

## Description

This application relates to N-naphthoyleglycine derivatives, therapeutically acceptable salts thereof, a process for their preparation, and to methods of use and to pharmaceutical compositions thereof. The derivatives have pharmacologic properties which render them beneficial for the treatment of diabetes mellitus and associated conditions.

For many years diabetes mellitus has been treated with two established types of drugs, namely insulin and oral hypoglycemic agents. These drugs have benefited hundreds of thousands of diabetics by improving their well-being and prolonging their lives. However, the resulting longevity of diabetic patients has led to complications such as neuropathy, nephropathy, retinopathy, cataracts and atherosclerosis. These complications have been linked to the undesirable accumulation of sorbitol in diabetic tissue, which in turn result from the high levels of glucose characteristic of the diabetic patient.

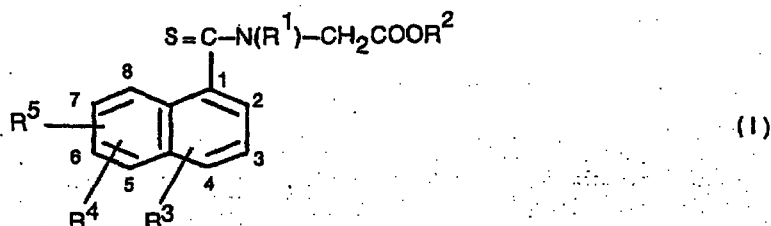
In mammals, including humans, the key enzyme involved in the conversion of hexoses to polyols (the sorbital pathway) is aldose reductase. J. H. Kinoshita and collaborators, see J. H. Kinoshita *et al.*, *Biochem. Biophys. Acta*, 158, 472 (1968) and references cited therein, have demonstrated that aldose reductase plays a central role in the etiology of galactosemic cataracts by effecting the conversion of galactose to dulcitol (galactitol) and that an agent capable of inhibiting aldose reductase can prevent the detrimental accumulation of dulcitol in the lens. Furthermore, a relationship between elevated levels of glucose and an undesirable accumulation of sorbitol has been demonstrated in the lens, peripheral nervous cord and kidney of diabetic animals, see A. Pirie and R. van Heyningen, *Exp. Eye Res.*, 3, 124 (1964); L. T. Chylack and J. H. Kinoshita, *Invest. Ophthalmol.*, 8, 401 (1969) and J. D. Ward and R. W. R. Baker, *Diabetol.*, 6, 531 (1970).

1,3-Dioxo-1H-benz[de]isoquinoline-2(3H)-acetic acid has been reported to be an effective inhibitor of aldose reductase, see D. Dvornik *et al.*, *Science*, 182, 1146 (1973), and to be useful for the treatment of diabetic complications such as diabetic cataracts, neuropathy, nephropathy and retinopathy, see K. Sestani, N. Simard-Duquesne and D. M. Dvornik, U.S. Patent No. 3,821,383, June 28, 1974.

(S)-6-Fluoro-2,3-dihydrospiro(4H-1-benzopyran-4,4'-imidazolidine)-2',5'-dione (sorbiniol) is still another compound that has received attention because of its aldose reductase inhibiting properties (see M. J. Peterson *et al.*, *Metabolism*, 28 (Suppl. 1), 456 (1979)). Accordingly, these compounds represent an important new approach for the treatment of diabetes mellitus.

The present application discloses novel N-naphthoyleglycine derivatives, represented below by formula I, which are effective inhibitors of aldose reductase. These new derivatives are structurally quite different from the above noted aldose reductase inhibitors. Close prior art compounds, on a structural basis, appear to be a group of thioacylamino acids, e.g. N-phenylthioxomethyl-N-methylglycine, prepared by A. Lawson and C. E. Searle, *J. Chem. Soc.*, 1556 (1957) as part of a chemical investigation of the chemical properties of such compounds. These last mentioned compounds were prepared by thiobenzoylation of various amino acids with (thiobenzoylthio)acetic acid. An important structural difference between these compounds and the present derivatives is the different type of aromatic group substituted on the thione portion of the thioamide. Thioacylamides also have been reported [see *Chem. Abstr.*, 86, 189582f (1977) for V. I. Cohen *et al.*, *Eur. J. Med. Chem.*, 5, 480 (1976) and *Chem. Abstr.*, 70, 11306a (1969) for von J. Voss and W. Walter, *Justus Liebig's Ann. Chem.*, 716, 209 (1968)]. The structure of the thiocylamides of Cohen *et al.* and Voss *et al.* differ from the structure of the present derivatives by having at least a different type of N-substitution. Another close prior art compound, on a structural basis, is N-[(1-naphthalenyl)carbonyl] glycine, [see *Chem. Abstr.*, 61, 4333f (1964) for E. Cioranescu *et al.*, *Rev. Chim. Acad. Rep. Populaire Roumaine*, 7 (2), 755 (1962)]. The compound, which has been used as a chemical intermediate, is distinguished from the compounds of the present invention by being an amide and not a thioamide.

The N-naphthoyleglycine derivatives of this invention are represented by formula I



wherein  $\text{R}^1$  is hydrogen, lower alkyl, lower alkenyl or phenylmethyl;  $\text{R}^2$  is hydrogen or lower alkyl;  $\text{R}^3$  is hydrogen, a lower alkoxy at position 6 of the naphthalene ring, or a substituent at position 4, 5 or 8 of the naphthalene ring, the substituent being selected from the group consisting of lower alkyl, lower alkoxy, halo, cyano, nitro, trihalomethyl and trihalomethylthio, and  $\text{R}^4$  and  $\text{R}^5$  each is hydrogen; or  $\text{R}^3$  and  $\text{R}^4$  each is a substituent at different positions selected from positions 3 to 7 of the naphthalene ring, the substituents being selected from the group consisting of lower alkyl, lower alkoxy, halo, trihalomethyl, trihalomethylthio, (lower)alkoxy(lower)alkoxy, phenylmethoxy and phenylmethoxy substituted on the phenyl portion with a lower alkyl, lower alkoxy, halo or trihalomethyl, and  $\text{R}^5$  is hydrogen; or  $\text{R}^3$ ,  $\text{R}^4$  and  $\text{R}^5$  each is a substituent at different positions selected from positions 4, 5 and 6 of the naphthalene ring, the substituent being

selected from the group consisting of lower alkoxy, halo and trihalomethyl; or a therapeutically acceptable salt with an organic or inorganic base of the compound of formula I wherein R<sup>2</sup> is hydrogen.

A group of preferred derivatives is represented by the compounds of formula I wherein R<sup>1</sup> is hydrogen, lower alkyl, 2-propenyl or phenylmethyl; R<sup>2</sup> is hydrogen or lower alkyl; R<sup>3</sup> is hydrogen, a lower alkoxy at position 6 of the naphthalene ring, or a substituent at positions 4, 5 or 8 of the naphthalene ring, the substituents being selected from the group consisting of lower alkyl, lower alkoxy, halo, cyano, nitro and trifluoromethyl, and R<sup>4</sup> and R<sup>5</sup> each is hydrogen; or R<sup>3</sup> and R<sup>4</sup> are a pair of substituents on the naphthalene ring, each substituent being at a different position of the ring, the pair of substituents being selected from the group of pairs consisting of 3-halo-4-lower alkoxy, 4,6-di(lower alkoxy), 5-halo-6-lower alkyl, 5-halo-6-lower alkoxy, 5,7-dihalo, 5-(trifluoromethyl)-6-lower alkoxy, 5-(trifluoromethylthio)-6-lower alkoxy, 5-halo-6-(lower)alkoxy(lower)alkoxy, 5-halo-6-[3-(trifluoromethyl)phenylmethoxy] and 5-halo-6-(4-chlorophenylmethoxy), and R<sup>5</sup> is hydrogen; or R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> each is a substituent on the naphthalene ring, each of the three substituents being at different positions on the ring, the three substituents being selected from the group of 4-lower alkoxy-5-halo-6-lower alkoxy and 4,6-di(lower alkoxy)-5-(trifluoromethyl); or a therapeutically acceptable salt with an organic or inorganic base of the compound of formula I wherein R<sup>2</sup> is hydrogen.

Another preferred group of the compounds is represented by the compounds of formula I wherein R<sup>1</sup> is hydrogen, lower alkyl or phenylmethyl; R<sup>2</sup> is hydrogen or lower alkyl; R<sup>3</sup> is 4-halo or 5-halo, and R<sup>4</sup> and R<sup>5</sup> each is hydrogen; or R<sup>3</sup> and R<sup>4</sup> are a pair of substituents on the naphthalene ring selected from the group of pairs consisting of 3-halo-4-lower alkoxy, 4,6-di(lower alkoxy), 5-halo-6-lower alkyl, 5-halo-6-lower alkoxy, 5,7-dihalo, 5-(trifluoromethyl)-6-lower alkoxy and 5-(trifluoromethylthio)-6-lower alkoxy, and R<sup>5</sup> is hydrogen; or R<sup>3</sup> is 4-lower alkoxy, R<sup>4</sup> is 5-(trifluoromethyl) and R<sup>5</sup> is 6-lower alkoxy; or a therapeutically acceptable salt with an organic or inorganic base of the compound of formula I wherein R<sup>2</sup> is hydrogen.

A most preferred group of the compounds is represented by the compounds of formula I wherein R<sup>1</sup> is lower alkyl; R<sup>2</sup> is hydrogen; R<sup>3</sup> is 5-halo and R<sup>4</sup> and R<sup>5</sup> each is hydrogen; or R<sup>3</sup> and R<sup>4</sup> are a pair of substituents on the naphthalene ring selected from the group of pairs consisting of 3-halo-4-lower alkoxy, 5-halo-6-lower alkoxy, 5-(trifluoromethyl)-6-lower alkoxy and 5-(trifluoromethylthio)-6-lower alkoxy, and R<sup>5</sup> is hydrogen; or R<sup>3</sup> is 4-lower alkoxy, R<sup>4</sup> is 5-(trifluoromethyl) and R<sup>5</sup> is 6-lower alkoxy; or a therapeutically acceptable salt thereof with an organic or inorganic base.

The compounds of formula I can be prepared by a process described hereinafter.

A method is provided for preventing or relieving diabetes mellitus associated complications in a diabetic mammal by administering to said mammal a prophylactic or alleviating amount of the compound of formula I or therapeutically acceptable salt thereof with an organic or inorganic base. The complications include neuropathy, nephropathy, retinopathy and cataracts.

The compound of formula I, or a therapeutically acceptable salt thereof with an organic or inorganic base, when admixed with a pharmaceutically acceptable carrier, forms a pharmaceutical composition which can be used according to the preceding method.

The compounds of this invention, represented by formula I, can exist in rotameric forms. More explicitly, mesomerism imparts a partial double bond character to the carbon-nitrogen bond of the thioamide group. This partial double bond character leads to restricted rotation about the carbon nitrogen bond giving rise to cis and trans rotamers, the restricted rotation being augmented by the bulkiness of neighboring groups. Interconversion of the rotamers is possible and is dependent on the physical environment. As evidenced by its physical properties, the thermodynamically more stable rotamer exists exclusively in the crystalline state of the compound and is the predominant isomer present in equilibrated solutions. Furthermore, the more stable rotamer is the more pharmacologically active. The less stable rotamer can be separated from the more stable rotamer by high performance liquid chromatography or by thin layer chromatography. The rotameric forms are included within the scope of this invention. For brevity, the compounds of this invention, including their rotameric forms, are referred to herein as compounds of formula I.

The term "lower alkyl" as used herein means a straight chain alkyl radical containing from one to four carbon atoms or a branched chain alkyl radical containing three or four carbon atoms and includes methyl, ethyl, propyl, 1-methylethyl, butyl, 2-methylpropyl and 1,1-dimethylethyl. Preferred lower alkyl radicals contain from one to three carbon atoms.

The term "lower alkenyl" is as used herein means a straight chain alkenyl radical containing from two to six carbon atoms, or a branched chain alkenyl radical containing from four to six carbon atoms and includes, for example, ethenyl, 2-propenyl, 2-methyl-2-propenyl and 2-ethyl-3-butenyl. Preferred lower alkenyl radicals contain two to three carbon atoms.

The term "lower alkoxy" as used herein means a straight chain alkoxy radical containing from one to six carbon atoms, preferably one to three carbon atoms, or a branched chain alkoxy radical containing three or four carbon atoms, and includes methoxy, ethoxy, 1-methylethoxy, butoxy and hexanoxo.

The term "halo" as used herein means a halo radical and includes fluoro, chloro, bromo and iodo.

The term "ar" as used mean an aromatic radical containing at least one benzene ring. The preferred aromatic radical is phenyl.

The compounds of formula I wherein R<sup>2</sup> is hydrogen form salts with suitable therapeutically acceptable inorganic and organic bases. These derived salts possess similar activity to their parent acid and are

included within the scope of this invention. The acid is transformed in excellent yield into the corresponding therapeutically acceptable salt by neutralization of said acid with the appropriate inorganic or organic base. The salts are administered usually in the same manner as the parent acid compounds. Suitable inorganic bases to form these salts include, for example, the hydroxides, carbonates or bicarbonates of the therapeutically acceptable alkali metals or alkaline earth metals, for example, sodium, potassium, magnesium, calcium and the like. Suitable organic bases include the following amines: benzylamine; lower mono-, di- and trialkylamines, the alkyl radicals of which contain up to three carbon atoms, such as methylamine, dimethylamine, trimethylamine, ethylamine, di- and triethylamine, methylamine, and the like; mono-, di- and trialkanolamines, the alkanol radicals of which contain up to three carbon atoms, for example, mono-, di- and triethanolamine; alkylene-diamines which contain up to six carbon atoms, such as hexamethylenediamine; cyclic saturated or unsaturated bases containing up to six carbon atoms, such as pyrrolidine, piperidine, morpholine, piperazine and their N-alkyl and N-hydroxyalkyl derivatives, such as N-methyl-morpholine and N-(2-hydroxyethyl)-piperidine, as well as pyridine. Furthermore, there may be mentioned the corresponding quaternary salts, such as the tetraalkyl (for example tetramethyl), alkyl-alkanol (for example methyltriethanol and trimethyl-monoethanol) and cyclic ammonium salts, for example the N-methylpyridinium, N-methyl-N-(2-hydroxyethyl)morpholinium, N,N-dimethylmorpholinium, N-methyl-N-(2-hydroxyethyl)morpholinium, N,N-dimethylpiperidinium salts, which are characterized by having good water-solubility. In principle, however, there can be used all the ammonium salts which are physiologically compatible.

The transformations to the salts can be carried out by a variety of methods known in the art. For example, in the case of the inorganic salts, it is preferred to dissolve the acid of formula I in water containing at least one equivalent amount of a hydroxide, carbonate, or bicarbonate corresponding to the inorganic salt desired. Advantageously, the reaction is performed in a water-miscible, inert organic solvent, for example, methanol, ethanol, dioxane, and the like in the presence of water. For example, such use of sodium hydroxide, sodium carbonate or sodium bicarbonate gives a solution of the sodium salt. Evaporation of the solution or addition of a water-miscible solvent of a more moderate polarity, for example, a lower alkanol, for instance, butanol, or a lower alkanone, for instance, ethyl methyl ketone, gives the solid inorganic salt in that form is desired.

To produce an amine salt, the acidic compound of formula I may be solved in a suitable solvent of either moderate or lower polarity, for example, ethanol, methanol, ethyl acetate, diethyl ether and benzene. At least an equivalent amount of the amine corresponding to the desired cation is then added to that solution. If the resulting salt does not precipitate, it can usually be obtained in solid form by addition of a miscible diluent of lower polarity, for example, benzene or petroleum ether, or by evaporation. If the amine is relatively volatile, any excess can easily be removed by evaporation. It is preferred to use substantially equivalent amounts of the less volatile amines.

Salts wherein the cation is quaternary ammonium may be produced by mixing the acid of formula I with an equivalent amount of the corresponding quaternary ammonium hydroxide in water solution, followed by evaporation of the water.

The compounds of formula I and their addition salts with pharmaceutically acceptable organic or inorganic bases may be administered to mammals, for example, man, cattle or rabbits, either alone or in dosage forms, e.g., capsules or tablets, combined with pharmacologically acceptable excipients, see below. Advantageously the compounds of this invention may be given orally. However, the method of administering the present active ingredients of this invention is not to be construed as limited to a particular mode of administration. For example, the compounds may be administered topically directly to the eye in the form of drops of sterile, buffered ophthalmic solutions, preferably of pH 7.2—7.6. Also, they may be administered orally in solid form containing such excipients as starch, milk sugar, certain types of clay and so forth. They may also be administered orally in the form of solutions or they may be injected parenterally. For parenteral administration they may be used in the form of a sterile solution, preferably of pH 7.2—7.6, containing a pharmaceutically acceptable buffer.

The dosage of the present therapeutic agents will vary with the form of administration and the particular compound chosen. Furthermore, it will vary with the particular horse under treatment. Generally, treatment is initiated with small dosages substantially less than the optimal dose of the compound. Thereafter, the dosage is increased by small increments until efficacy is obtained. In general, the compounds of this invention are most desirably administered at a concentration level that will generally afford effective results without causing any harmful or deleterious side effects. For topical administration a 0.05—0.2% solution may be administered dropwise to the eye. The frequency of instillation varies with the subject under treatment from a drop every two or three days to once daily. For oral or parenteral administration a preferred level of dosage ranges from about 0.1 mg to about 200 mg per kilo of body weight per day, although aforementioned variations will occur. However, a dosage level that is in the range of from about 0.5 mg to about 30 mg per kilo of body weight per day is most satisfactory.

Unit dosage forms such as capsules, tablets, pills and the like may contain from about 5.0 mg to about 250 mg of the active ingredients of this invention, preferably with a significant quantity of a pharmaceutical carrier. Thus, for oral administration, capsules can contain from between about 5.0 mg to about 250 mg of the active ingredients of this invention with or without a pharmaceutical diluent. Tablets, either effervescent or noneffervescent, can contain between about 5.0 to 250 mg of the active ingredients of this inven-

tion together with conventional pharmaceutical carriers. Thus, tablets which may be coated and either effervescent or noneffervescent may be prepared according to the known art. Inert diluents or carriers, for example, magnesium carbonate or lactose, can be used together with conventional disintegrating agents for example, magnesium stearate.

5 Syrups of elixirs suitable for oral administration can be prepared from water soluble salts, for example, sodium N-[[5-(trifluoromethyl)-6-methoxy-1-naphthalenyl]thioxomethyl]-N-methylglycinate, and may advantageously contain glycerol and ethyl alcohol as solvents or preservatives.

