hexahydro-7-methyl-9-(2-trifluormethylphenyl)-1,1-dioxothiacycloheptenо[3,2-b]pyridin-8-carboxylat.
23) N-Benzyl-N-methylaminoethyl-10-(2-chlorphenyl)-3,4,5,6,7,10-hexahydro-8-methyl-1,1-dioxocyclooctenо[3,2-b]pyridin-9-carboxylat.
24) N-Benzyl-N-methylaminoethyl-10-(2,3-dichlorphenyl-3,4,5,6,7,10-hexahydro-8-methyl-1,1-dioxothiacyclooctenо[3,2-b]pyridin-9-carboxylat.
25) N-Benzyl-N-methylaminoethyl-10-(2-difluormethoxyphenyl)-3,4,5,6,7,10-hexahydro-8-methyl-1,1-dioxothiacyclooctenо[3,2-b]pyridin-9-carboxylat.
26) N-Benzyl-N-methylaminoethyl-10-(2-chlor-6-fluorphenyl)-3,4,5,6,7,10-hexahydro-8-methyl-1,1-dioxothiacyclooctenо[3,2-b]pyridin-9-carboxylat.
27) N-Benzyl-N-methylaminoethyl-10-(2-chlor-3-trifluormethylphenyl)-3,4,5,6,7,10-hexahydro-8-methyl-1,1-dioxothiacyclooctenо[3,2-b]pyridin-9-carboxylat.
28) N-Benzyl-N-methylaminoethyl-12-(2-chlor-3-trifluormethylphenyl)-2,3,4,5,6,7,8,11-octahydro-9-methyl-1,1-dioxothiacyclononeno-[3,2-b]pyridin-10-carboxylat.
29) N-Methyl-N-phenylaminoethyl-10-(2,3,4,5,6-pentafluorphenyl)-3,4,5,6,7,10-hexahydro-8-methyl-1,1-dioxothiacyclooctenо[3,2-b]pyridin-9-carboxylat.

3. Verbindung der Formel VIII

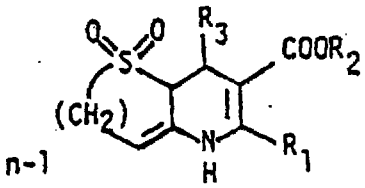


(VIII)

in der n, R_1, R_2 und R_3 die in Anspruch 1 angegebene Bedeutung aufweisen, deren optische Antipoden oder deren pharmazeutisch verträgliche Säure- und Baseadditionssalze.

4. Verbindung nach Anspruch 3, die Methyl-2,3,3a,4,7,7a-hexahydro-3a-hydroxy-5-methyl-7-(2-nitrophenyl)-1,1-dioxothieno-[3,2-b]-pyridin-6-carboxylat ist.

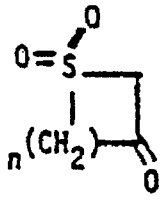
5. Verbindung der Formel XII



(XII)

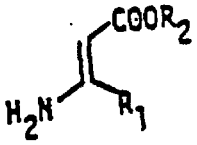
in der n eine ganze Zahl von 3 bis 12 ist und R_1, R_2 und R_3 die in Anspruch 1 angegebene Bedeutung aufweisen, deren optische Antipoden oder deren pharmazeutisch verträgliche Säure- und Baseadditionssalze.

6. Verfahren zur Herstellung einer Verbindung nach Anspruch 1 oder Anspruch 2, das umfaßt:
das Umsetzen einer Verbindung der Formel V



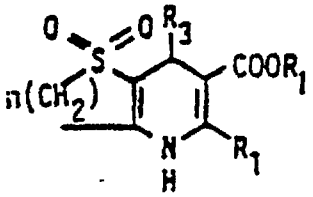
(V)

mit einer Verbindung der Formel VI



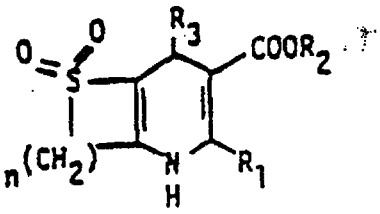
(VI)

und einer Verbindung der Formel R_3CHO, um eine Verbindung der Formel VIII nach Anspruch 3 herzustellen, für den Fall, daß n gleich 2 ist, und danach Dehydratisieren der Verbindung VIII, um eine Verbindung der Formel Ia



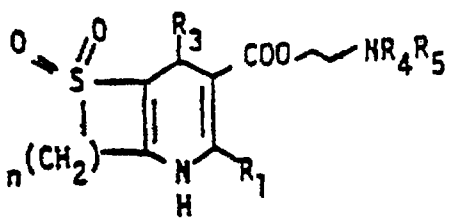
(Ia)

herzustellen oder um eine Verbindung der Formel Ib



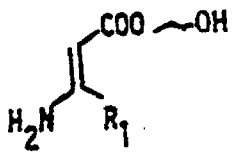
(Ib)

herzustellen, für den Fall, daß n gleich 3, 4, 5 oder 6 ist; oder um eine Verbindung der Formel XII nach Anspruch 5 herzustellen, wobei das letztere Verfahren das Umsetzen einer Verbindung der Formel V mit einer Verbindung der Formel VI und einer Verbindung der Formel R_3CHO umfaßt, um die Verbindung der Formel XII herzustellen, und danach, falls gewünscht, Umwandeln der Verbindung XII in die Verbindung Ib; oder, für den Fall, in dem es gewünscht ist, eine Endverbindung der Formel Id



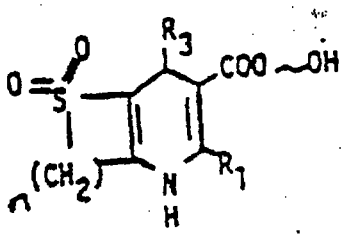
(Id)

herzustellen, Umsetzen einer Verbindung der Formel V mit einer Verbindung der Formel VIa



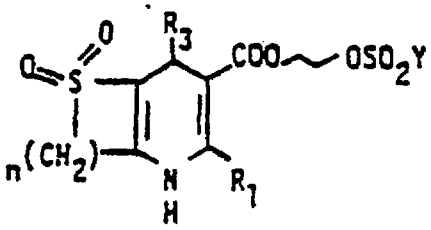
(VIa)

und einer Verbindung der Formel R_3CHO, um eine Verbindung der Formel Ic



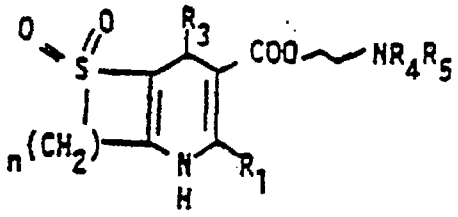
(Ic)

herzustellen, dann Umsetzen der Verbindung Ic mit einer Verbindung der Formel YSO_2Cl, wobei Y gleich p-Methylphenyl oder Alkyl ist, um eine Verbindung der Formel X



(X)

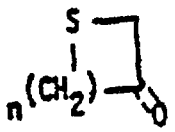
herzustellen, und danach Umsetzen der Verbindung X mit einer Verbindung der Formel HNR_4R_5, um eine Verbindung der Formel Id



(Id)

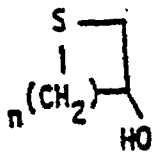
herzustellen.

7. Verfahren nach Anspruch 6, wobei die Verbindung der Formel V, für den Fall, daß n gleich 2 oder 3 ist, ursprünglich durch Reduzieren einer Verbindung der Formel II mit $NaBH_4$



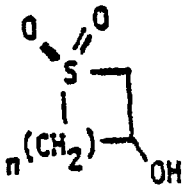
(II)

hergestellt wird, um eine Verbindung der Formel III



(III)

herzustellen, und anschließend Oxydieren der Verbindung III mit m-Chlorbenzoesäure, um eine Verbindung der Formel IV



(IV)

herzustellen, und dann die Verbindung IV mit Jones-Reagenz zu reoxidieren, um die Verbindung V herzustellen.