The compound of formula I, or a therapeutically acceptable salt thereof, also can be used in combination with insulin or oral hypoglycemic agents to produce a beneficial effect in the treatment of diabetes mellitus. In this instance, commercially available insulin preparations or oral hypoglycemic agents, exemplified by acetohexamide, chlorpropamide, tolazamide, tolbutamide and phenformin, are suitable. The compound of formula I, or a therapeutically acceptable salt thereof, can be administered sequentially or simultaneously with insulin or the oral hypoglycemic agent. Suitable methods of administration, compositions and doses of the insulin preparation or oral hypoglycemic agent are described in medical textbooks; for instance, "Physicians' Desk Reference", 34 ed., Medical Economics Co., Oradell, N. J., U.S.A., 1980. When used in combination, the compound of formula I, or its therapeutically acceptable salt, is administered as described previously. The compound of formula I, or its therapeutically acceptable salt, can be administered with the oral hypoglycemic agent in the form of a pharmaceutical composition comprising effective amounts of each agent.

20 The aldose reductase inhibiting effects of the compounds of formula I and their pharmaceutically acceptable salts with organic or inorganic bases can be demonstrated by employing an in vitro testing procedure similar to that described by S. Hayman and J. H. Kinoshita, J. Biol. Chem., 240, 877 (1965). In the present case the procedure of Hayman and Kinoshita is modified in that the final chromatography step is omitted in the preparation of the enzyme from bovine lens.

25 The following results were obtained when the foregoing listed compounds of formula I were evaluated in the above in vitro test.

| Compound of Formula I (R <sup>5</sup> = H) | Example In Which Compound Is Prepared |                 |                     |                                                     | % Inhibition at Different Molar Concentrations (in vitro) |                  |                  |
|--------------------------------------------|---------------------------------------|-----------------|---------------------|-----------------------------------------------------|-----------------------------------------------------------|------------------|------------------|
|                                            | R <sup>1</sup>                        | R <sup>2</sup>  | R <sup>3</sup>      | R <sup>4</sup>                                      | 10 <sup>-5</sup>                                          | 10 <sup>-6</sup> | 10 <sup>-7</sup> |
| 30                                         | CH <sub>3</sub>                       | CH <sub>3</sub> | 5-Br                | H                                                   | 3                                                         | 8                |                  |
|                                            | CH <sub>3</sub>                       | CH <sub>3</sub> | 5-CF <sub>3</sub>   | 6-CH <sub>3</sub> O                                 | 23                                                        | 9                |                  |
| 35                                         | CH <sub>3</sub>                       | H               | 5-Br                | H                                                   | 32                                                        | 93               | 87               |
| 40                                         | H                                     | H               | 3-Cl                | 4-CH <sub>3</sub> O                                 | 32                                                        | 61               | 16               |
|                                            | CH <sub>3</sub>                       | H               | 4-Br                | H                                                   | 33                                                        | 91               | 77               |
| 45                                         | CH <sub>3</sub>                       | H               | 8-Br                | H                                                   | 34                                                        | 88               | 75               |
|                                            | CH <sub>3</sub>                       | H               | 5-CH <sub>3</sub> O | H                                                   | 35                                                        | 83               | 64               |
| 50                                         | CH <sub>3</sub>                       | H               | 5-CH <sub>3</sub>   | H                                                   | 36                                                        | 89               | 74               |
|                                            | CH <sub>3</sub>                       | H               | 5-Br                | 6-CH <sub>3</sub> (CH <sub>2</sub> ) <sub>4</sub> O | 37                                                        | 93               | 91               |
|                                            | CH <sub>3</sub>                       | H               | 5-CN                | H                                                   | 38                                                        | 89               | 79               |
| 55                                         | CH <sub>3</sub>                       | H               | 5-NO <sub>2</sub>   | H                                                   | 39                                                        | 91               | 83               |
|                                            | CH <sub>3</sub>                       | H               | 5-Cl                | H                                                   | 40                                                        | 91               | 83               |
| 60                                         | CH <sub>3</sub>                       | H               | 5-Br                | 6-CH <sub>3</sub> O                                 | 41                                                        | 99               | 91               |
|                                            | CH <sub>3</sub>                       | H               | 5-Br                | 6-CH <sub>3</sub>                                   | 42                                                        | 92               | 88               |
| 65                                         | CH <sub>3</sub>                       | H               | H                   | H                                                   | 43                                                        | 85               | 51               |

| 5  | Compound of Formula I ( $R^5 = H$ )           |       |                                        |                                                                          | Example<br>In Which<br>Compound | % Inhibition at<br>Different Molar<br>Concentrations<br>(in vitro) |           |           |
|----|-----------------------------------------------|-------|----------------------------------------|--------------------------------------------------------------------------|---------------------------------|--------------------------------------------------------------------|-----------|-----------|
|    | $R^1$                                         | $R^2$ | $R^3$                                  | $R^4$                                                                    |                                 | $10^{-5}$                                                          | $10^{-6}$ | $10^{-7}$ |
|    | CH <sub>3</sub>                               | H     | 4-Cl                                   | H                                                                        | 44                              | 88                                                                 | 73        | 25        |
| 10 | CH <sub>3</sub>                               | H     | 3-Cl                                   | 4-CH <sub>3</sub> O                                                      | 45                              | 85                                                                 | 78        | 33        |
|    | CH <sub>3</sub>                               | H     | 5-Cl                                   | 7-Cl                                                                     | 46                              | 88                                                                 | 75        | 29        |
| 15 | CH <sub>3</sub>                               | H     | 5-I                                    | 6-CH <sub>3</sub> O                                                      | 47                              | 98                                                                 | 95        | 72        |
|    | CH <sub>3</sub>                               | H     | 5-CN                                   | 6-CH <sub>3</sub> O                                                      | 48                              | 98                                                                 | 93        | 74        |
|    | CH <sub>3</sub>                               | H     | 5-Br                                   | 6-CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>3</sub> O                     | 49                              | 92                                                                 | 87        | 38        |
| 20 | CH <sub>3</sub>                               | H     | 5-CH <sub>2</sub> =C(CH <sub>3</sub> ) | H                                                                        | 50                              | 92                                                                 | 74        | 19        |
|    | CH <sub>3</sub>                               | H     | 5-(CH <sub>3</sub> ) <sub>2</sub> CH   | H                                                                        | 51                              | 91                                                                 | 72        | 21        |
| 25 | CH <sub>3</sub>                               | H     | 5-CF <sub>3</sub>                      | 6-CH <sub>3</sub> O                                                      | 52                              | 98                                                                 | 94        | 65        |
|    | CH <sub>3</sub>                               | H     | 5-Br                                   | 6-[(3-CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> )CH <sub>2</sub> O] | 53                              | 86                                                                 | 37        | 11        |
|    | CH <sub>3</sub>                               | H     | 5-Br                                   | 6-[(4-Cl-C <sub>6</sub> H <sub>4</sub> )CH <sub>2</sub> O]               | 53a                             | 88                                                                 | 44        | 4         |
| 30 | CH <sub>3</sub>                               | H     | 5-CF <sub>3</sub>                      | H                                                                        | 53b                             | 93                                                                 | 84        | 33        |
|    | H                                             | H     | 5-Br                                   | H                                                                        | 54                              | 54                                                                 | 14        |           |
| 35 | n-C <sub>3</sub> H <sub>7</sub>               | H     | 5-Br                                   | H                                                                        | 55                              | 91                                                                 | 70        | 19        |
|    | CH <sub>2</sub> =CH-CH <sub>2</sub>           | H     | 5-Br                                   | H                                                                        | 56                              | 92                                                                 | 77        | 27        |
|    | C <sub>2</sub> H <sub>5</sub>                 | H     | 5-Br                                   | H                                                                        | 57                              | 85                                                                 | 72        | 24        |
| 40 | n-C <sub>4</sub> H <sub>9</sub>               | H     | 5-Br                                   | H                                                                        | 58                              | 86                                                                 | 65        | 19        |
|    | CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> | H     | 5-Br                                   | H                                                                        | 59                              | 86                                                                 | 69        | 20        |
| 45 | CH <sub>3</sub>                               | H     | 5-CF <sub>3</sub> S                    | 6-CH <sub>3</sub> O                                                      | 65                              | 96                                                                 | 94        | 73        |

The aldose reductase inhibiting property of the compounds of this invention and the utilization of the compounds in preventing, diminishing and alleviating diabetic complications are demonstrable in experiments using galactosemic rats, see Dvornik *et al.*, cited above. Such experiments are exemplified herein-  
below after the listing of the following general comments pertaining to these experiments:

(a) Four or more groups of six male rats, 50—70 g, Sprague-Dawley strain, were used. The first group, the control group, was fed a mixture of laboratory chow (rodent laboratory chow, Purina) and glucose at 20% (w/w %) concentration. The untreated galactosemic group was fed a similar diet in which galactose is substituted for glucose. The third group was fed on a diet prepared by mixing a given amount of the test compound with the galactose containing diet. The concentration of galactose in the diet of the treated groups was the same as that for the untreated galactosemic group.

(b) After four days, the animals were killed by decapitation. The eyeballs were removed and punctured with a razor blade; the freed lenses were rolled gently on filter paper and weighed. The sciatic nerves were dissected as completely as possible and weighed. Both tissues were frozen and can be kept up to two weeks before being analyzed for dulcitol.

(c) The polyol determination was performed by a modification of the procedure of M. Kraml and L. Cosyns, Clin. Biochem., 2, 373 (1969). Only two minor reagent changes were made: (a) The rinsing mixture was an aqueous 5% (w/v) trichloroacetic acid solution and (b) the stock solution was prepared by dissolving 25 mg of dulcitol in 100 ml of an aqueous trichloroacetic acid solution. [N.B.: For each experi-

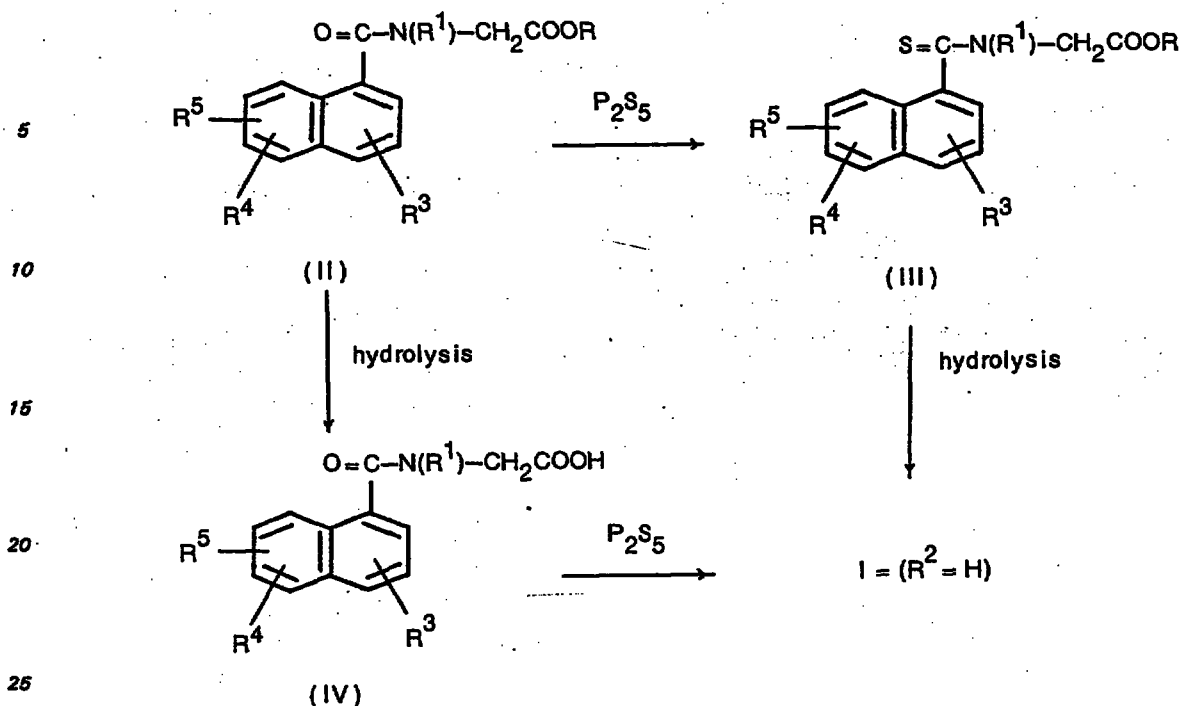
ment the average value found in the tissue from rats fed the glucose diet was subtracted from the individual values found in the corresponding rat tissue to obtain the amount of polyol accumulated.]

The following tabulated results show that the compounds of this invention diminish the accumulation of dulcitol in the lenses and sciatic nerves of rats fed galactose. The figures under L and N represent the percentage decrease of dulcitol accumulation in the tissues of the lens and sciatic nerve, respectively, for treated rats as compared to untreated rats.

|    | Compound of Formula I |                 |                     |                     |                     | Dose      |    |    |
|----|-----------------------|-----------------|---------------------|---------------------|---------------------|-----------|----|----|
|    | R <sup>1</sup>        | R <sup>2</sup>  | R <sup>3</sup>      | R <sup>4</sup>      | R <sup>5</sup>      | mg/kg/day | L  | N  |
| 10 | CH <sub>3</sub>       | H               | 5-Br                | H                   | H                   | 189       | 24 | 79 |
|    |                       |                 |                     |                     |                     | 121       | 20 | 70 |
| 15 |                       |                 |                     |                     |                     | 62        | 14 | 53 |
|    | CH <sub>3</sub>       | H               | 5-Cl                | H                   | H                   | 156       | 34 | 70 |
| 20 | CH <sub>3</sub>       | H               | 5-Br                | 6-CH <sub>3</sub> O | H                   | 162       | 34 | —  |
|    |                       |                 |                     |                     |                     | 58        | —  | 78 |
|    |                       |                 |                     |                     |                     | 29        | —  | 58 |
| 25 |                       |                 |                     |                     |                     | 15        | —  | 32 |
|    | CH <sub>3</sub>       | H               | 3-Cl                | 4-CH <sub>3</sub> O | H                   | 163       | 15 | —  |
| 30 |                       |                 |                     |                     |                     | 25        | —  | 27 |
|    | CH <sub>3</sub>       | H               | 5-Cl                | 7-Cl                | H                   | 52        | 29 | 45 |
| 35 | CH <sub>3</sub>       | H               | 5-CF <sub>3</sub>   | 6-CH <sub>3</sub> O | H                   | 26        | 15 | 94 |
|    | CH <sub>3</sub>       | CH <sub>3</sub> | 5-CF <sub>3</sub>   | 6-CH <sub>3</sub> O | H                   | 11        | 10 | 44 |
|    | CH <sub>3</sub>       | H               | 5-CF <sub>3</sub>   | H                   | H                   | 11        | 2  | 36 |
| 40 | CH <sub>3</sub>       | H               | 6-CH <sub>3</sub> O | H                   | H                   | 162       | —  | 32 |
|    | CH <sub>3</sub>       | H               | 4-CH <sub>3</sub> O | 5-CF <sub>3</sub>   | 6-CH <sub>3</sub> O | 144       | 33 | 85 |
|    |                       |                 |                     |                     |                     | 25        | —  | 48 |
| 45 | CH <sub>3</sub>       | H               | 5-CF <sub>3</sub> S | 6-CH <sub>3</sub> O | H                   | 20.5      | 20 | 96 |
|    |                       |                 |                     |                     |                     | 9.1       | —  | 55 |
| 50 |                       |                 |                     |                     |                     | 4.4       | —  | 29 |

A process for the preparation of the compounds of formula I is illustrated by the following scheme wherein R<sup>1</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are as defined hereinbefore and COOR is an ester group which may be, for example, a lower alkyl or an ar(lower)alkyl ester; i.e., R is lower alkyl or ar(lower)alkyl.

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More specifically, a process for preparing the compounds of formula I comprises:

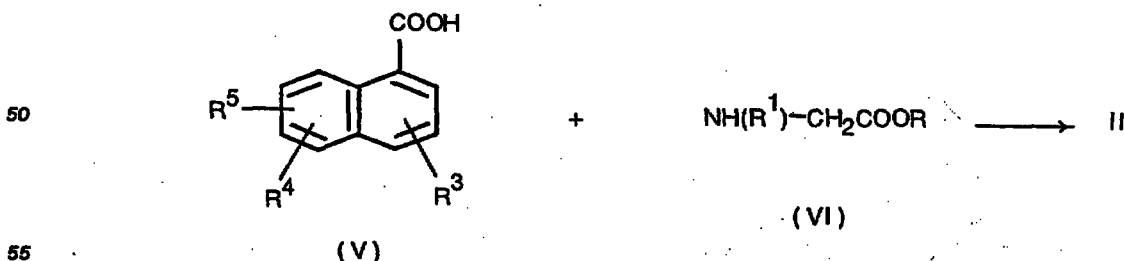
30 (a) reacting an amidoester of formula II wherein  $R^1$ ,  $R^3$ ,  $R^4$  and  $R^5$  are as defined herein and R is lower alkyl or ar(lower)alkyl with phosphorus pentasulfide to give the corresponding thioester of formula III wherein  $R^1$ ,  $R^3$ ,  $R^4$ ,  $R^5$  and R are as defined herein; or

(b) hydrolyzing the thioester of formula III wherein  $R^1$ ,  $R^3$ ,  $R^4$ ,  $R^5$  and R are as defined herein to obtain the corresponding compound of formula I wherein  $R^1$ ,  $R^3$ ,  $R^4$  and  $R^5$  are as defined herein and  $R^2$  is hydrogen; or

35 (c) hydrolyzing the amidoester of formula II wherein  $R^1$ ,  $R^3$ ,  $R^4$ ,  $R^5$  and R are as defined herein to obtain the corresponding amidoacid of formula IV wherein  $R^1$ ,  $R^3$ ,  $R^4$  and  $R^5$  are as defined herein, and reacting the last-named compound with phosphorus pentasulfide to obtain the corresponding compound of formula I wherein  $R^1$ ,  $R^3$ ,  $R^4$  and  $R^5$  are as defined herein and  $R^2$  is hydrogen.

Referring to the above section (a) of the last paragraph, the thioester of formula III includes those 40 corresponding compounds of formula I wherein  $R^2$  is lower alkyl, when R of the compound of formula III is lower alkyl. For clarity and convenience in the following discussion of the process, these latter compounds of formula I are included in the discussion and preparation of the compounds of formula III.