8. Calciumkanal-Antagonist-Zusammensetzung, umfassend einen inerten Träger und, als Wirksstoff, eine wirksame Menge eines Calciumkanal-Antagonisten der Verbindung nach einem der Ansprüche 1 bis 5.

9. Pharmazeutische Zusammensetzung, die als ein Calciumkanal-Antagonist verwendbar ist, in Form einer topischen, oralen, sublingualen, Aerosol- oder intravenösen Dosiseinheit, umfassend von 0,001 mg/kg bis 100 mg/kg der Verbindung nach einem der Ansprüche 1 bis 5, gemischt mit einem pharmazeutisch verträglichen Träger.

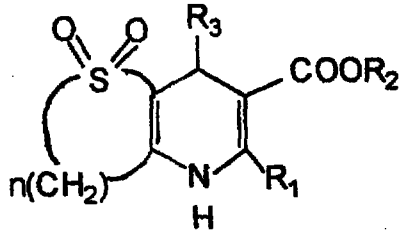
10. Zusammensetzung nach Anspruch 9, umfassend von 0,001 mg/kg bis 20 mg/kg der Verbindung gemischt mit dem pharmazeutisch verträglichen Träger.

11. Verbindung nach einem der Ansprüche 1 bis 5 oder Zusammensetzung nach einem der Ansprüche 8 bis 10 zur Verwendung bei der Behandlung von Myokardinsuffizienzen, einschließlich Angina, Gefäßkrampf und Infarkt, kardiovaskulären Störungen, einschließlich Bluthochdruck, Migräne, Schlaganfall und Plättchenaggregation, Allergien, Hypersensitivitäten, bronchospastischen Störungen, Diarrhoe oder Hypermotilität des G-I-Trakts bei einem Säuger.

12. Verfahren zur Herstellung einer Zusammensetzung nach einem der Ansprüche 8 bis 10, umfassend das Mischen des Wirkstoffs mit dem pharmazeutisch verträglichen Träger.

Revendications

1. Composé de formule I



(I)

où :
n est un entier de 1 à 12;
R_1 est un hydrogène, un alkyle en C_1-C_8 ou un haloalkyle en C_1-C_8;

R_2 est un alkyle en C_1-C_8, un cycloalkyle en C_3-C_7 ou un alcylène-X ayant au moins deux atomes de carbone, où X = alcoxy ayant jusqu'à 4 atomes de carbone, hydroxy, halo, p-tosyloxy, mésyloxy, amino, pyridyle ou $-NR_4R_5$, où R_4 et R_5 sont identiques ou différents, et sont sélectionnés parmi un hydrogène, un alkyle en C_1-C_8, un phényle, un benzyle, un phénéthyle, ou R_4/R_5 et l'atome d'azote auquel ils sont attachés forment un noyau hétérocyclique à 5, 6 ou 7 membres qui contient un oxygène ou un soufre ou un atome additionnel d'azote, ou ledit noyau hétérocyclique peut être fusionné à un noyau benzène comme dans l'indoline, l'isoindoline, la tétrahydroquinoline ou la tétrahydroisoquinoline, et dans le cas où ledit noyau hétérocyclique est un pipérazino, ledit pipérazino peut optionnellement être substitué en position 4 par le substituant R_6, qui est choisi parmi un alkyle en C_1-C_8, un benzyle, un phényle ou un phényle substitué par un alcoxy ayant jusqu'à 4 atomes de carbone, un halo, un alkyle en C_1-C_8, un nitro ou un trifluorométhyle;

R3 est un 2-pyridile, 3-pyridile, 3-pyridile substitué aux positions 2, 4, 5 ou 6 avec un ou plusieurs groupes choisis parmi un halogène, un nitro, un alcoxy ou alkylthio ayant jusqu'à 4 atomes de carbone, un cyano, un difluorométhoxy, un difluorométhylthio ou un alkylsulfonyle en C_1-C_8; un 2-thiényle, un 3-thiényle, un 2,1,3-benzoxadiazolyle, un 2,1,3-benzathiadiazolyle ou un phényle optionnellement substitué aux positions 2 à 6 avec un ou plusieurs groupes choisis parmi un hydrogène, un alkyle en C_1-C_8, un alcoxy ayant jusqu'à 4 atomes de carbone, un cyano, un difluorométhoxy, un difluorométhylthio, un alkylsulfonyle en C_1-C_8, un halo, un nitro ou un trifluorométhyle,

leurs antipodes optiques ou les sels d'addition de base et d'acide pharmaceutiquement acceptables de ceux-ci.

2. L'un quelconque des composés 1 à 29 listés ci-après:

1) Ethyl 2, 3, 4, 7-tétrahydro-5-méthyl-7-(3-nitrophényl)-1,1-dioxothiéno[3,2-b]pyridine-6-carboxylate.

2) N,N-Diméthylaminoéthyl 2,3,4,7-tétrahydro-5-méthyl-7-(3-nitrophényl)-1,1-dioxothiéno[3,2-b]-pyridine-6-carboxylate.

3) N-Benzyl-N-méthylaminoéthyl 2,3,4,7-tétrahydro-5-méthyl-7-(3-nitrophényl)-1,1-dioxothieno[3,2-b]-pyridine-6-carboxylate.

4) Ethyl 3,4,5,8-tétrahydro-6-méthyl-8-(3-nitrophényl)-1,1-dioxo-2H-thio-pyrano[3,2-b]pyridine-7-carboxylate.

5) N,N-Diméthylaminoéthyl 3,4,5,8-tétrahydro-6-méthyl-8-(3-nitrophényl)-1,1-dioxo-2H-thiopyrano[3,2-b]pyridine-7-carboxylate.

6) N-Benzyl-N-méthylaminoéthyl 3,4,5,8-tétrahydro-6-méthyl-8-(3-nitrophényl) -1,1-dioxo-2H-thiopyrano[3,2-b] pyridine-7-carboxylate.

7) N-Benzyl-N-méthylaminoéthyl 3,4,5,8-tétrahydro-6-méthyl-8-(2,3,4,5,6-pentafluorophényl)-1,1-dioxo-2H-thiopyrano[3,2-b]pyridine-7-carboxylate.

8) Ethyl 9-(2,3,4,5,6-pentafluorophényl)-2,3,4,5,6,9-hexahydro-7-méthyl-1,1-dioxothiacyclohepténo-[3,2-b]pyridine-8-carboxylate.

9) N-Benzyl-N-méthylaminoéthyl 2,4,5,6,9-hexahydro-7-méthyl-9-(3-nitrophényl)-1,1-dioxothiacyclohepténo[3,2-b] pyridine-8-carboxylate.

10) N,N-Diméthylaminoéthyl 2,3,4,5,6,9-hexahydro-7-méthyl-9-(3-nitrophényl)-1,1-dioxothiacyclohepténo[3,2-b]pyridine-8-carboxylate.

11) 2-Méthoxyéthyl 2,3,4,5,6,9-hexahydro-7-méthyl-9-(3-nitrophényl)-1,1-dioxo-thiacyclohepténo[3,2-b]pyridine-8-carboxylate.

12) N-Benzyl-N-méthylaminoéthyl 9-(2,3,4,5,6-pentafluorophényl)-2,3,4,5,6,9-hexahydro-7-méthyl-1,1-dioxothiacyclohepténo[3,2-b]pyridine-8-carboxylate.

13) Ethyl 10-(2,3,4,5,6-pentafluorophényl)-3,4,5,6,7,10-hexahydro-8-méthyl-1,1-dioxo-2H-thiacycloocténo[3,2-b] pyridine-9-carboxylate.

14) N-Benzyle-N-méthylaminoéthyl 10-(2,3,4,5,6-pentafluorophényl)-3,4,5,6,7,10-hexahydro-8-méthyl-1,1-dioxo-2H-thiacycloocténo[3,2-b]pyridine-9-carboxylate.