Still more specifically, the starting material of formula II can be prepared by coupling a naphthalene-carboxylic acid of formula V wherein  $R^3$ ,  $R^4$  and  $R^5$  are as defined herein with an amino acid ester of formula 45 VI wherein  $R^1$  and R are as defined herein.



The compounds of formula V and VI are known or can be prepared by known methods. For example, see "Elsevier's Encyclopaedia of Organic Chemistry," F. Radt, Ed., Series III, Vol. 12B, Elsevier Publishing Co., Amsterdam, 1953, pp 3965—4473. The preparation of a number of the naphthalenecarboxylic acids is 60 illustrated by examples 1, 1a to 1k and 61 to 63, described hereinafter. The coupling of the naphthalene-carboxylic acid V and the amino acid ester VI is done preferably by the "carboxyl activation" coupling procedure. Descriptions of carboxyl-activating groups are found in general textbooks of peptide chemistry; for example, K. D. Kopple, "Peptides and Amino Acids," W. A. Benjamin, Inc., New York, 1966, pp. 45—51, and E. Schröder and K. Lüoke, "The Peptides"; Vol. 1, Academic Press, New York, 1965, pp. 77—128. 65 Examples of the activated form of the terminal carboxyl are the acid chloride, acid bromide, anhydride,

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azide, activated ester, or O-acyl urea obtained from a dialkylcarbodiimide. Preferred activated forms of the carboxyl are the acid chloride or the 1-benzotriazolyl, 2,4,5-trichlorophenyl or succinimido activated esters.

Returning to the flow diagram again, the amidoester of formula II may be reacted, for example, under anhydrous conditions with about two to five molar equivalents of phosphorus pentasulfide in an inert solvent, e.g. xylene or toluene, to obtain the corresponding thioester of formula III. This reaction is performed conveniently at temperatures ranging from 80 to about 150°C and at times ranging from 20 minutes to four hours. Preferably, the reaction is performed in the presence of an organic base for instance, N-ethyl morpholine, triethylamine or pyridine.

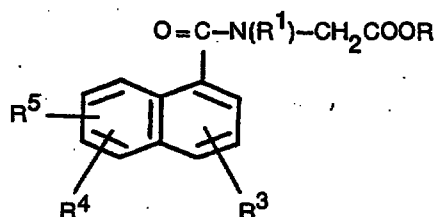
Thereafter, the thioester of formula III may be hydrolysed with a hydrolysing agent to give the corresponding product of formula I in which R<sup>2</sup> is hydrogen. Generally speaking, this conversation is most conveniently performed by employing a base as the hydrolysing agent. The hydrolysis may be performed in the presence of sufficient water, followed by acidification of the reaction mixture, to yield the desired acid. However, it should be understood that the manner of hydrolysis for the process of this invention is not intended to be limited to basic hydrolysis since hydrolysis under acidic conditions and other variations, for example, treatment with lithium iodide in collidine (see L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", John Wiley and Sons, Inc., New York, 1969, pp 615—617), also are applicable. Hydrolysis under acidic conditions is preferred when the ester is a tert butyl ester.

For basis hydrolysis, a preferred embodiment involves subjecting the ester to the action of a strong base, for example, sodium or potassium hydroxide, in the presence of sufficient water to effect hydrolysis of the ester. The hydrolysis may be performed using a suitable solvent, for example, methanol, ethanol or 2-methoxyethanol. The reaction mixture may be maintained at a temperature of from about 25° to 100°C or at the reflux temperature of the solvent employed until hydrolysis occurs. Usually ten minutes to six hours is sufficient for this hydrolysis. The reaction mixture is then rendered acidic with an acid, for example, acetic acid, hydrochloric acid or sulphuric acid to release the free acid.

Alternatively, the amidoester of formula II can be hydrolysed under the same conditions as described hereinbefore to give the corresponding amidoacid of formula IV wherein R<sup>1</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are as defined herein. The latter compound, when reacted with phosphorus pentasulfide in the manner described hereinbefore, then gives the corresponding compound of formula I wherein R<sup>1</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are as defined herein and R<sup>2</sup> is hydrogen. Note that the standard first step of the work up of the pentasulfide reaction mixture requires that the reaction mixture be decomposed in water. This action causes any corresponding thioacid, present in the reaction mixture as a result of the carboxy group reacting with phosphorus pentasulfide, to be converted to the desired carboxylic acid.

The amidoacid of formula IV also can be prepared by a previously reported process involving the reaction of the appropriate naphthalenecarboxylic acid chloride with the appropriate aminoacid corresponding to the aminoacid ester of formula VI in the presence of a base (proton acceptor). This process has been used to prepare N-[(1-naphthalenyl)carbonyl]glycine, see Chem. Abstr., 61, 4333 f (1964) for E. Cioranescu, *et al.*, Rev. Chim., Acad., Rep. Populaire Roumaine, 7 (2), 755 (1962). However, this process for preparing N-[(1-naphthalenyl)carbonyl] glycine is generally inferior, based on yields, to the described process above.

An interesting aspect of this invention is that certain amidoesters of formula II and certain amidoacids of formula IV having the following formula



wherein R<sup>1</sup> is lower alkyl, lower alkenyl or phenylmethyl; R<sup>3</sup> is a substituent at position 4, 5 or 8 of the naphthalene ring, the substituent being selected from the group consisting of lower alkyl, lower alkoxy, halo, cyano, nitro and trihalomethyl, and R<sup>4</sup> and R<sup>5</sup> each is hydrogen; or R<sup>3</sup> and R<sup>4</sup> each is a substituent at different positions of the naphthalene ring, the positions selected from positions 3 to 7 and the substituents being selected from the group consisting of lower alkyl, lower alkoxy, halo, trihalomethyl, trihalomethylthio, (lower)alkoxy(lower)alkoxy, phenylmethoxy and phenylmethoxy substituted on the phenyl portion with a lower alkyl, lower alkoxy, halo or trihalomethyl and R<sup>5</sup> is hydrogen; or R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> each is a substituent at different positions selected from positions 4, 5 and 6 of the naphthalene ring, the substituent being selected from the group consisting of lower alkoxy, halo and trihalomethyl; and R is hydrogen or lower alkyl; or a therapeutically acceptable salt thereof with an organic or inorganic base, also have aldose reductase inhibiting effects. For example, in the above noted in vitro test, the following results were obtained for the amidoacids, described in example 60:

N-[(5-bromo-1-naphthalenyl)carbonyl]-N-methylglycine (10<sup>-5</sup>, 64%; 10<sup>-6</sup>, 21%); and  
N-[(5-(trifluoromethyl)-6-methoxy-1-naphthalenyl)carbonyl]-N-methylglycine (10<sup>-5</sup>, 94%; 10<sup>-6</sup>, 93%; 10<sup>-7</sup>, 60%).

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Accordingly, the latter amidoesters, amidoacids and the therapeutically acceptable salts with organic or inorganic bases, of the amidoacids are included within the scope of this invention.

The following examples illustrate further this invention.

#### Example 1

5-(1-Methylethenyl)-1-naphthalenecarboxylic Acid ( $V$ ,  $R^3 = 5\text{-CH}_2=\text{C}(\text{CH}_3)$  and  $R^4$  and  $R^5 = \text{H}$ )

In a nitrogen atmosphere, a solution of 1-bromo-5-(1-methylethenyl)naphthalene [14.21 g, described by W. F. Short and H. Wang, J. Chem. Soc., 991 (1950)] in diethyl ether (140 ml) was added dropwise to a mixture of ethyl magnesium bromide (prepared from 2.94 g of magnesium and 4.29 ml of ethyl bromide) in diethyl ether (30 ml) at 0°C. The mixture was stirred at 20°C for 18 hr and then heated at reflux for 1 hr. The cooled solution was poured onto an excess of solid carbon dioxide. The mixture was dissolved in diethyl ether. The resulting solution was washed with a 2N aqueous solution of  $\text{H}_2\text{SO}_4$ , brine and 10% aqueous  $\text{NaHCO}_3(4x)$ . The basic washes were combined and made acidic (pH<sub>3</sub>) with 6N aqueous HCl. The resulting solid was collected, washed with water and dried to give 9.7 g of the title compound; mp 138—140°C; NMR( $\text{CDCl}_3$ )  $\delta$  2.15 (s, 3H), 5.0 and 5.38 (2s, 2H), 8.0 (m, 6H), 10.75 (s, 1H).

#### Example 1a

5-(1-Methylethenyl)-1-naphthalenecarboxylic Acid ( $V$ ,  $R^3 = 5\text{-(CH}_3)_2\text{CH}$  and  $R^4$  and  $R^5 = \text{H}$ )

5-(1-Methylethenyl)-1-naphthalenecarboxylic acid (4.36 g, described in Example 1), dissolved in ethanol (150 ml), was hydrogenated using 5% palladium on charcoal as catalyst at 20°C. Absorption of hydrogen was complete after 3 hr. The catalyst was removed by filtration. The filtrate was evaporated to give the title compound; mp 148—150°C; NMR ( $\text{CDCl}_3$ )  $\delta$  1.4 (d,  $J = 7\text{Hz}$ , 6H), 3.75 (septuplet,  $J = 7\text{Hz}$ , 1H), 8.0 (m, 6H), 10.1 (s, 1H).

#### Example 1b

5-Bromo-6-methoxy-1-naphthalenecarboxylic Acid ( $V$ ,  $R^3 = 5\text{-Br}$ ,  $R^4 = 6\text{-CH}_3\text{O}$  and  $R^5 = \text{H}$ )

A solution of bromine (2.49 ml, 45 mmoles) in glacial acetic acid (50 ml) was added dropwise to a stirred solution of 6-methoxy-1-naphthalenecarboxylic acid [8.9 g, 44 mmoles, described by C. C. Price, *et al.*, J. Am. Chem. Soc., 69, 2261 (1947)] in glacial acetic acid (300 ml), cooled in an ice bath. The resulting precipitate was collected and washed with acetic acid and then water. Crystallization of collected precipitate from glacial acetic acid gave the title compound; mp 262—264°C; NMR( $\text{DMSO-d}_6$ )  $\delta$  3.96 (s, 3H), 7.5—7.8 (m, 3H), 7.95 (d, 1H), 8.25 (d, 1H), 8.82 (d, 1H).

#### Example 1c

5-Bromo-6-methyl-1-naphthalenecarboxylic Acid ( $V$ ,  $R^3 = 5\text{-Br}$ ,  $R^4 = 6\text{-CH}_3$  and  $R^5 = \text{H}$ )

By the following procedure of Example 1b, but replacing 6-methoxy-1-naphthalenecarboxylic acid with an equivalent amount of 6-methyl-1-naphthalenecarboxylic acid, described by C. C. Price *et al.*, J. Am. Chem. Soc., 63, 1857 (1941), the title compound; mp 253—255°C [after crystallization from ethanol-methanol (3:1)], NMR ( $\text{DMSO-d}_6$ )  $\delta$  2.6 (s, 3H), 8.0 (m, 5H), 10.5 (broad, 1H), was obtained.

#### Example 1d

3-Chloro-4-methoxy-1-naphthalenecarboxylic Acid ( $V$ ,  $R^3 = 3\text{-Cl}$ ,  $R^4 = 4\text{-CH}_3\text{O}$  and  $R^5 = \text{H}$ )

3-Chloro-4-methoxy-1-naphthalenecarboxaldehyde [15.5 g, 70.2 mmoles, described by A. J. Ablewhite and K. R. H. Wooldridge, J. Chem. Soc. (C), 2488 (1967)] was added to a suspension of silver oxide in 10% sodium hydroxide (16.9 g of sodium hydroxide in 170 ml of water) and dioxane (100 ml). The mixture was stirred and heated at 80°C for 7 hr. The precipitate was removed by filtration through diatomaceous earth (sold under the trademark Celite). The clear filtrate was evaporated to dryness. The residue was dissolved in water. The solution was acidified and the resulting precipitate was separated by filtration. The precipitate was dissolved in ethyl acetate. The resulting solution was extracted with saturated sodium bicarbonate solution. The combined aqueous extracts were acidified. The resulting precipitate was separated by filtration and recrystallized from ethanol-water to give the title compound; mp 187—189°C; NMR ( $\text{DMSO-d}_6$ )  $\delta$  4.0 (s, 3H), 8.15 (m, 5H), 13.3 (broad 1H); IR (Nujol\*) 2900, 1700, 1260, 1160  $\text{cm}^{-1}$ ; UV $\lambda_{\text{max}}$  (EtOH) 303 ( $\epsilon$ 7,400), 231 ( $\epsilon$ 6,300); Anal. Calcd: C, 60.90% H, 3.83% Found: C, 60.71% H, 3.87%.

#### Example 1e

5,7-Dichloro-1-naphthalenecarboxylic Acid ( $V$ ,  $R^3 = 5\text{-Cl}$ ,  $R^4 = 7\text{-Cl}$  and  $R^5 = \text{H}$ )

Sulfuryl chloride (36.8 g, 273 mmoles) was added dropwise to a stirred suspension of benz[c,d]indole-2(1H)-one (20 g, 119 mmoles) in glacial acetic acid (275 ml) at 20 to 22°C. The mixture was heated at reflux for 1.5 hr, cooled and filtered. The collected solid was washed with glacial acetic acid and recrystallized from toluene to afford 6,8-dichloro-benz[c,d]indole-2(1H)-one, mp 265°C, described by Y. T. Rozhinskii, Zhur. Org. Khim., 8, 2388 (1972). A mixture of the latter compound (14 g, 58.8 mmoles) in 2% aqueous sodium hydroxide was refluxed for 4 hr. The mixture was cooled, mixed with sodium nitrite (3.8 g, 55 mmoles) and added dropwise to a cooled (0—5°C) solution of concentrated sulfuric acid (45 ml) in water (180 ml). The diazonium salt was salted out by addition of sodium bromide, collected by filtration and while

\*Nujol is a trademark for a brand of white mineral oil

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still wet (drying dangerous) was added to a solution of sodium hypophosphate (39.2 g of  $\text{NaH}_2\text{PO}_2 \cdot \text{H}_2\text{O}$ ) in water (100 ml). The mixture was stirred at 20–22°C for 48 hr. The resulting solid was collected by filtration and suspended in saturated sodium bicarbonate (300 ml). The insoluble material was collected by filtration and resuspended in hot, saturated sodium bicarbonate (200 ml). The suspension was filtered and the filtrate was cooled. The resulting precipitate of the sodium salt of the product was collected by filtration. The free acid was prepared by suspending the sodium salt in water and rendering the suspension acidic. More product was obtained by acidification of filtrates of the sodium salt. The combined crops were recrystallized from ethanol to yield 5.8 g of the title compound; mp 253–254°C; NMR ( $\text{DMSO-d}_6$ )  $\delta$  8.3 (m, 5H), 10.6 (broad, 1H),  $\text{UV}\lambda_{\text{max}}$  (EtOH) 333 nm ( $\epsilon$  2,350), 298 (7,000), 230 (53,300).

## Example 1f

5-Iodo-6-methoxy-1-naphthalenecarboxylic Acid ( $\text{V}$ ,  $\text{R}^3 = 5\text{-I}$ ,  $\text{R}^4 = 6\text{-CH}_3\text{O}$  and  $\text{R}^5 = \text{H}$ )

Iodine (7.08 g) and iodic acid (2.78 g) were added to a stirred solution of 6-methoxy-1-naphthalenecarboxylic acid methyl ester [15 g, 69.4 mmol, described by C. C. Price *et al.*, J. Amer. Chem. Soc., 69, 2261 (1947)] in 80% acetic acid (110 ml) and 98% sulfuric acid (0.97 ml). The solution was heated at 50°C for 5 hr, cooled and poured into water (100 ml). After the addition of sodium bisulfite to destroy the unreacted iodine, the precipitate was collected, washed with water and recrystallized from ethanol to afford the corresponding methyl ester of the title compound; mp 98–99°C; NMR ( $\text{CDCl}_3$ )  $\delta$  3.95 (s, 3H), 4.00 (s, 3H), 8.00 (m, 5H). A mixture of the latter ester (7.1 g, 21 mmol), 10% aqueous sodium hydroxide (35 ml) and methanol (19.5 ml) was heated at reflux for 1 hr. The solution was cooled to ice bath temperature and made acidic with 1N aqueous hydrochloric acid. The resulting precipitate was collected, washed with water and dried under reduced pressure over phosphorus pentoxide to give 7 g of the title compound; mp 259–261°C; NMR ( $\text{DMSO-d}_6$ )  $\delta$  4.0 (s, 3H), 8.15 (m, 5H), 10.56 (broad, 1H).

## Example 1g

5-Cyano-6-methoxy-1-naphthalenecarboxylic Acid ( $\text{V}$ ,  $\text{R}^3 = 5\text{-CN}$ ,  $\text{R}^4 = 6\text{-CH}_3\text{O}$  and  $\text{R}^5 = \text{H}$ )

A solution of bromine (26.6 g, 0.167 mole) in glacial acetic acid (25 ml) was added dropwise to a cooled suspension of 6-methoxy-1-naphthalenecarboxylic acid methyl ester (30 g, 0.139 moles) in glacial acetic acid (2.75 ml). The precipitate was collected, washed with water and crystallized from ethanol to give 33.3 g of 5-bromo-6-methoxy-1-naphthalenecarboxylic acid methyl ester; mp 119°C; NMR ( $\text{CDCl}_3$ )  $\delta$  3.97 (s, 3H), 4.03 (s, 3H), 7.35 (d,  $J = 9.25$  Hz, 1H), 7.4 (m, 1H), 8.05 (d,  $J = 6.75$  Hz, 1H), 8.45 (d,  $J = 8.25$  Hz, 1H), 8.9 (d,  $J = 9.25$  Hz, 1H). The latter ester (10.1 g, 34 mmol) and  $\text{Cu}_2(\text{CN})_2 \cdot \text{H}_2\text{O}$  (3.4 g, 17 mmol) in distilled dimethylformamide (75 ml) containing 15 drops of pyridine was heated at 180°C for 5 hr. The hot mixture was poured into a mixture of ice (50 g) and conc.  $\text{NH}_4\text{OH}$  (50 ml). The resulting precipitate was collected, washed with water, dried and recrystallized from chloroform-ethyl acetate to afford 5.6 g of 5-cyano-6-methoxy-1-naphthalenecarboxylic acid methyl ester; mp 210–211°C, NMR ( $\text{CDCl}_3$ )  $\delta$  3.95 (s, 3H), 4.15 (s, 3H). To a stirred solution of the latter ester (5.95 g, 24.66 mmol) in 2-methoxyethanol (100 ml) at 20–22°C, 4N aqueous NaOH solution (12.3 ml) was added. The reaction mixture was stirred at 20–22°C for 60 hr, diluted with water, cooled to 0°C and rendered acidic with 1N aqueous HCl. The precipitate was collected and dried to yield 5.6 g of the title compound; mp > 290°C; NMR ( $\text{DMSO-d}_6$ )  $\delta$  4.1 (s, 3H), 8.1 (m, 5H).