15) N-Benzyl-N-méthylaminoéthyl 3,4,5,6,7,10-hexahydro-8-méthyl-10-(3-nitrophényl)-1,1-dioxo-2H-thiacycloocténo[3,2-b] pyridine-9-carboxylate.

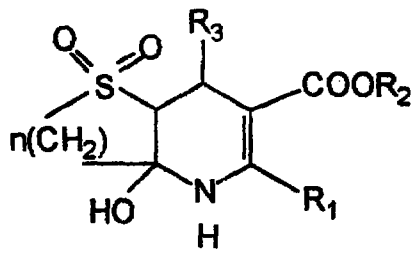
16) N-Benzyl-N-méthylaminoéthyl-11-(3-nitrophényl)2,3,4,6,7,8,11-octahydro-9-méthyl-1,1-dioxothiacyclononéno[3,2-b]pyridine-10-carboxylate.

17) N-Benzyle-N-méthylaminoéthyl 2,4,5,6,9-hexahydro-6-méthyl-9-(3-nitrophényl)-1,1-dioxothiacyclohepténo[3,2-b] pyridine-8-carboxylate.

18) N-Benzyle-N-méthylaminoéthyl 9-(2-chlorophényle)-2,4,5,6,9-hexahydro-7-méthyl-1,1-dioxothiacyclohepténo[3,2-b] pyridine-8-carboxylate.

19) N-Benzyl-N-méthylaminoéthyl 9-(2,3-dichlorophényl)-2,4,5,6,9-hexahydro-7-méthyl-1,1-dioxothiacyclohepténo[3,2-b] pyridine-8-carboxylate.
20) N-Benzyl-N-méthylaminoéthyl 9-(2-chloro-6-fluorophényl)-2,4,5,6,9-hexahydro-7-méthyl-1,1-dioxothiacyclohepténo[3,2-b]pyridine-8-carboxylate.
21) N-Benzyl-N-méthylaminoéthyl 9-(2-cifluorométhoxyphényl)-2,4,5,6,9-hexahydro-7-méthyl-1,1-dioxothiacyclohepténo[3,2-b]pyridine-8-carboxylate.
22) N-Benzyl-N-méthylaminoéthyl 2,4,5,6,9-hexahydro-7-méthyl-9-(2-trifluorométhylphényl)-1,1-dioxothiacyclohepténo[3,2-b]pyridine-8-carboxylate.
23) N-Benzyl-N-méthylaminoéthyl 10-(2-chlorophényl)-3,4,5,6,7,10-hexahydro-8-méthyl-1,1-dioxocycloocténo[3,2-b] pyridine-9-carboxylate.
24) N-Benzyl-N-méthylaminoéthyl 10-(2,3-dichlorophényl-3,4,5,6,7,10-hexahydro-8-méthyl-1,1-dioxothiacycloocténo [3,2-b]pyridine-9-carboxylate.
25) N-Benzyl-N-méthylaminoéthyl 10-(2-difluorométhoxyphényl)-3,4,5,6,7,10-hexahydro-8-méthyl-1,1-dioxothiacycloocténo[3,2-b]pyridine-9-carboxylate.
26) N-Benzyl-N-méthylaminoéthyl 10-(2-chloro-6-fluorophényl)-3,4,5,6,7,10-hexahydro-8-méthyl-1,1-dioxothiacycloocténo[3,2-b]pyridine-9-carboxylate.
27) N-Benzyl-N-méthylaminoéthyl 10-(2-chloro-3-trifluorométhylphényl)-3,4,5,6,7,10-hexahydro-8-méthyl-1,1-dioxothiacycloocténo[3,2-b]pyridine-9-carboxylate.
28) N-Benzyl-N-méthylaminoéthyl 12-(2-chloro-3-trifluorométhylphényl)-2,3,4,5,6,7,8,11-octahydro-9-méthyl-1,1-dioxothiacyclononéno[3,2-b]pyridine-10-carboxylate.
29) N-Méthyl-N-phénylaminoéthyl 10-(2,3,4,5,6-pentafluorophényl)-3,4,5,6,7,10-hexahydro-8-méthyl-1,1-dioxothiacycloocténo[3,2-b]pyridine-9-carboxylate.

3. Composé de formule VIII

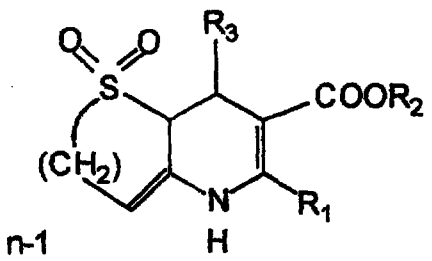


(VIII)

où n, R_1, R_2 et R_3 sont comme définis à la revendication 1, leurs antipodes optiques et les sels d'addition de base et d'acide pharmaceutiquement acceptables de ceux-ci.

4. Composé selon la revendication 3, qui est le méthyle 2,3,3a,4,7,7a-hexahydro-3a-hydroxy-5-méthyl-7-(2-nitrophényl)-1,1-dioxothiéno[3,2-b]pyridine-6-carboxylate.

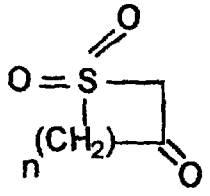
5. Composé de formule XII



(XII)

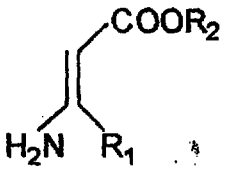
où n est un entier de 3 à 12 et R_1, R_2 et R_3 sont tels que définis en revendication 1, leurs antipodes optiques ou les sels d'addition de base et d'acide pharmaceutiquement acceptables de ceux-ci.

6. Procédé pour préparer un composé selon la revendication 1 ou la revendication 2 qui comprend : réaction d'un composé de formule V



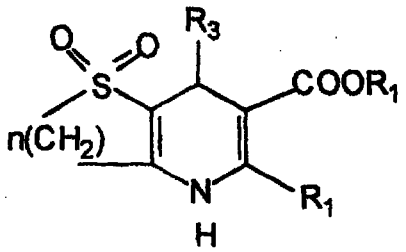
(V)

avec un composé de formule VI



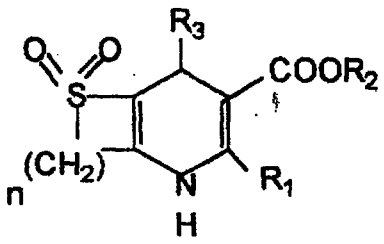
(VI)

et un composé de formule R_3CHO, pour préparer un composé de formule VIII comme défini en revendication 3 dans le cas où n égale 2, et après cela déshydratation dudit composé VIII de façon à préparer un composé de formule Ia



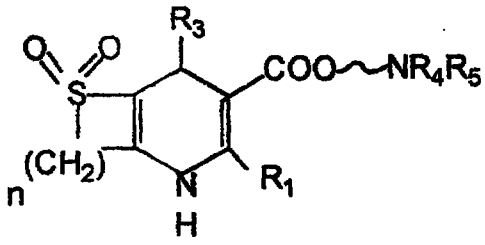
(Ia)

ou pour préparer un composé de formule Ib



(Ib)

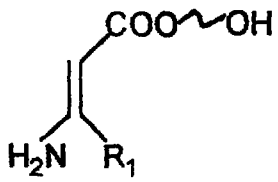
dans le cas où n égale 3, 4, 5 ou 6; ou pour préparer un composé de formule XII comme défini en revendication 5, ledit dernier procédé comprenant la réaction d'un composé de formule V avec un composé de formule VI et un composé de formule R_3CHO de façon à préparer ledit composé de formule XII et après cela, si souhaité, la conversion du composé XII en le composé Ib; ou, dans le cas où il est souhaité préparer un composé final de formule Id