## Example 1h

5-(Trifluoromethyl)-6-methoxy-1-naphthalenecarboxylic Acid ( $\text{V}$ ,  $\text{R}^3 = 5\text{-CF}_3$ ,  $\text{R}^4 = 6\text{-CH}_3\text{O}$  and  $\text{R}^5 = \text{H}$ )

A mixture of 5-iodo-6-methoxy-1-naphthalenecarboxylic acid methyl ester (10.26 g, 30 mmol, described in Example 1f), trifluoromethyl iodide (12 g, 61.2 mmol), freshly prepared copper powder (5.7 g, prepared according to the procedure of R.Q. Brewster and T. Groening, "Organic Syntheses", Coll. Vol. II, John Wiley and Sons, New York, N.Y., U.S.A., 1948, p. 445) and pyridine (45 ml) was charged into a stainless steel autoclave. The vessel was shaken and heated at 120°C for 20 hr and cooled to room temperature. The mixture was diluted with diethyl-ether-ethyl acetate (1:1). The insoluble material was removed by filtration. The filtrate was washed with 1N aqueous HCl, water and dried ( $\text{MgSO}_4$ ). The solvent was removed under reduced pressure. The residue was crystallized from ethanol to give 6.4 g of 5-(trifluoromethyl)-6-methoxy-1-naphthalenecarboxylic acid methyl ester; mp 79–80°C; NMR ( $\text{CDCl}_3$ )  $\delta$  3.95 (s, 6H), 8.00 (m, 5H). A mixture of the latter ester (6.3 g, 27 mmol), 1N aqueous NaOH solution (34.12 ml) and methanol (100 ml) was stirred at 20–22°C for 4 hr. The mixture was adjusted to pH 7 with 1N aqueous HCl, methanol was removed from the mixture by distillation and the concentrated mixture was made acidic (pH 2) with 1N aqueous HCl. The resulting precipitate was collected and dried and yield 6 g of the title compound; mp 218–219°C; NMR ( $\text{DMSO-d}_6$ )  $\delta$  4.0 (s, 3H), 8.3 (m, 5H), 10.6 (broad, 1H).

## Example 1i

5-Bromo-6-[3-(trifluoromethyl)phenylmethoxy]-1-naphthalenecarboxylic Acid [ $\text{V}$ ,  $\text{R}^3 = 5\text{-Br}$ ,  $\text{R}^4 = 6\text{-}[(3\text{-CF}_3\text{-C}_6\text{H}_4)\text{-CH}_2\text{O}]$  and  $\text{R}^5 = \text{H}$ ]

A mixture of 5-bromo-6-methoxy-1-naphthalenecarboxylic acid (33.35 g, 0.11 moles, described in example 1b) in glacial acetic acid (460 ml) and 47% aqueous HBr (417 ml) was heated at reflux for 9 hr. The resulting precipitate was collected, washed with water and dried over  $\text{P}_2\text{O}_5$  under reduced pressure. The

precipitate was recrystallized from ethanol-water to give 21.45 g of 5-bromo-6-hydroxy-1-naphthalene-carboxylic acid; mp > 225°C; NMR (DMSO- $d_6$ )  $\delta$  8.0 (m, 5H), 11.0 (broad, 1H), 12.6 (broad, 1H).

The latter acid (1.2 g, 4.5 mmoles) was suspended in dry dimethylformamide (DMF, 25 ml). Sodium hydride (0.43 g, 9.0 mmoles, 50% mineral oil suspension) was added in small portions to the stirred suspension. Stirring was continued until the evolution of hydrogen ceased. A solution of 3-(trifluoromethyl)phenylmethyl chloride (2.63 g, 13.5 mmoles) in dry DMF (5 ml) was added dropwise and the mixture was heated to 50–60°C for 1 hr. The solvent was evaporated under reduced pressure to dryness. The residue was triturated with water. The solid was separated from the water by filtration. The collected solid was washed with hexane to remove residual mineral oil and then recrystallized from ethanol-water to give 1.7 g of 5-bromo-6-[(3-trifluoromethyl)phenylmethoxy]-1-naphthalene-carboxylic acid, 3-trifluoromethyl ester; mp 114–115°C, IR (CHCl<sub>3</sub>) 1715 cm<sup>-1</sup>.

A mixture of the latter ester (1.7 g, 2.9 mmoles), methanol (20 ml) and 1N aqueous NaOH (4 ml) was stirred for 24 hr at 20–22°C. Additional 1N aqueous NaOH was added and the mixture was stirred at 40°C for 3 hr. The solvent was evaporated. The residue was dissolved in water and the solution made acidic. The resulting precipitate was collected, washed with water, dried and recrystallized from ethanol to give 1.0 g of the title compound; mp 229–230°C; NMR (DMSO- $d_6$ )  $\delta$  5.5 (s, 2H), 8.1 (m, 9H), 10.5 (broad, 1H).

5-Bromo-6-(4-chlorophenylmethoxy)-1-naphthalenecarboxylic acid, NMR (DMSO- $d_6$ )  $\delta$  5.4 (s, 2H), 7.7 (m, 9H), 11.0 (broad, 1H), is obtained by following the procedure of Example 1i but replacing 3-(trifluoromethyl)phenylmethyl chloride with an equivalent amount of 4-chlorophenylmethyl chloride.

#### Example 1j

5-(Trifluoromethyl)-1-naphthalenecarboxylic Acid (V, R<sup>3</sup> = 5-CF<sub>3</sub> and R<sup>4</sup> and R<sup>5</sup> = H)

A mixture of 5-iodo-1-naphthalenecarboxylic acid methyl ester [8.8 g, 28 mmoles, described by C. Seer and R. School, *Justus Leibigs Ann. Chem.*, 398, 82 (1913)], trifluoromethyl iodide (12 g, 61.2 mmoles), freshly prepared copper powder (5.7 g, prepared according to the procedure of R. Q. Brewster and T. Groening, "Organic Syntheses", Coll. Vol. II, John Wiley and Sons, New York, N.Y., U.S.A., 1948, p. 445) and pyridine (45 ml) was charged into a stainless steel autoclave. The vessel was shaken and heated at 130°C for 24 hr and cooled to room temperature. The mixture was filtered to remove insoluble material. The filtrate was washed with 1N aqueous HCl, water and brine, dried (MgSO<sub>4</sub>) and concentrated to dryness. The residue was crystallized from methanol to give 4.3 g of 5-(trifluoromethyl)-1-naphthalenecarboxylic acid methyl ester, NMR (CDCl<sub>3</sub>)  $\delta$  4.0 (s, 3H), 8.0 (m, 6H).

The ester (4.25 g, 16.72 mmoles) was suspended in methanol (100 ml). A 2N aqueous NaOH solution (16.72 ml, 2 equivalents) was added to the suspension. The mixture was stirred at 20–22°C for 18 hr. The resulting clear solution was adjusted to pH 8 with 1N aqueous HCl and concentrated under reduced pressure. The concentrate was adjusted to pH 3 with 1N aqueous HCl. The resulting precipitate was collected, washed with water and dried under reduced pressure to give the title compound; mp 206–208°C.

#### Example 2

N-[(5-Bromo-1-naphthalenyl)carbonyl]-N-methylglycine Methyl Ester (II, R<sup>1</sup> and R = CH<sub>3</sub>, R<sup>3</sup> = 5-Br and R<sup>4</sup> and R<sup>5</sup> = H)

##### Procedure A:

A catalytic amount (5 drops) of dry DMF was added to a suspension of the starting material of formula V, 5-bromo-1-naphthalenecarboxylic acid [10 g, 39.8 mmoles, described by W. F. Short and H. Wang, *J. Chem. Soc.*, 990 (1950)], in thionyl chloride (100 ml). The suspension was heated cautiously to reflux (caution: a vigorous reaction can occur). The mixture was refluxed for 20 min. The mixture was evaporated to dryness. Toluene was added to the solid residue and the mixture was evaporated to dryness. The residue was dissolved in pyridine (100 ml). The solution was cooled in an ice bath. Dry N-methylglycine methyl ester hydrochloride (11.1 g, 79.6 mmoles), a starting material of formula VI, was added portionwise to the cooled solution. The mixture was stirred for 2 hr at 20°C and then heated at reflux for 1 hr. The pyridine was removed by evaporation. Water was added to the oily residue. The mixture was extracted with ethyl acetate (3 × 150 ml). The combined extracts were washed with 1N aqueous HCl solution, a saturated solution of sodium bicarbonate and brine. After drying over MgSO<sub>4</sub>, the extract was treated with charcoal, filtered and evaporated. The residue was crystallized from diethyl ether or ethanol to give the title compound; mp 91–92°C; NMR (CDCl<sub>3</sub>)  $\delta$  2.8 and 3.25 (2s, 3H), 3.6 and 3.85 (2s, 3H), 4.35 (broad, 2H), 7.75 (m, 6H); UVλ<sub>max</sub> (EtOH) 321 nm ( $\epsilon$ 775), 316 (1,110), 299 (6,660), 289 (9,250), 279 (7,400), 225 (66,600); *Anal.* Calcd: C, 53.59% H, 4.20% N, 4.17%; Found: C, 53.60% H, 4.27% N, 4.21%.

##### Procedure B:

A mixture of the starting material of formula V, 5-bromo-1-naphthalene-carboxylic acid (12.8 g, 52 mmoles), and 1-hydroxybenzotriazole (HOBt, 7.0 g, 52 mmoles) in DMF (200 ml) was prepared. N,N'-dicyclohexylcarbodiimide (DCC, 10.6 g, 52 mmoles) in DMF (30 ml) was added to the mixture. The resulting mixture was stirred at 20°C for 1 hr and then cooled to 0°C. N-Methylglycine methyl ester hydrochloride (7.25 g, 52 mmoles) and then N-ethylmorpholine (6.7 ml, 52 mmoles) were added to the cooled mixture. The mixture was stirred for 30 min at 0°C and then for 18 hr at 20°C. Thereafter, the mixture was filtered and concentrated to dryness under reduced pressure. The residue was subjected to chromatography on 325 g of silica gel using ethyl acetate-hexane (1:1) as the eluant. The pure fractions were pooled to yield 10.5 g of

product which was recrystallized from ethyl acetate to give the title compound, identical to the product of procedure A of this example.

## Example 3

N-[(5-Bromo-1-naphthalenyl)thioxomethyl]-N-methylglycine Methyl Ester (I,  $R^1$  and  $R^2 = \text{CH}_3$ ,  $R^3 = 5\text{-Br}$  and  $R^4$  and  $R^5 = \text{H}$ )

To a stirred solution of N-[(5-bromo-1-naphthalenyl)carbonyl]-N-methyl-glycine methyl ester (35.5 g, 106 mmoles, described in Example 2) in dry pyridine (100 ml), phosphorus pentasulfide (44.5 g, 200 mmoles) was added portionwise. The mixture was stirred and refluxed for 1.5 hr and then poured into a liter of water at 50 to 80°C (caution: evolution of copious quantities of  $\text{H}_2\text{S}$ ). The mixture was allowed to cool to 20 to 22°C (room temperature), filtered and the filtrate was extracted with ethyl acetate. The extract was washed with 1N aqueous HCl solution, brine, a saturated solution of sodium carbonate and brine, dried ( $\text{MgSO}_4$ ), filtered and evaporated to dryness. The residue was recrystallized from ethanol-water (4:1) to give the title compound; mp 85–86°C; NMR ( $\text{CDCl}_3$ )  $\delta$  3.0 (s, 3H), 3.85 (s, 3H), 4.58 and 5.37 (2d,  $J = 17\text{Hz}$ , 2H), 7.1–8.3 (m, 6H); UV $\lambda_{\text{max}}$  (EtOH) 281 nm ( $\epsilon$  14,480), 218 (14,480).

By following serially the procedures of Examples 2 and 3 and using the appropriate starting material of formula V instead of 5-bromo-1-naphthalene-carboxylic acid, other compounds of formula I in which  $R^1$  and  $R^2$  each is methyl are obtained. Examples of the latter compounds are listed as products in Tables I and II together with the appropriate starting material of formula V used for their preparation.

TABLE I

| Example | $R^3$                    | Starting Material<br>of Formula V ( $R^5 = \text{H}$ ) |  | Product: N-[(prefix listed<br>below-1-naphthalenyl)-<br>thioxomethyl]-N-methyl-<br>glycine methyl ester                                                                                                                    |
|---------|--------------------------|--------------------------------------------------------|--|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|         |                          | $R^4$                                                  |  |                                                                                                                                                                                                                            |
| 4       | 4-Br                     | H                                                      |  | 4-bromo; NMR ( $\text{CDCl}_3$ ) $\delta$ 2.85 & 3.25 (2s, 3H), 3.6 & 3.85 (2s, 3H), 4.35 (m, 2H), 7.7 (m, 6H); IR ( $\text{CHCl}_3$ ) 1730, 1620 $\text{cm}^{-1}$                                                         |
| 5       | 8-Br                     | H                                                      |  | 8-bromo; IR ( $\text{CHCl}_3$ ) 1730, 1480, 1380, 1080 $\text{cm}^{-1}$ ; NMR ( $\text{CDCl}_3$ ) $\delta$ 3.0 (s, 3H), 3.8 (s, 3H), 3.65 (m, 2H), 7.5 (m, 6H)                                                             |
| 6       | 5- $\text{CH}_3\text{O}$ | H                                                      |  | 5-methoxy; NMR ( $\text{CDCl}_3$ ) $\delta$ 2.81 & 3.21 (2s, 3H), 3.58 & 3.80 (2s, 3H), 3.97 (s, 3H), 4.37 (broad, 2H), 6.80 (d, 1H), 7.40 (m, 4H), 8.27 (m, 1H); IR ( $\text{CHCl}_3$ ) 1740, 1630, 1578 $\text{cm}^{-1}$ |
| 7       | 5-Me                     | H                                                      |  | 5-methyl; NMR ( $\text{CDCl}_3$ ) $\delta$ 2.68 (s, 3H), 3.05 (3H), 3.85 (3H, 3.75 & 4.9 (m, 2H), 7.6 (s, 6H)                                                                                                              |
| 8       | 5-Br                     | 6- $[\text{CH}_3(\text{CH}_2)_4\text{O}]$              |  | 5-bromo-6-pentyloxy; mp 80–83°C; NMR ( $\text{CDCl}_3$ ) $\delta$ 0.9 (t, $J = 7\text{Hz}$ , 3H), 1.1–2.0 (broad, 2H), 3.0 (s, 3H), 3.8 (s, 3H), 4.1 (m, 2H), 7.1–8.5 (broad, 5H)                                          |
| 9       | 5-CN                     | H                                                      |  | 5-cyano; NMR ( $\text{CDCl}_3$ ) $\delta$ 3.00 (s, 3H), 3.85 (s, 3H), 4.45 & 5.45 (d, 2H), 7.18 (m, 6H)                                                                                                                    |
| 9a      | 4-CN                     | H                                                      |  | 4-cyano; NMR ( $\text{CDCl}_3$ ) $\delta$ 3.1 (s, 3H), 3.85 (s, 3H), 4.55 & 5.25 (2d, $J = 17\text{Hz}$ , 2H), 7.0–8.4 (m, 6H)                                                                                             |

TABLE I — continued

| Example | R <sup>3</sup>    | R <sup>4</sup>      | Product: N-[(prefix listed below-1-naphthalenyl)-thioxomethyl]-N-methylglycine methyl ester                                                                                                                                                                                                                                                    |
|---------|-------------------|---------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 10      | 5-NO <sub>2</sub> | H                   | 5-nitro; mp 116—117°C                                                                                                                                                                                                                                                                                                                          |
| 11      | 5-Cl              | H                   | 5-chloro; mass spectrum m/e: 307/309 (M <sup>+</sup> ), 274/276 (M <sup>+</sup> —H, S), 248/246 (M <sup>+</sup> —COOMe)                                                                                                                                                                                                                        |
| 12      | 5-Br              | 6-CH <sub>3</sub> O | 5-bromo-6-methoxy; mp 115—117°C; NMR (CDCl <sub>3</sub> ) δ 3.00 (s, 3H), 3.84 (s, 3H), 3.98 (s, 3H)                                                                                                                                                                                                                                           |
| 13      | 5-Br              | 6-CH <sub>3</sub>   | 5-bromo-6-methyl; NMR (CDCl <sub>3</sub> ) δ 2.6 (s, 3H), 3.0 (s, 3H), 3.85 (s, 3H), 4.5 & 5.35 (d, J = 16.5Hz, 2H), 7.7 (m, 5H)                                                                                                                                                                                                               |
| 14      | H                 | H                   | *; IR (CHCl <sub>3</sub> ) 1735 cm <sup>-1</sup>                                                                                                                                                                                                                                                                                               |
| 15      | 4-Cl              | H                   | 4-chloro; mp 100—101°C; NMR (CDCl <sub>3</sub> ) δ 3.10 & 3.62 (2s, 3H); 3.90 & 3.70 (2s, 3H) 4.04, 4.55 & 5.37 (s, 2d, J = 16Hz, 2H,) 7.2—8.4 (m, 6H); IR (CHCl <sub>3</sub> ) 1740 cm <sup>-1</sup> ; UVλ <sub>max</sub> (EtOH) 283 nm (ε 7,100), 219 (52,000); Anal. Calcd: C, 58.54% H, 4.58% N, 4.55%; Found: C, 58.58% H, 4.76% N, 4.58% |
| 16      | 3-Cl              | 4-CH <sub>3</sub> O | 3-chloro-4-methoxy; mp 85—86°C; NMR (CDCl <sub>3</sub> ) δ 3.05 (s, 3H), 3.85 (s, 3H), 4.00 (s, 3H), 4.58 & 5.3 (2d, J = 17Hz, 2H), 7.6 (m, 5H)                                                                                                                                                                                                |
| 17      | 5-Cl              | 7-Cl                | 5,7-dichloro; m/e: 325/327/329 (M <sup>+</sup> ), 266, 268, 270 (M <sup>+</sup> —COOCH <sub>3</sub> ), 223/225/227 (M <sup>+</sup> —CH <sub>3</sub> —N—CH <sub>2</sub> —COOCH <sub>3</sub> )                                                                                                                                                   |
| 18      | 5-I               | 6-CH <sub>3</sub> O | 5-iodo-6-methoxy; mp 149—150°C; NMR (CDCl <sub>3</sub> ) δ 3.00 (s, 3H), 3.85 (s, 3H), 3.95 (s, 3H), 4.4 & 5.45 (d, 2H), 7.6 (m, 5H)                                                                                                                                                                                                           |
| 19      | 5-CN              | 6-CH <sub>3</sub> O | 5-cyano-6-methoxy; mp 164—165°C; NMR (CDCl <sub>3</sub> ) δ 3.05 (s, 3H), 3.90 (s, 3H), 4.07 (s, 3H), 4.35 & 5.55 (d, J = 16.8Hz, 2H), 7.80 (m, 5H)                                                                                                                                                                                            |

\* No prefix as compound is N-(1-naphthalenyl)thioxomethyl)-N-methylglycine methyl ester

With reference to Table I the starting materials of formula V are described by T. L. Jacobs, *et al.*, J. Org. Chem., 11, 27 (1946) for example 4; by H. G. Rule *et al.*, J. Chem. Soc., 168 (1934) for example 5; by A. Girardet and N. Lorusso, *Helv. Chim. Acta.*, 49, 471 (1966) for example 6; by M. J. S. Dewar and P. J. Grisdale, J. Am. Chem. Soc., 84, 3541 (1962) for example 7; in example 1c for example 8; by M. J. S. Dewar and P. J. Grisdale, J. Am. Chem. Soc., 84, 3541 (1962) for examples 9, 9a, 10 and 11; in example 1b for example 12; in example 1c for example 13; by H. Gilman *et al.*, "Organic Syntheses", Coll. Vol. II, John Wiley and Sons, New York, N.Y., U.S.A., 1948, p.425 for example 14; by T. L. Jacobs *et al.*, J. Org. Chem., 11, 27 (1946) for example 15; in example 1d for example 16; in example 1e for example 17; in example 1f for example 18; and in example 1g for example 19.

TABLE II

| Example | Starting Material<br>of Formula V ( $R^5 = H$ ) |                                                                          | Product: N-[[prefix listed<br>below-1-naphthalenyl]-<br>thioxomethyl]-N-methyl-<br>glycine methyl ester                                                                                                                               |
|---------|-------------------------------------------------|--------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|         | $R^3$                                           | $R^4$                                                                    |                                                                                                                                                                                                                                       |
| 20      | 5-Br                                            | 6-[CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>3</sub> O]                   | 5-bromo-6-(3-methoxypropoxy); NMR (CDCl <sub>3</sub> ) $\delta$ 2.1 (m, 4H), 3.35 (s, 6H), 3.55 (m, 4H), 4.25 (t, J = 6Hz, 2H), 4.45 (t, J = 6Hz, 2H), 7.4 (m, 2H), 8.0 (d, J = 8Hz, 1H), 8.4 (d, J = 8Hz, 1H), 8.85 (d, J = 8Hz, 1H) |
| 21      | 5-[CH <sub>2</sub> =C(CH <sub>3</sub> )]        | H                                                                        | 5-(1-methylethenyl); mp 93—95°C; NMR (CDCl <sub>3</sub> ) $\delta$ 2.15 (s, 3H), 3.05 (s, 3H), 3.85 (s, 3H), 4.55 & 5.3 (2s, 2H), 5.0 & 5.35 (2s, 2H), 7.6 (m, 6H)                                                                    |
| 22      | 5-[(CH <sub>3</sub> ) <sub>2</sub> CH]          | H                                                                        | 5-(1-methylethyl); NMR (CDCl <sub>3</sub> ) $\delta$ 1.35 (m, 6H), 3.0 & 3.55 (2s, 3H), 3.65 & 3.85 (2s, 3H), 4.95 (2H), 7.5 (m, 6H)                                                                                                  |
| 23      | 5-CF <sub>3</sub>                               | 6-CH <sub>3</sub> O                                                      | 5-(trifluoromethyl)-6-methoxy; mp 109—110°C; NMR (CDCl <sub>3</sub> ) $\delta$ 3.00 (s, 3H), 3.85 (s, 3H), 3.95 (s, 3H), 4.35 & 5.45 (d, 2H), 7.7 (m, 5H)                                                                             |
| 24      | 5-Br                                            | 6-[(3-CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> )CH <sub>2</sub> O] | 5-bromo-6-[3-(trifluoromethyl)phenylmethoxy]; NMR (CDCl <sub>3</sub> ) $\delta$ 3.00 (s, 3H), 3.85 (s, 3H), 4.4 & 5.4 (2d, J = 16.5Hz, 2H), 5.25 (s, 2H), 7.6 (m, 9H)                                                                 |
| 24a     | 5-Br                                            | 6-[(4-Cl-C <sub>6</sub> H <sub>4</sub> )CH <sub>2</sub> O]               | 5-bromo-6-(4-chlorophenylmethoxy); NMR (CDCl <sub>3</sub> ) $\delta$ 3.00 (s, 3H), 3.85 (s, 3H), 4.40 & 5.40 (d, 2H), 5.2 (s, 2H), 7.5 (m, 9H)                                                                                        |
| 24b     | 5-CF <sub>3</sub>                               | H                                                                        | 5-(trifluoromethyl); NMR (CDCl <sub>3</sub> ) $\delta$ 3.00 (s, 3H), 3.85 (s, 3H), 4.5 & 5.4 (d, 2H), 7.2—8.3 (m, 6H).                                                                                                                |

With reference to Table II, the starting materials of formula V are described in example 1b, herein, for example 20; in example 1 for example 21; in example 1a for example 22; in example 1h for example 23; in example 1i for example 24 and example 24a; and in example 1j for example 24b.

By following serially the procedures of examples 2 and 3, but using the appropriate starting material of formula VI instead of N-methylglycine other compounds of formula I in which R<sup>2</sup> is lower alkyl, R<sup>3</sup> is 5-bromo, R<sup>4</sup> is hydrogen are obtained. Examples of the latter compounds are listed as products in Table III together with the appropriate starting material of formula VI used for their preparation.

TABLE III

| Example | R <sup>3</sup>                                | Starting Material of Formula VI | R <sup>4</sup>                | Product: N-[(5-bromo-1-naphthalenyl)thioxomethyl]-suffix listed below                                                                                                                                                                                           |
|---------|-----------------------------------------------|---------------------------------|-------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 25      | H                                             |                                 | CH <sub>3</sub>               | glycine methyl ester; mp 126—130°C; NMR (CDCl <sub>3</sub> ) δ 3.8 (s, 3H), 4.6 (d, J = 7Hz, 2H), 7.15—8.15 (m, 6H)                                                                                                                                             |
| 26      | n-C <sub>3</sub> H <sub>7</sub>               |                                 | C <sub>2</sub> H <sub>5</sub> | N-propylglycine ethyl ester; NMR (CDCl <sub>3</sub> ) δ 0.65 (t, J = 7Hz, 3H), 1.4 (t, 3H), 1.45 (m, 2H), 3.2 (t, J = 7Hz, 2H), 4.3 (q, J = 7Hz, 2H), 4.35 (d, J = 17Hz, 1H), 5.3 (d, J = 17Hz, 1H), 7.7 (m, 6H); IR (CHCl <sub>3</sub> ) 1740 cm <sup>-1</sup> |
| 27      | CH <sub>2</sub> =CH—CH <sub>2</sub>           |                                 | CH <sub>3</sub>               | N-(2-propenyl)glycine methyl ester; mp 72—74°C                                                                                                                                                                                                                  |
| 28      | C <sub>2</sub> H <sub>5</sub>                 |                                 | CH <sub>3</sub>               | N-ethylglycine methyl ester; NMR (CDCl <sub>3</sub> ) δ 1.10 (t, 3H), 3.35 (q, 2H), 3.85 (s, 3H), 4.40 & 5.25 (d, 2H), 7.6 (m, 6H)                                                                                                                              |
| 29      | n-C <sub>4</sub> H <sub>9</sub>               |                                 | C <sub>2</sub> H <sub>5</sub> | N-butylglycine ethyl ester; NMR (CDCl <sub>3</sub> ) δ 0.65 (t, J = 5.5Hz, 3H), 1.0 (m, 2H), 1.38 (t, 3H), 1.40 (m, 2H), 3.25 (m, 2H), 4.25 & 5.30 (d, J = 16Hz, 2H), 7.7 (m, 6H)                                                                               |
| 30      | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> |                                 | C <sub>2</sub> H <sub>5</sub> | N-(phenylmethyl)glycine ethyl ester; mp 141—142°C; NMR (CDCl <sub>3</sub> ) δ 1.35 (t, J = 7Hz, 3H), 4.50 (m, 6H), 7.50 (m, 11H); IR (Nujol*) 1743 cm <sup>-1</sup>                                                                                             |

## Example 31

By following serially the procedure of Examples 2 and 3, but using the appropriate starting material of formula V and the appropriate amino acid ester of formula VI, still other compounds of formula I in which R<sup>2</sup> is lower alkyl are obtained. For example, by using 3-chloro-4-methoxy-1-naphthalenecarboxylic acid, described in Example 1d, as the starting material of formula V, and using glycine ethyl ester hydrochloride as the starting material of formula VI, N-[(3-chloro-4-methoxy-1-naphthalenyl)thioxomethyl] glycine ethyl ester; IR (CHCl<sub>3</sub>) 3420, 3340, 1740, 1665 cm<sup>-1</sup>; mp 217°C (dec.); NMR (DMSO-d<sub>6</sub>) δ 3.96 (s, 3H), 4.42 (d, J = 6Hz, 2H), 7.40 (s, 1H), 7.65 (m, 2H), 8.18 (m, 2H); IR (Nujol\*) 3150, 2900, 1720, 1140 cm<sup>-1</sup>; UVλ<sub>max</sub> (EtOH) 277 nm (ε 11,400), 224 (51,300); Anal. Calcd: C, 54.28% H, 3.91% N, 4.52%; Found: C, 54.26% H, 4.06% N, 4.62% via N-[(3-chloro-4-methoxy-1-naphthalenyl)carbonyl]glycine ethyl ester; mp 140—141°C; NMR (CDCl<sub>3</sub>) δ 1.3 (t, J = 7Hz, 3H), 4.2 (m, 4H), 6.55 (broad, 1H), 7.55 (m, 3H), 8.2 (m, 2H), was obtained.

\* Trademark

## Example 32

(a) 1N aqueous NaOH solution (25 ml) was added to a suspension of N-[(5-bromo-1-naphthalenyl)thioxomethyl]-N-methylglycine methyl ester (7.3 g, 20.7 mmoles; described in Example 3) in methanol (75 ml). The mixture was stirred at 20 to 22°C for 2½ hr, neutralized to pH 7 with aqueous HCl and concentrated under reduced pressure to remove methanol. The residual solution was rendered acidic (pH = 2) with the addition of aqueous HCl solution and extracted with ethyl acetate. The extract was dried (MgSO<sub>4</sub>) and evaporated to dryness. The residue was crystallized from ethyl acetate-hexane to give 5.3 g of the title compound; mp 181°C; NMR (DMSO-d<sub>6</sub>) δ 2.95 (s, 3H), 4.65 & 5.2 (2d, J = 16.8 Hz, 2H), 7.85 (m, 6H), 49.72% H, 3.58% N, 4.14%; Found: C, 49.63% H, 3.63% N, 4.18%.

(b) In the same manner, but replacing N-[(5-bromo-1-naphthalenyl)thioxomethyl]-N-methylglycine methyl ester with an equivalent amount of N-[(3-chloro-4-methoxy-1-naphthalenyl)thioxomethyl]glycine ethyl ester, described in Example 31, N-[(3-chloro-4-methoxy-1-naphthalenyl)thioxomethyl]glycine [mp 217°C (dec); NMR (DMSO-d<sub>6</sub>) δ 3.96 (s, 3H), 4.42 (d, J = 6Hz, 2H), 7.40 (s, 1H), 7.65 (m, 2H), 8.18 (m, 2H); IR (Nujol\*) 3150, 2900, 1720, 1140 cm<sup>-1</sup>; UVλmax (EtOH) 277 nm (ε 11,400), 224 (51,300); Anal Calcd: C, 54.28% H, 3.91% N, 4.52%; Found: C, 54.26% H, 4.06% N, 4.62%] was obtained.

By following the procedure of Example 32, but replacing N-[(5-bromo-1-naphthalenyl)thioxomethyl]-N-methylglycine methyl ester with an equivalent amount of another ester compound of formula I in which R<sup>2</sup> is lower alkyl, or corresponding compounds in which R is ar(lower)alkyl, the corresponding compound of formula I in which R<sup>2</sup> is hydrogen was obtained. Examples of the latter compounds are listed as products in Tables IV, V and VI together with a notation to the corresponding compound of formula I in which R<sup>2</sup> is lower alkyl from which they are prepared. In each case the compound of formula I in which R<sup>2</sup> is lower alkyl, the starting material, is noted by the example in which it was prepared.

TABLE IV

| Example | No. of the example in which starting material was prepared | Product: N-[(prefix listed below-1-naphthalenyl)-thioxomethyl]-N-methylglycine                                                                                                                                                                                                                                                                                                                                              |
|---------|------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 30      | 33                                                         | 4                                                                                                                                                                                                                                                                                                                                                                                                                           |
|         |                                                            | 4-bromo; mp 168—169°C, NMR (DMSO-d <sub>6</sub> ) δ 3.0 (s, 3H), 4.65 & 5.15 (d, J = 16.5Hz, 2H), 7.7 (m, 6H); Anal Calcd: C, 49.71% H, 3.58% N, 4.14%; Found: C, 49.56% H, 3.42% N, 4.22%                                                                                                                                                                                                                                  |
| 35      | 34                                                         | 5                                                                                                                                                                                                                                                                                                                                                                                                                           |
|         |                                                            | 8-bromo; mp 65—85°C; Anal Calcd: C, 49.72% H, 3.58% N, 4.14%; Found: C, 53.54% H, 4.05% N, 4.40%                                                                                                                                                                                                                                                                                                                            |
| 40      | 35                                                         | 6                                                                                                                                                                                                                                                                                                                                                                                                                           |
|         |                                                            | 5-methoxy; mp 120°C; NMR (DMSO-d <sub>6</sub> ) δ 2.93 (s, 3H), 3.90 (s, 3H), 4.65 & 5.16 (2d, J = 17Hz, 2H), 6.95 (2d, J <sub>1</sub> = 7Hz, J <sub>2</sub> = 3Hz, 1H), 7.35 (m, 4H), 8.11 (2d, J <sub>1</sub> = 8Hz, J <sub>2</sub> = 2Hz, 1H); IR (Nujol*) 2900, 1734, 1715 cm <sup>-1</sup> ; UVλmax EtOH) 281 nm (ε 11,600), 233 (30,600); Anal Calcd: C, 62.27% H, 5.23% N, 4.84%; Found: C, 61.62% H, 5.95% N, 4.22% |
| 45      | 36                                                         | 7                                                                                                                                                                                                                                                                                                                                                                                                                           |
|         |                                                            | 5-methyl; mp 190—191°C, NMR (CDCl <sub>3</sub> ) δ 2.66 (s, 3H), 3.05 (s, 3H), 3.85 & 5.0 (m, 2H), 7.5 (m, 6H), 8.75 (broad, 1H); IR (CHCl <sub>3</sub> ) 3000, 1755, 1720 cm <sup>-1</sup> ; UVλmax (EtOH) 282 nm (ε 15,280), 226 (39,690), 218 (41,385); Anal Calcd: C, 65.90% H, 5.53% N, 5.12%; Found: C, 65.79% H, 5.57% N, 5.08%                                                                                      |
| 50      |                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 55      | 37                                                         | 8                                                                                                                                                                                                                                                                                                                                                                                                                           |
|         |                                                            | 5-bromo-6-pentyloxy; mp 211—217°C; NMR (DMSO-d <sub>6</sub> ) δ 0.9 (t, J = 6Hz, 3H), 1.6 (m, 2H), 2.9 (s, 3H), 4.2 (t, J = 6Hz, 2H), 3.95 & 5.15 (d, J = 15Hz, 2H), 7.1—8.55 (m, 5H); IR (Nujol*) 3000, 1650 cm <sup>-1</sup>                                                                                                                                                                                              |
| 60      | 38                                                         | 9                                                                                                                                                                                                                                                                                                                                                                                                                           |
|         |                                                            | 5-cyano; mp 190—200°C; NMR (DMSO-d <sub>6</sub> ) δ 3.00 (s, 3H), 4.65 & 5.15 (d, J = 17Hz, 2H), 7.95 (m, 6H); IR (Nujol*) 3000, 2230, 1730 cm <sup>-1</sup> ; UVλmax (EtOH) 313 nm (ε 5,600), 271 (13,850), 249 (14,620), 222 (48,340); Anal Calcd: C, 63.36% H, 4.34% N, 9.85%; Found: C, 62.01% H, 4.34% N, 9.36%                                                                                                        |