(Id)

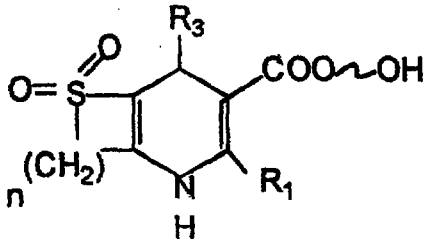
* C L M S *

la réaction d'un composé de formule V avec un composé de formule VIa



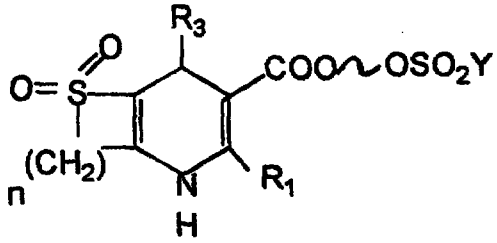
(VIa)

et un composé de formule R_3CHO de façon à préparer un composé de formule Ic



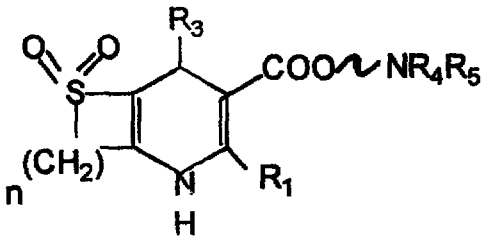
(Ic)

puis la réaction dudit composé Ic avec un composé de formule YSO_2Cl, où Y est un p-méthylphényle ou un alkyle, de façon à préparer un composé de formule X



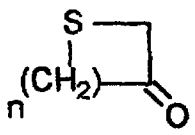
(X)

et après cela la réaction dudit composé X avec un composé de formule HNR_4R_5 pour préparer un composé de formule Id



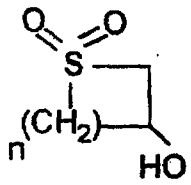
(Id)

7. Procédé selon la revendication 6, où ledit composé de formule V, dans le cas où n égale 2 ou 3, est initialement préparé par réduction d'un composé de formule II avec $NaBH_4$



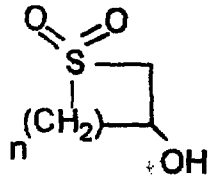
(II)

de façon à préparer un composé de formule III



(III)

suivie par l'oxydation dudit composé III avec un acide m-chlorobenzoïque, de façon à préparer un composé de formule IV



(IV)

et ensuite la réoxydation dudit composé IV avec un réactif de Jones de façon à préparer ledit composé V.

8. Composition antagoniste de canaux de calcium comprenant un porteur inerte, en tant qu'ingrédient actif, une quantité efficace d'antagoniste de canaux de calcium du composé selon l'une quelconque des revendications 1 à 5.

9. Composition pharmaceutique utile en tant qu'antagoniste de canaux de calcium sous forme de dosage unitaire, topique, orale, sublinguale, aérosol ou intraveineuse, comprenant de 0,001mg/kg à 100mg/kg du composé selon l'une quelconque des revendications 1 à 5 en mélange avec un porteur pharmaceutiquement acceptable.

10. Composition selon la revendication 9, comprenant de 0,001mg/kg à 20mg/kg du composé en mélange avec le porteur pharmaceutiquement acceptable.

11. Composé selon l'une quelconque des revendications 1 à 5 ou composition selon l'une quelconque des revendications 8 à 10 pour utilisation dans le traitement des insuffisances du myocarde, incluant l'angine, les vasospasmes et l'infarctus, les désordres cardiovasculaires, incluant l'hypertension, la migraine, les attaques et l'agrégation des plaquettes, les allergies, les hypersensibilités, les désordres bronchospasmiques, les diarrhées ou l'hypermobilité du tractus G-I chez un mammifère.

12. Méthode de production d'une composition selon l'une quelconque des revendications 8 à 10 comprenant le mélange de l'agent actif avec le porteur pharmaceutiquement acceptable.