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TABLE IV (continued)

| Example | No. of the example in which starting material was prepared | Product: N-[(prefix listed below-1-naphthalenyl)-thioxomethyl]-N-methylglycine                                                                                                                                                                                                                                                                                                 |
|---------|------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 35a     | 9a                                                         | 4-cyano; mp 192—193°C; NMR (DMSO- $d_6$ ) $\delta$ 3.0 (s, 3H), 4.7 & 5.2 (d, J = 17Hz, 2H), 7.8 (m, 6H), 10.05 (broad, 1H); IR (Nujol*) 3180, 2230, 1745 (with inflection at 1755) $cm^{-1}$                                                                                                                                                                                  |
| 39      | 10                                                         | 5-nitro; mp 142—143°C; NMR (CDCl <sub>3</sub> ) $\delta$ 3.05 (s, 3H), 4.65 & 5.4 (d, 2H), 7.9 (m, 6H), 9.4 (broad, 1H); IR (Nujol*) 2900, 1715, 1530, 1345 $cm^{-1}$ ; UV $\lambda$ max (EtOH) 332 nm ( $\epsilon$ 4,110) 269 (17,010); Anal Calcd: C, 55.26% H, 3.96% N, 9.20%; Found: C, 55.17% H, 3.86% N, 9.10%                                                           |
| 40      | 11                                                         | 5-chloro; mp 153—154°C; NMR (CDCl <sub>3</sub> ) $\delta$ 3.03 (s, 3H), 4.67 & 5.33 (d, J = 17Hz, 2H), 7.50 (m, 4H), 7.90 (d, J = 8Hz, 1H), 8.25 (d, J = 8Hz, 1H); IR (CHCl <sub>3</sub> ) 3000, 1720 $cm^{-1}$ ; UV $\lambda$ max (EtOH) 280 nm ( $\epsilon$ 16,780), 212 (52,290); Anal Calcd: C, 57.23% H, 4.12% N, 4.77%; Found: C, 58.02% H, 4.28% N, 4.94%               |
| 41      | 12                                                         | 5-bromo-6-methoxy; mp 166—168°C; NMR (CDCl <sub>3</sub> ) $\delta$ 3.02 (s, 3H), 4.06 (s, 3H), 4.61 & 5.39 (d, J = 17Hz, 2H); IR (CHCl <sub>3</sub> ) 3000, 1718 $cm^{-1}$ ; UV $\lambda$ max (EtOH) 341 nm (4,350), 329 (4,015), 273 (13,150), 237 (51,260); Anal Calcd: C, 48.92% H, 3.83% N, 3.80%; Found: C, 49.11% H, 3.90% N, 3.91%                                      |
| 42      | 13                                                         | 5-bromo-6-methyl; mp 190—192°C; NMR (CDCl <sub>3</sub> ) $\delta$ 2.6 (s, 3H), 3.05 (s, 3H), 4.56 & 5.3 (d, 2H), 7.6 (m, 5H); IR (CHCl <sub>3</sub> ) 3000, 1720 $cm^{-1}$ ; UV $\lambda$ max (EtOH) 280 nm ( $\epsilon$ 14,055), 223 (43,400); Anal Calcd: C, 51.14% H, 4.01% N, 3.98%; Found: C, 51.21% H, 4.03% N, 4.00%                                                    |
| 43      | 14                                                         | **; mp 146—147°C; NMR (CDCl <sub>3</sub> ) $\delta$ 3.05 & 3.70 (2s, 3H), 4.07, 4.75 & 5.30 (s, 2d, J = 17Hz, 2H), 6.8—8.0 (m, 7H), 9.20 (broad, 1H); IR (CHCl <sub>3</sub> ) 3000, 1720 (inflection at 1755) $cm^{-1}$ ; UV $\lambda$ max (EtOH) 280 nm ( $\epsilon$ 14,415), 215 (53,450); Anal Calcd: C, 64.87% H, 5.05% N, 5.40%; Found: C, 64.89% H, 5.14% N, 5.51%       |
| 44      | 15                                                         | 4-chloro; mp 165—166°C; NMR (CDCl <sub>3</sub> ) $\delta$ 3.05 & 3.70 (2s, 3H), 4.10, 4.70 & 5.3 (s, 2d, J = 17Hz, 2H), 7.2—8.4 (m, 6H), 10.5 (s, 1H); IR (CHCl <sub>3</sub> ) 3000, 1725 (with inflection at 1765) $cm^{-1}$ ; UV $\lambda$ max (EtOH) 283 nm ( $\epsilon$ 13,500), 220 (49,600); Anal Calcd: C, 57.24% H, 4.12% N, 4.77%; Found: C, 57.56% H, 4.28% N, 4.84% |
| 45      | 16                                                         | 3-chloro-4-methoxy; mp 138—139°C NMR (DMSO- $d_6$ ) $\delta$ 3.0 (s, 3H), 3.45 (s, 3H), 4.6 & 5.15 (2d, J = 16.8Hz, 2H), 7.3 (s, 1H), 7.8 (m, 4H); IR (Nujol*) 2900, 1723 $cm^{-1}$ ; UV $\lambda$ max (EtOH) 329 nm ( $\epsilon$ 2,200), 282 (13,210), 224 (53,980); Anal Calcd: C, 55.64% H, 4.36% N, 4.33%; Found: C, 55.63% H, 4.48% N, 4.40%                              |

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\*\* No prefix as compound is N-((1-naphthalenyl)thioxomethyl)-N-methylglycine

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TABLE IV (continued)

| Example | No. of the example in which starting material was prepared | Product: N-[(prefix listed below-1-naphthalenyl)-thioxomethyl]-N-methylglycine                                                                                                                                                                                                                                                                                                   |
|---------|------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 46      | 17                                                         | 5,7-dichloro; mp 174—175°C; NMR (DMSO- $d_6$ ) $\delta$ 2.97 (3H), 4.57 & 5.27 (2d, J = 17Hz, 2H), 7.3—8.3 (m, 5H); IR (Nujol*) 3000, 1708 $\text{cm}^{-1}$ ; UV $\lambda_{\text{max}}$ (EtOH) 334 nm ( $\epsilon$ 3,050), 273 (15,810), 226 (63,800); <i>Anal</i> Calcd: C, 51.23% H, 3.38% N, 4.27%; Found: C, 51.44% H, 3.52% N, 4.40%                                        |
| 47      | 18                                                         | 5-iodo-6-methoxy; mp 161—163°C; NMR (DMSO- $d_6$ ) $\delta$ 2.95 (s, 3H), 3.95 (s, 3H), 4.6 & 5.2 (d, J = 17Hz, 2H), 7.5 (m 5H); IR (Nujol*) 2900, 1720 $\text{cm}^{-1}$ ; UV $\lambda_{\text{max}}$ (EtOH) 343 nm ( $\epsilon$ 7,900), 333 (7,250) 308 (12,400), 273 (20,500), 240 (74,200); <i>Anal</i> Calcd: C, 43.39% H, 3.40% N, 3.37%; Found: C, 42.75% H, 3.35% N, 3.37% |
| 48      | 19                                                         | 5-cyano-6-methoxy; mp 155—157°C; NMR (CDCl $_3$ ) $\delta$ 3.05 (s, 3H), 4.05 (s, 3H), 4.55 & 5.45 (d, J = 17Hz, 2H), 7.7 (m, 5H); IR (CHCl $_3$ ) 2900, 2220, 1725 $\text{cm}^{-1}$ ; UV $\lambda_{\text{max}}$ (EtOH) 346 nm ( $\epsilon$ 5,600), 339 (5,500), 232 (46,500)                                                                                                    |

TABLE V

| Example | No. of the example in which starting material was prepared | Product: N-[[prefix listed below-1-naphthalenyl]-thioxomethyl]-N-methylglycine                                                                                                                                                                                                                                                                                                                                                                                                                   |
|---------|------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 49      | 20                                                         | 5-bromo-6-(3-methoxy-propoxy); NMR (CDCl <sub>3</sub> ) $\delta$ 2.1 (q, J = 6Hz, 2H), 3.0 (s, 3H), 3.35 (s, 3H), 3.65 (t, J = 6Hz, 2H), 4.25 (t, J = 6Hz, 2H), 4.55 (d, J = 16Hz, 1H), 5.4 (d, J = 16Hz, 1H), 7.4 (m, 3H), 7.95 (d, J = 8Hz, 1H), 8.2 (d, J = 8Hz, 1H); IR (CHCl <sub>3</sub> ) 2900, 1720 cm <sup>-1</sup> ; UV $\lambda$ max (EtOH) 341 nm ( $\epsilon$ 3,920), 330 (3,730), 238 (49,400); <i>Anal</i> Calcd: C, 50.69% H, 4.73% N, 3.29%; Found: C, 50.29% H, 4.89% N, 3.23% |
| 50      | 21                                                         | 5-(1-methylethenyl); mp 146—148°C; NMR (CDCl <sub>3</sub> ) $\delta$ 2.2 (s, 3H), 3.1 (s, 3H), 4.75 & 5.35 (d, 2H), 5.05 & 5.4 (d, 2H), 7.6 (m, 6H), 8.5 (broad, 1H); IR (CHCl <sub>3</sub> ) 2900, 1760, 1720 cm <sup>-1</sup> ; UV $\lambda$ max (EtOH) 282 nm ( $\epsilon$ 14,000), 216 (38,900); <i>Anal</i> Calcd: C, 68.20% H, 5.72% N, 4.68% Found: C, 69.06% H, 6.03% N, 4.39%                                                                                                           |
| 51      | 22                                                         | 5-(1-methylethyl); mp 136°C; NMR (CDCl <sub>3</sub> ) $\delta$ 1.40 (m, 6H), 3.05 & 3.65 (d, 3H), 3.65 (m, 1H), 5.05 (m, 2H), 7.5 (m, 6H), 9.60 (broad, 1H); IR (CHCl <sub>3</sub> ) 2900, 1755, 1720 cm <sup>-1</sup> ; <i>Anal</i> Calcd: C, 67.74% H, 6.35% N, 4.65%; Found: C, 66.44% H, 6.56% N, 4.16%                                                                                                                                                                                      |
| 52      | 23                                                         | 5-(trifluoromethyl)-6-methoxy; mp 164—165°C; NMR (CDCl <sub>3</sub> ) $\delta$ 3.05 (s, 3H), 3.95 (s, 3H), 4.55 & 5.4 (d, J = 17Hz, 2H), 7.6 (m, 5H), 9.8 (broad, 1H); IR (CHCl <sub>3</sub> ) 2900, 1720 cm <sup>-1</sup> ; UV $\lambda$ max (EtOH) 337 nm ( $\epsilon$ 3,895), 268 (13,260), 226 (49,315); <i>Anal</i> Calcd: C, 53.78% H, 3.95% N, 3.92%; Found: C, 53.56% H, 3.95% N, 3.87%                                                                                                  |
| 53      | 24                                                         | 5-bromo-6-(3-trifluoromethyl)-phenylmethoxy; mp 125°C; NMR (DMSO-d <sub>6</sub> ) $\delta$ 3.0 (s, 3H), 4.65 & 5.25 (2d, J = 17Hz, 2H), 5.5 (s, 2H), 7.8 (m, 9H); IR (Nujol*) 2900, 1720 cm <sup>-1</sup> ; UV $\lambda$ max (EtOH) 340 nm ( $\epsilon$ 3,950), 270 (13,900), 263 (14,200), 238 (54,200); <i>Anal</i> Calcd C, 51.57% H, 3.35% N, 2.73% Found: C, 52.11% H, 3.22% N, 2.94%                                                                                                       |
| 53a     | 24a                                                        | 5-bromo-6-(4-chlorophenylmethoxy); mp 88—90°C (dec); NMR (DMSO-d <sub>6</sub> ) $\delta$ 2.95 (s, 3H), 4.63 & 5.20 (d, J = 17.25Hz, 2H), 5.4 (s, 2H), 7.6 (m, 9H); IR (CHCl <sub>3</sub> ) 3000, 1720 cm <sup>-1</sup> ; UV $\lambda$ max (EtOH) 340 nm ( $\epsilon$ 3,495), 326 (3,450), 238 (53,480)                                                                                                                                                                                           |
| 53b     | 24b                                                        | (5-trifluoromethyl); mp 156—158°C; NMR (CDCl <sub>3</sub> ) $\delta$ 3.05 (s, 3H), 4.65 & 5.4 (d, J = 17Hz, 2H), 7.85 (m, 6H), 10.4 (b, 1H); IR (CHCl <sub>3</sub> ) 2900, 1720 (with inflection at 1755), 1305 cm <sup>-1</sup> ; UV $\lambda$ max (EtOH) 278 nm ( $\epsilon$ 12,900) 216 (68,800); <i>Anal</i> Calcd: C, 55.03% H, 3.70% N, 4.27% Found: C, 54.69% H, 3.70% N, 4.27%                                                                                                           |

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TABLE VI

| 5  | Example | No. of the example in which starting material was prepared | Product: N-[(5-bromo-1-naphthalenyl)thioxomethyl]-suffix listed below                                                                                                                                                                                                                                                                                                      |
|----|---------|------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |         |                                                            |                                                                                                                                                                                                                                                                                                                                                                            |
| 10 | 54      | 25                                                         | glycine; mp 232—237°C; NMR (DMSO-d <sub>6</sub> ) δ 4.5 (d, J = 5.5Hz, 2H), 7.8 (m, 6H), 10.8 (broad, 1H); IR (Nujol*) 3200, 1720; UVλmax (EtOH) 275 nm (ε 11,700), 217 (44,800); <i>Anal</i> /Calcd C, 48.15% H, 3.10% N, 4.30%; Found: C, 48.65% H, 3.18% N, 4.37%                                                                                                       |
| 15 | 55      | 26                                                         | N-propylglycine; NMR (CDCl <sub>3</sub> ) δ 0.65 (t, J = 8Hz, 3H), 1.55 (sextet, J = 8Hz, 2H), 3.25 (t, J = 8Hz, 3H), 4.55 (d, J = 17Hz, 1H), 5.3 (d, J = 17Hz, 1H), 7.7 (m, 6H); IR (CHCl <sub>3</sub> ) 2900, 1723 cm <sup>-1</sup> ; UVλmax (EtOH) 277 nm (ε 14,800), 216 (61,200); <i>Anal</i> /Calcd: C, 52.44% H, 4.41% N, 3.83%; Found: C, 52.53% H, 4.44% N, 3.73% |
| 20 | 56      | 27                                                         | N-(2-propylene)glycine; NMR (CDCl <sub>3</sub> ) δ 3.5 (m, 2H), 3.9 (m, 2H), 5.4 (m, 3H), 6.95 (m, 1H), 7.2—8.4 (m, 6H); IR (CHCl <sub>3</sub> ) 2900, 1720 with inflection at 1760 cm <sup>-1</sup> ; UVλmax (EtOH) 277 nm (ε 14,400), 219 (39,700); <i>Anal</i> /Calcd: C, 52.76% H, 3.87% N, 3.84%; Found: C, 52.93% H, 4.28% N, 3.68%                                  |
| 25 | 57      | 28                                                         | N-ethylglycine; mp 182—184°C; NMR (DMSO-d <sub>6</sub> ) δ 0.95 (t, J = 7Hz, 3H), 3.25 (q, J = 7Hz, 2H), 4.58 & 5.05 (d, J = 16.5Hz, 2H), 7.7 (m, 6H); IR (Nujol*) 2900, 1720 cm <sup>-1</sup> ; UVλmax (EtOH) 276 nm (ε 14,795), 219 (42,305); <i>Anal</i> /Calcd: C, 51.14% H, 4.00% N, 3.97%; Found: C, 51.33% H, 4.08% N, 4.05%                                        |
| 30 | 58      | 29                                                         | N-butylglycine; mp 65—68°C (dec); NMR (CDCl <sub>3</sub> ) δ 0.63 (t, J = 5.5Hz, 3H), 1.2 (m, 4H), 3.25 (t, J = 7.5Hz, 2H), 4.5 & 5.3 (d, J = 16.8Hz, 2H), 6.9 (broad, 1H), 7.7 (m, 6H); IR (CHCl <sub>3</sub> ) 2900, 1720 cm <sup>-1</sup> ; UVλmax (EtOH) 378 nm (ε 13,900), 219 (42,000)                                                                               |
| 35 | 59      | 30                                                         | N-(phenylmethyl)glycine; mp 98°C (decomp); NMR (CDCl <sub>3</sub> ) δ 4.5 & 5.35 (d, 2H), 4.45 (m, 2H), 7.6 (m, 11H); IR (Nujol*) 2900, 1710 cm <sup>-1</sup> ; UVλmax (EtOH) 278 nm (ε 15,620), 219 (43,465); <i>Anal</i> /Calcd: C, 58.01% H, 3.94% N, 3.35%; Found: C, 58.29% H, 4.27% N, 3.24%                                                                         |

## Example 60

N-[(5-Bromo-1-naphthalenyl)carbonyl]-N-methylglycine (IV, R<sup>1</sup> = CH<sub>3</sub>, R<sup>2</sup> = 5-Br and R<sup>4</sup> and R<sup>5</sup> = H)

N-[(5-Bromo-1-naphthalenyl)carbonyl]-N-methylglycine methyl ester (3.7 g, 11.0 mmoles, a compound of formula II described in Example 2) was suspended in methanol (50 ml). A solution of 1N aqueous NaOH (13.2 ml) was added to the suspension. The mixture was stirred at 20—22°C for 1.5 hr. The mixture was neutralized with aqueous HCl and concentrated under reduced pressure to remove the methanol. The residual solution was made acidic with aqueous HCl and extracted with ethyl acetate. The extract was dried (MgSO<sub>4</sub>), filtered and evaporated to dryness. The residue was crystallized from ethanol-water to give 3.25 g of the title compound; mp 205°C; NMR (DMSO-d<sub>6</sub>) δ 2.75 & 3.10 (2s, 3H), 3.75 & 4.25 (2s, 2H), 7.3—8.3 (m, 6H); IR (Nujol\*) 1745 with inflection at 1720, 1580 cm<sup>-1</sup>; UVλmax (EtOH) 322 nm (ε 680), 316 (1,000), 299 (6,510), 289 (9,055), 279 (7,150) 226 (63,080); *Anal*/Calcd: C, 52.19% H, 3.76% N, 4.35%; Found: C, 52.09% H, 3.84% N, 4.48%.

By following the procedure of example 60 but replacing N-[(5-bromo-1-naphthalenyl)carbonyl]-N-methylglycine methyl ester with an equivalent amount of another ester compound of formula II in which R is lower alkyl or ar(lower)alkyl, the corresponding compound of formula IV is obtained. For example, replacement with N-[[5-(trifluoromethyl)-6-methoxy-1-naphthalenyl]carbonyl]-N-methylglycine methyl ester, NMR (CDCl<sub>3</sub>) δ 2.85 (s, 3H), 3.5—4.5 (m, 2H), 3.4 & 3.75 (2s, 6H), 7.0—8.4 (m, 5H), prepared according to the procedure of example 2, gives N-[[5-(trifluoromethyl)-6-methoxy-1-naphthalenyl]carbonyl]-N-

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methylglycine, mp 174—175°C; NMR (DMSO- $d_6$ )  $\delta$  2.75 & 3.1 (2s, 3H), 4.03 (s, 3H), 4.30 (d, 2H), 7.8 (m, 5H); IR (Nujol\*) 2500, 1720 with inflection at 1745, 1580  $\text{cm}^{-1}$ ; UV $\lambda_{\text{max}}$  (EtOH) 335 nm ( $\epsilon$  3,050), 322 (2,700), 295 (5,100), 283 (5,750), 275 (4,450), 220 (57,100); Anal Calcd: C, 56.30% H, 4.13% N, 4.10% Found: C, 55.29% H, 4.02% N, 3.99%.

## Example 61

4,6-Dimethoxy-1-naphthalenecarboxylic Acid (V,  $R^3 = 4\text{-CH}_3\text{O}$ ,  $R^4 = 6\text{-CH}_3\text{O}$  and  $R^5 = \text{H}$ )

A stream of chlorine gas was passed through a cooled solution of NaOH (17.28 g, 0.432 mole) in water (24 ml) containing 100 g of ice until 12.7 g (0.18 mole) of chlorine was absorbed into the solution. Solid (4,6-dimethoxy-1-naphthalenyl)ethanone [9.2 g, 0.04 mole, described by N.P. Buu-Hoi, J. Org. Chem., 21 1257 (1956)], was added at 20—22°C to the chlorine solution. The mixture was stirred at 65°C for one hr, cooled in an ice bath and treated with  $\text{NaHSO}_3$  (5 g) in water (20 ml). The mixture was made neutral by the addition of dilute HCl. The resulting precipitate was collected, washed well with water, dried over  $\text{P}_2\text{O}_5$  and recrystallized from methanol to give 4,6-dimethoxy-1-naphthalenecarboxylic acid (7.0 g); mp 227—229°C; NMR (DMSO- $d_6$ )  $\delta$  3.85 (s, 3H), 4.0 (s, 3H), 7.7 (m, 5H); IR (white mineral oil) 2900, 1670  $\text{cm}^{-1}$ ; UV $\lambda_{\text{max}}$  (MeOH) 339 nm ( $\epsilon$  4,910), 328 (4,500), 304 (8,180), 240 (40,100); Anal Calcd: C, 67.23% H, 5.21; Found: C, 67.15% H, 5.23%.

## Example 62

4,6-Dimethoxy-5-(trifluoromethyl)-1-naphthalenecarboxylic Acid (V,  $R^3 = 4\text{-CH}_3\text{O}$ ,  $R^4 = 5\text{-CF}_3$  and  $R^5 = 6\text{-CH}_3\text{O}$ )

4,6-Dimethoxy-1-naphthalenecarboxylic acid (98.5 g, 0.425 mole, described in Example 61) was added to an ice-cooled solution of  $\text{SOCl}_2$  (59.5 g, 0.5 mole) in anhydrous methanol (225 ml). The mixture was heated at reflux for 18 hr. Another portion of  $\text{SOCl}_2$  (35.5 ml) was added and the reflux was continued for another 7 hr. The mixture was extracted with diethyl ether. The ether extract was washed with water and then aqueous  $\text{NaHCO}_3$  solution, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated to dryness. The solid residue was crystallized from methanol (720 ml) to give 64.5 g of 4,6-dimethoxy-1-naphthalenecarboxylic acid methyl ester; mp 102—104°C; NMR ( $\text{CDCl}_3$ )  $\delta$  3.9 (s, 6H), 4.0 (s, 3H), 7.7 (m, 5H).

The latter compound (4.93 g, 0.02 mole) was suspended in 20% (v/v) aqueous acetic acid and concentrated  $\text{H}_2\text{SO}_4$  (0.279 ml). The mixture was stirred and heated at 60°C. Iodine (2 g, 0.008 mole) and periodic acid (2.76 g, 0.012 mole) was added to the mixture. The reaction mixture was stirred for one hr at the same temperature, cooled, poured into water and extracted with chloroform. The chloroform extract was washed with aqueous sodium bisulphite solution, washed with water and dried ( $\text{Na}_2\text{SO}_4$ ). The chloroform extract was poured onto a column of 250 g of silica gel (prepared with 10% (v/v) ethyl acetate in hexane). The column was eluted with 1.5 liters of the same solvent system and then with 20% (v/v) ethyl acetate in hexane. The appropriate fractions were combined to give 5-iodo-4,6-dimethoxy-1-naphthalenecarboxylic acid methyl ester (1.4 g, 80% pure). The pure compound, mp 120—122°C, was obtained by crystallization from ethyl acetate-hexane.

A mixture of the latter compound (7.1 g, 0.019 mole), freshly prepared copper powder (4.5 g, prepared according to the procedure of R.Q. Brewster and T. Groening, "Organic Synthesis", Coll. Vol. II, John Wiley and Sons, New York, N.Y., U.S.A., 1948, p. 445), trifluoromethyl iodide (8.5 g, 0.43 mole) and dry pyridine (35 ml) was heated for 20 hr at 120°C in an autoclave. After cooling to 22 to 24°C, the mixture was taken up in toluene and the toluene suspension was filtered. The filtrate was concentrated to dryness under reduced pressure. The residue was dissolved in chloroform. Insoluble material in the chloroform solution was removed by filtration. The filtrate was passed through a column of 75 g of silica gel and the column was eluted with chloroform. The pure fractions were combined and crystallized from ethyl acetate hexane to give 2.83 g of 4,6-dimethoxy-5-(trifluoromethyl)-1-naphthalenecarboxylic acid methyl ester; mp 120—123°C, NMR ( $\text{CDCl}_3$ )  $\delta$  3.95 (m, 9H), 6.8 and 8.05 (2d,  $J = 10\text{Hz}$ , 2H), 7.21 and 9.1 (2d,  $J = 10\text{Hz}$ , 2H).

A suspension of the latter compound (2.83 g, 0.009 mol) in methanol (16.2 ml) and NaOH (5.4 ml of a 4N aqueous solution) was heated at reflux under nitrogen for 10 min. The resulting clear solution was cooled in an ice bath and rendered acid (pH = 3) with 2N aqueous HCl. The precipitate was collected, washed with water and dried over  $\text{P}_2\text{O}_5$  to give 2.7 g of the title compound, m/e 300 ( $\text{M}^+$ ).

## Example 63

5-(Trifluoromethylthio)-6-methoxy-1-naphthalenecarboxylic Acid (V,  $R^3 = 5\text{-CF}_3\text{S}$ ,  $R^4 = 6\text{-CH}_3\text{O}$  and  $R^5 = \text{H}$ )

An intimate mixture of copper dust (1.84 g, 29 mmoles) and  $\text{Hg}(\text{SF}_3)_2$  [3.27 g, 8 mmoles, prepared according to the method of E.H. Man et al., J. Amer. Chem. Soc., 81 3575 (1959)] was heated between 80 to 100°C for 2.5 hr. Thereafter, the temperature was increased to 150°C for 30 min. The mixture, containing  $\text{CuSCF}_3$ , was cooled to room temperature (ca. 22 to 24°C). A solution of 5-iodo-6-methoxy-1-naphthalenecarboxylic acid methyl ester (1.87 g, 5.4 mmoles, described in example 1f) in distilled dimethylformamide (DMF, 10 ml) was added to the mixture. The resulting mixture was stirred at 110 to 120°C for 3 hr, and then at room temperature for 18 hr. The mixture was poured into water. The diluted mixture was extracted with diethyl ether (3x). The extract was washed with water, dried ( $\text{MgSO}_4$ ) and evaporated to dryness to give the corresponding methyl ester of the title compound (1.7 g) as a solid residue; mp 93—94°C; NMR ( $\text{CDCl}_3$ )  $\delta$  3.90 (s, 3H), 4.00 (s, 3H), 7.00—9.20 (m, 5H).

\* Trademark

The latter ester compound (2.45 g, 7.7 m moles), dissolved in 2-methoxyethanol (60 ml), was mixed with an aqueous NaOH solution (1N, 15.5 ml). The resulting solution was stirred at room temperature for 24 hr, cooled in an ice-bath, made acidic (pH = 3) by the addition of 1N aqueous HCl and diluted with water. The resulting solid was collected, washed with water and recrystallized from ethanol to give the title compound (1.7 g); mp 204—205°C; NMR (DMSO-d<sub>6</sub>) δ 4.00 (s, 3H), 8.20 (m, 5H), 10.30 (broad, 1H).

## Example 64

(a) By following serially the procedures of examples 2 and 3 and using an equivalent amount of 4,6-dimethoxy-1-naphthalenecarboxylic acid of example 61 instead of 5-bromo-1-naphthalenecarboxylic acid; N-[(4,6-dimethoxy-1-naphthalenyl)thioxomethyl]-N-methylglycine methyl ester (I, R<sup>1</sup> and R<sup>2</sup> = CH<sub>3</sub>, R<sup>3</sup> = 4-CH<sub>3</sub>O, R<sup>4</sup> = 6-CH<sub>3</sub>O and R<sup>5</sup> = H); mp 105—107°C; NMR (CDCl<sub>3</sub>) δ 3.05 (s, 3H), 3.85 (s, 3H), 3.90 (s, 3H), 4.0 (s, 3H), 4.8 (2d, J = 20Hz, 2H), 7.3 (m, 5H); was obtained via N-[(4,6-dimethoxy-1-naphthalenyl)carbonyl]-N-methylglycine methyl ester; NMR (CDCl<sub>3</sub>) δ 2.75 (s, 1H), 3.7 (s, 3H), 3.9 (s, 3H), 4.0 (s, 3H), 4.35 (s, 2H), 7.4 (m, 5H).

(b) Likewise, the substitution of an equivalent amount of 6-methoxy-1-naphthalenecarboxylic acid, described by C.C. Price *et al.*, J. Am. Chem. Soc., 69, 2261 (1947), gives N-[(6-methoxy-1-naphthalenyl)thioxomethyl]-N-methylglycine methyl ester (I, R<sup>1</sup> and R<sup>2</sup> = CH<sub>3</sub>, R<sup>3</sup> = 6-methoxy, and R<sup>4</sup> and R<sup>5</sup> = H), NMR (CDCl<sub>3</sub>) δ 3.02 (s, 3H), 3.86 (s, 3H), 3.89 (s, 3H), 4.53 and 4.35 (d, J = 17Hz, 2H) 6.90—8.10 (m, 6H), via N-[(6-methoxy-1-naphthalenyl)carbonyl]-N-methylglycine methyl ester.

(c) Likewise the substitution of an equivalent amount of 4,6-dimethoxy-5-(trifluoromethyl)-1-naphthalenecarboxylic acid of example 62 gives N-[(4,6-dimethoxy-5-(trifluoromethyl)-1-naphthalenyl)thioxomethyl]-N-methylglycine methyl ester (I, R<sup>1</sup> and R<sup>2</sup> = CH<sub>3</sub>O, R<sup>3</sup> = 4-CH<sub>3</sub>O, R<sup>4</sup> = 5-CF<sub>3</sub>, and R<sup>5</sup> = 6-CH<sub>3</sub>O), NMR (CDCl<sub>3</sub>) δ 3.0 (s, 3H), 3.7 (s, 3H), 3.85 (s, 3H) 3.95 (s, 3H), 4.35 & 5.45 (2d, J = 17Hz, 2H), 6.8—8.2 (m, 4H), via N-[(4,6-dimethoxy-5-(trifluoromethyl)-1-naphthalenyl)carbonyl]-N-methylglycine methyl ester, NMR (CDCl<sub>3</sub>) δ 2.78 (s, 3H), 3.6 (s, 3H), 3.85 (s, 3H), 3.9 (s, 3H), 4.35 (m, 2H), 6.7—8.3 (m, 4H).

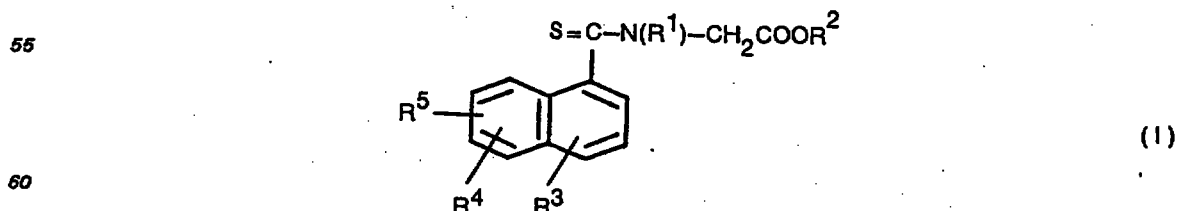
(d) Likewise, the substitution of an equivalent amount of 5-(trifluoromethylthio)-6-methoxy-1-naphthalenecarboxylic acid of example 63 gives N-[[5-(trifluoromethylthio)-6-methoxy-1-naphthalenyl]thioxomethyl]-N-methylglycine methyl ester, (I, R<sup>1</sup> and R<sup>2</sup> = CH<sub>3</sub>, R<sup>3</sup> = 5-CF<sub>3</sub>S, R<sup>4</sup> = 6-CH<sub>3</sub>, and R<sup>5</sup> = H); mp 121—123°C; NMR (CDCl<sub>3</sub>) δ 3.00 (s, 3H), 3.75 (s, 3H), 4.00 (s, 3H), 4.35 & 4.5 (d, 2H), 7.0—8.5 (m, 5H); via N-[[5-(trifluoromethylthio)-6-methoxy-1-naphthalenyl]carbonyl]-N-methylglycine methyl ester, NMR (CDCl<sub>3</sub>) δ 3.00 (s, 3H), 3.75 (s, 3H), 4.00 (s, 3H), 4.35 and 4.50 (d, 2H), 7.0—8.5 (m, 5H).

## Example 65

By following the procedure of Example 32, but replacing N-[(5-bromo-1-naphthalenyl)thioxomethyl]-N-methylglycine methyl ester with an equivalent amount of one of the ester compounds of formula I in which R<sup>2</sup> is lower alkyl, described in example 64, the corresponding compounds of formula I in which R<sup>2</sup> is hydrogen was obtained, namely (a) N-[(4,6-dimethoxy-1-naphthalenyl)thioxomethyl]-N-methylglycine; NMR (DMSO-d<sub>6</sub>) δ 3.05 (s, 3H), 3.90 (s, 3H), 3.97 (s, 3H), 4.27 & 4.67 (2d, J = 17Hz, 2H), 6.50—8.00 (m, 5H), 9.12 (broad, 1H); IR (CHCl<sub>3</sub>) 2900, 1720 cm<sup>-1</sup>; UVλmax (MeOH) 337 nm (ε 10,280), 322 (9,675), 278 (35,385) shoulder at 242 (66,830), 224 (114,600); Anal calcd: C, 60.17% H, 5.36% N, 4.38%; Found: C, 58.38% H, 5.20% N, 4.80%; (b) N-[(6-methoxy-1-naphthalenyl)thioxomethyl]-N-methylglycine; mp 153—154°C, NMR (DMSO-d<sub>6</sub>) δ 2.95 (s, 3H), 3.9 (s, 3H), 4.65 and 5.2 (2d, J = 16.5Hz, 2H), 7.5 (m, 6H); (c) N-[(4,6-dimethoxy-5-(trifluoromethyl)-1-naphthalenyl)thioxomethyl]-N-methylglycine; NMR (CDCl<sub>3</sub>) δ 3.05 (s, 3H), 3.9 (s, 3H), 3.95 (s, 3H), 4.5 and 5.11 (2d, J = 17Hz, 2H), 6.75 (s, 1H), 7.2 (m, 4H); IR (CHCl<sub>3</sub>) 3000, 1720, 1270, 1130 cm<sup>-1</sup>; Anal Calcd: C, 52.70% H, 4.16% N, 3.61%; Found: C, 52.83% H, 4.46% N, 3.57% and (d) N-[[5-(trifluoromethylthio)-6-methoxy-1-naphthalenyl]thioxomethyl]-N-methylglycine; mp 168—169°C; NMR (DMSO-d<sub>6</sub>) δ 3.0 (s, 3H), 4.0 (s, 3H), 4.6 & 5.2 (d, J = 16.5Hz, 2H), 7.7 (m, 5H); IR (white mineral oil) 2900, 1720, 1465 cm<sup>-1</sup>; UVλmax (MeOH) 342 nm (ε 4970), 334 (4800), 230 (46,800).

Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. A compound of formula I



wherein R<sup>1</sup> is hydrogen, lower alkyl, lower alkenyl or phenylmethyl; R<sup>2</sup> is hydrogen or lower alkyl; R<sup>3</sup> is hydrogen, a lower alkoxy at position 6 of the naphthalene ring, or a substituent at position 4, 5 or 8 of the naphthalene ring, the substituent being selected from the group consisting of lower alkyl, lower alkoxy,



The latter ester compound (2.45 g, 7.7 m moles), dissolved in 2-methoxyethanol (60 ml), was mixed with an aqueous NaOH solution (1N, 15.5 ml). The resulting solution was stirred at room temperature for 24 hr, cooled in an ice-bath, made acidic (pH = 3) by the addition of 1N aqueous HCl and diluted with water. The resulting solid was collected, washed with water and recrystallized from ethanol to give the title compound (1.7 g); mp 204–205°C; NMR (DMSO- $d_6$ )  $\delta$  4.00 (s, 3H), 8.20 (m, 5H), 10.30 (broad, 1H).

#### Example 64

(a) By following serially the procedures of examples 2 and 3 and using an equivalent amount of 4,6-dimethoxy-1-naphthalenecarboxylic acid of example 61 instead of 5-bromo-1-naphthalenecarboxylic acid; N-[(4,6-dimethoxy-1-naphthalenyl)thioxomethyl]-N-methylglycine methyl ester (I,  $R^1$  and  $R^2 = CH_3$ ,  $R^3 = 4-CH_3O$ ,  $R^4 = 6-CH_3O$  and  $R^5 = H$ ); mp 105–107°C; NMR (CDCl<sub>3</sub>)  $\delta$  3.05 (s, 3H), 3.85 (s, 3H), 3.90 (s, 3H), 4.0 (s, 3H), 4.8 (2d, J = 20Hz, 2H), 7.3 (m, 5H); was obtained via N-[(4,6-dimethoxy-1-naphthalenyl)carbonyl]-N-methylglycine methyl ester; NMR (CDCl<sub>3</sub>)  $\delta$  2.75 (s, 1H), 3.7 (s, 3H), 3.9 (s, 3H), 4.0 (s, 3H), 4.35 (s, 2H), 7.4 (m, 5H).

(b) Likewise, the substitution of an equivalent amount of 6-methoxy-1-naphthalenecarboxylic acid, described by C.C. Price *et al.*, J. Am. Chem. Soc., 69, 2261 (1947), gives N-[(6-methoxy-1-naphthalenyl)thioxomethyl]-N-methylglycine methyl ester (I,  $R^1$  and  $R^2 = CH_3$ ,  $R^3 = 6-methoxy$ , and  $R^4$  and  $R^5 = H$ ), NMR (CDCl<sub>3</sub>)  $\delta$  3.02 (s, 3H), 3.86 (s, 3H), 3.89 (s, 3H), 4.53 and 4.35 (d, J = 17Hz, 2H) 6.90–8.10 (m, 6H), via N-[(6-methoxy-1-naphthalenyl)carbonyl]-N-methylglycine methyl ester.

(c) Likewise the substitution of an equivalent amount of 4,6-dimethoxy-5-(trifluoromethyl)-1-naphthalenecarboxylic acid of example 62 gives N-[(4,6-dimethoxy-5-(trifluoromethyl)-1-naphthalenyl)thioxomethyl]-N-methylglycine methyl ester (I,  $R^1$  and  $R^2 = CH_3O$ ,  $R^3 = 4-CH_3O$ ,  $R^4 = 5-CF_3$  and  $R^5 = 6-CH_3O$ ), NMR (CDCl<sub>3</sub>)  $\delta$  3.0 (s, 3H), 3.7 (s, 3H), 3.85 (s, 3H) 3.95 (s, 3H), 4.35 & 5.45 (2d, J = 17Hz, 2H), 6.8–8.2 (m, 4H), via N-[(4,6-dimethoxy-5-(trifluoromethyl)-1-naphthalenyl)carbonyl]-N-methylglycine methyl ester, NMR (CDCl<sub>3</sub>)  $\delta$  2.78 (s, 3H), 3.6 (s, 3H), 3.85 (s, 3H), 3.9 (s, 3H), 4.35 (m, 2H), 6.7–8.3 (m, 4H).

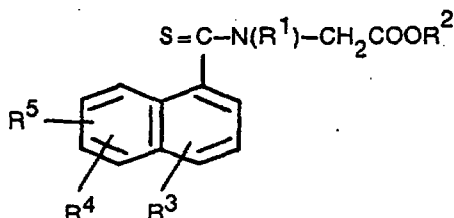
(d) Likewise, the substitution of an equivalent amount of 5-(trifluoromethylthio)-6-methoxy-1-naphthalenecarboxylic acid of example 63 gives N-[(5-(trifluoromethylthio)-6-methoxy-1-naphthalenyl)thioxomethyl]-N-methylglycine methyl ester, (I,  $R^1$  and  $R^2 = CH_3$ ,  $R^3 = 5-CF_3S$ ,  $R^4 = 6-CH_3$  and  $R^5 = H$ ); mp 121–123°C; NMR (CDCl<sub>3</sub>)  $\delta$  3.00 (s, 3H), 3.75 (s, 3H), 4.00 (s, 3H), 4.35 & 4.5 (d, 2H), 7.0–8.5 (m, 5H); via N-[(5-(trifluoromethylthio)-6-methoxy-1-naphthalenyl)carbonyl]-N-methylglycine methyl ester, NMR (CDCl<sub>3</sub>)  $\delta$  3.00 (s, 3H), 3.75 (s, 3H), 4.00 (s, 3H), 4.35 and 4.50 (d, 2H), 7.0–8.5 (m, 5H).

#### Example 65

By following the procedure of Example 32, but replacing N-[(5-bromo-1-naphthalenyl)thioxomethyl]-N-methylglycine methyl ester with an equivalent amount of one of the ester compounds of formula I in which  $R^2$  is lower alkyl, described in example 64, the corresponding compounds of formula I in which  $R^2$  is hydrogen was obtained, namely (a) N-[(4,6-dimethoxy-1-naphthalenyl)thioxomethyl]-N-methylglycine; NMR (DMSO- $d_6$ )  $\delta$  3.05 (s, 3H), 3.90 (s, 3H), 3.97 (s, 3H), 4.27 & 4.67 (2d, J = 17Hz, 2H), 6.50–8.00 (m, 5H), 9.12 (broad, 1H); IR (CHCl<sub>3</sub>) 2900, 1720  $cm^{-1}$ ; UV $\lambda$ max (MeOH) 337 nm ( $\epsilon$  10,280), 322 (9,675), 278 (35,385) shoulder at 242 (66,830), 224 (114,600); Anal calcd: C, 60.17% H, 5.36% N, 4.38%; Found: C, 58.38% H, 5.20% N, 4.80%; (b) N-[(6-methoxy-1-naphthalenyl)thioxomethyl]-N-methylglycine; mp 153–154°C, NMR (DMSO- $d_6$ )  $\delta$  2.95 (s, 3H), 3.9 (s, 3H), 4.65 and 5.2 (2d, J = 16.5Hz, 2H), 7.5 (m, 6H); (c) N-[(4,6-dimethoxy-5-(trifluoromethyl)-1-naphthalenyl)thioxomethyl]-N-methylglycine; NMR (CDCl<sub>3</sub>)  $\delta$  3.05 (s, 3H), 3.9 (s, 3H), 3.95 (s, 3H), 4.5 and 5.11 (2d, J = 17Hz, 2H), 6.75 (s, 1H), 7.2 (m, 4H); IR (CHCl<sub>3</sub>) 3000, 1720, 1270, 1130  $cm^{-1}$ ; Anal Calcd: C, 52.70% H, 4.16% N, 3.61%; Found: C, 52.83% H, 4.46% N, 3.57% and (d) N-[(5-(trifluoromethylthio)-6-methoxy-1-naphthalenyl)thioxomethyl]-N-methylglycine; mp 168–169°C; NMR (DMSO- $d_6$ )  $\delta$  3.0 (s, 3H), 4.0 (s, 3H), 4.6 & 5.2 (d, J = 16.5Hz, 2H), 7.7 (m, 5H); IR (white mineral oil) 2900, 1720, 1465  $cm^{-1}$ ; UV $\lambda$ max (MeOH) 342 nm ( $\epsilon$  4970), 334 (4800), 230 (46,800).

Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. A compound of formula I



(I)

wherein  $R^1$  is hydrogen, lower alkyl, lower alkenyl or phenylmethyl;  $R^2$  is hydrogen or lower alkyl;  $R^3$  is hydrogen, a lower alkoxy at position 6 of the naphthalene ring, or a substituent at position 4, 5 or 8 of the naphthalene ring, the substituent being selected from the group consisting of lower alkyl, lower alkoxy,



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halo, cyano, nitro, trihalomethyl and trifluoromethylthio, and R<sup>4</sup> and R<sup>5</sup> each is hydrogen; or R<sup>3</sup> and R<sup>4</sup> each is a substituent at different positions selected from positions 3 to 7 of the naphthalene ring, the substituents being selected from the group consisting of lower alkyl, lower alkoxy, halo, trihalomethyl, trihalomethylthio, (lower)alkoxy(lower)alkoxy, phenylmethoxy and phenylmethoxy substituted on the phenyl portion with a lower alkyl, lower alkoxy, halo or trihalomethyl, and R<sup>5</sup> is hydrogen; or R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> each is a substituent at different positions selected from positions 4, 5 and 6 of the naphthalene ring, the substituent being selected from the group consisting of lower alkoxy, halo and trihalomethyl; or a therapeutically acceptable salt with an organic or inorganic base of the compound of formula I wherein R<sup>2</sup> is hydrogen.

2. A compound of claim 1 wherein R<sup>1</sup> is hydrogen, lower alkyl, 2-propenyl or phenylmethyl; R<sup>2</sup> is hydrogen or lower alkyl; R<sup>3</sup> is hydrogen, a lower alkoxy at position 6 of the naphthalene ring, or a substituent at positions 4, 5 or 8 of the naphthalene ring, the substituents being selected from the group consisting of lower alkyl, lower alkoxy, halo, cyano, nitro and trifluoromethyl, and R<sup>4</sup> and R<sup>5</sup> each is hydrogen; or R<sup>3</sup> and R<sup>4</sup> are a pair of substituents on the naphthalene ring, each substituent being at a different position of the ring, the pair of substituents being selected from the group of pairs consisting of 3-halo-4-lower alkoxy, 4,6-di(lower alkoxy), 5-halo-6-lower alkyl, 5-halo-6-lower alkoxy, 5,7-dihalo, 5-(trifluoromethyl)-6-lower alkoxy, 5-(trifluoromethylthio)-6-lower alkoxy, 5-halo-6-(lower)alkoxy(lower)alkoxy, 5-halo-6-[3-(trifluoromethyl)phenylmethoxy] and 5-halo-6-(4-chlorophenylmethoxy), and R<sup>5</sup> is hydrogen; or R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> each is a substituent on the naphthalene ring, each of the three substituents being at different positions on the ring, the three substituents being selected from the group of 4-lower-alkoxy-5-halo-6-lower alkoxy and 4,6-di(lower alkoxy)-5-(trifluoromethyl); or when R<sup>2</sup> is hydrogen a therapeutically acceptable salt thereof with an organic or inorganic base.

3. A compound of claim 1 wherein R<sup>1</sup> is hydrogen, lower alkyl or phenylmethyl; R<sup>2</sup> is hydrogen or lower alkyl; R<sup>3</sup> is 4-halo or 5-halo and R<sup>4</sup> and R<sup>5</sup> each is hydrogen; or R<sup>3</sup> and R<sup>4</sup> are a pair of substituents on the naphthalene ring selected from the group of pairs consisting of 3-halo-4-lower alkoxy, 4,6-di(lower alkoxy), 5-halo-6-lower alkyl, 5-halo-6-lower alkoxy, 5,7-dihalo, 5-(trifluoromethyl)-6-lower alkoxy, and 5-(trifluoromethylthio)-6-lower alkoxy, and R<sup>5</sup> is hydrogen; or R<sup>3</sup> is 4-lower alkoxy, R<sup>4</sup> is 5-(trifluoromethyl) and R<sup>5</sup> is 6-lower alkoxy; or when R<sup>2</sup> is hydrogen a therapeutically acceptable salt thereof with an organic or inorganic base.

4. A compound of claim 1 wherein R<sup>1</sup> is lower alkyl; R<sup>2</sup> is hydrogen; R<sup>3</sup> is 5-halo and R<sup>4</sup> and R<sup>5</sup> each is hydrogen; or R<sup>3</sup> and R<sup>4</sup> are a pair of substituents on the naphthalene ring selected from the group of pairs consisting of 3-halo-4-lower alkoxy, 5-halo-6-lower alkoxy, 5-(trifluoromethyl)-6-lower alkoxy and 5-(trifluoromethylthio)-6-lower alkoxy, and R<sup>5</sup> is hydrogen; or R<sup>3</sup> is 4-lower alkoxy, R<sup>4</sup> is 5-(trifluoromethyl) and R<sup>5</sup> is 6-lower alkoxy; or a therapeutically acceptable salt thereof with an organic or inorganic base.

5. A compound of Claim 1 which is N-[(5-bromo-1-naphthalenyl)thioxomethyl]-N-methylglycine, N-[(5-chloro-1-naphthalenyl)thioxomethyl]-N-methylglycine, N-[(5-bromo-1-naphthalenyl)thioxomethyl]glycine, N-[(5-bromo-1-naphthalenyl)thioxomethyl]-N-propylglycine, N-[(5-bromo-1-naphthalenyl)thioxomethyl]-N-(2-propenyl)glycine, N-[(5-bromo-1-naphthalenyl)thioxomethyl]-N-ethylglycine, N-[(5-bromo-1-naphthalenyl)thioxomethyl]-N-butylglycine, or N-[(5-bromo-1-naphthalenyl)thioxomethyl]-N-(phenylmethyl)glycine, or the corresponding methyl ester thereof.

6. A compound of Claim 1 which is N-[(5-(trifluoromethyl)-6-methoxy-1-naphthalenyl)thioxomethyl]-N-methylglycine, N-[(5-(trifluoromethyl)-6-methoxy-1-naphthalenyl)thioxomethyl]-N-methylglycine, N-[(5-(trifluoromethyl)-1-naphthalenyl)thioxomethyl]-N-methylglycine, or N-[[4,6-dimethoxy-5-(trifluoromethyl)-1-naphthalenyl]thioxomethyl]-N-methylglycine, or the corresponding methyl ester thereof.

7. A compound of Claim 1 which is N - [(3 - chloro - 4 - methoxy - 1 - naphthalenyl)thioxomethyl] - N - methylglycine, or N - (3 - chloro - 4 - methoxy - 1 - naphthalenyl)thioxomethyl]glycine, or the corresponding methyl ester thereof.

8. A compound of Claim 1 which is N - [(5 - bromo - 6 - methoxy - 1 - naphthalenyl)thioxomethyl] - N - methylglycine, N - [(5,7 - dichloro - 1 - naphthalenyl)thioxomethyl] - N - methylglycine, N - [(5 - bromo - 6 - pentyloxy - 1 - naphthalenyl)thioxomethyl] - N - methylglycine, N - [(5 - bromo - 6 - methyl - 1 - naphthalenyl) - thioxomethyl] - N - methylglycine, N - [(5 - iodo - 6 - methoxy - 1 - naphthalenyl)thioxomethyl] - N - methylglycine, N - [(5 - bromo - 6 - (3 - methoxypropoxy) - 1 - naphthalenyl)thioxomethyl] - N - methylglycine, N - [(5 - bromo - 6 - (3 - (trifluoromethyl)phenylmethoxy) - 1 - naphthalenyl)thioxomethyl] - N - methylglycine, or N - [(5 - bromo - 6 - (4 - chlorophenylmethoxy) - 1 - naphthalenyl)thioxomethyl] - N - methylglycine, or the corresponding methyl ester thereof.

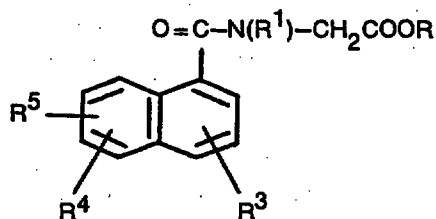
9. A pharmaceutical composition for preventing or relieving diabetic complications in a diabetic mammal, which comprises a compound as claimed in any one of claims 1 to 8 and a pharmaceutically acceptable carrier.

10. A compound as claimed in any one of claims 1 to 8 for use as an agent for preventing or relieving a diabetic complication in a diabetic mammal.



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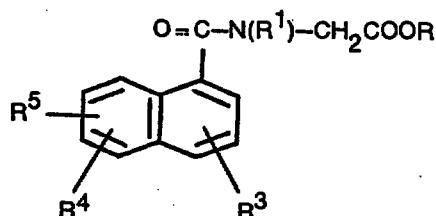
11. A compound of the formula



wherein  $\text{R}^1$  is lower alkyl, lower alkenyl or phenylmethyl;  $\text{R}^3$  is a substituent at position 4, 5 or 8 or the naphthalene ring, the substituent being selected from the group consisting of lower alkyl, lower alkoxy, halo, cyano, nitro and trihalomethyl, and  $\text{R}^4$  and  $\text{R}^5$  each is a substituent at different positions of the naphthalene ring, the positions selected from positions 3 to 7 and the substituents being selected from the group consisting of lower alkyl, lower alkoxy, halo, trihalomethyl, trihalomethylthio, (lower)alkoxy(lower)alkoxy, phenylmethoxy and phenylmethoxy substituted on the phenyl portion with a lower alkyl, lower alkoxy, halo or trihalomethyl and  $\text{R}^5$  is hydrogen; or  $\text{R}^3$ ,  $\text{R}^4$  and  $\text{R}^5$  each is a substituent at different positions selected from positions 4, 5 and 6 of the naphthalene ring, the substituent being selected from the group consisting of lower alkoxy, halo and trihalomethyl; and  $\text{R}$  is hydrogen or lower alkyl or a therapeutically acceptable salt with an organic or inorganic base of the compound wherein  $\text{R}$  is hydrogen.

12. A process for preparing a compound claimed in claim 1 which comprises:

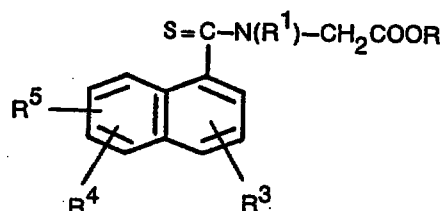
(a) reacting an amidoester of formula II



(II)

wherein  $\text{R}^1$ ,  $\text{R}^3$ ,  $\text{R}^4$  and  $\text{R}^5$  are as defined in claim 1 and  $\text{R}$  is lower alkyl with phosphorus pentasulfide to obtain the corresponding compound of claim 1 wherein  $\text{R}^1$ ,  $\text{R}^3$ ,  $\text{R}^4$  and  $\text{R}^5$  are as defined herein and  $\text{R}^2$  is lower alkyl; or

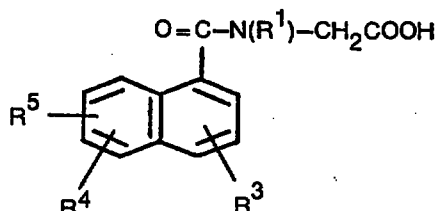
(b) hydrolyzing the compound of formula III



(III)

wherein  $\text{R}^1$ ,  $\text{R}^3$ ,  $\text{R}^4$  and  $\text{R}^5$  are as defined in claim 1 and  $\text{R}$  is lower alkyl or ar(lower)alkyl to obtain the corresponding compound of formula I wherein  $\text{R}^1$ ,  $\text{R}^3$ ,  $\text{R}^4$  and  $\text{R}^5$  are as defined herein and  $\text{R}^2$  is hydrogen; or

(c) reacting an amido acid of formula (IV)



(IV)

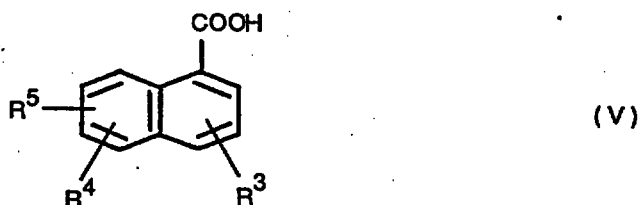
wherein  $\text{R}^1$ ,  $\text{R}^3$ ,  $\text{R}^4$  and  $\text{R}^5$  are as defined in claim 1 with phosphorus pentasulfide to obtain the corresponding compound of claim 1 wherein  $\text{R}^1$ ,  $\text{R}^3$ ,  $\text{R}^4$  and  $\text{R}^5$  are as defined herein and  $\text{R}^2$  is hydrogen; and,

(d) if required, transforming the compound of formula I wherein  $\text{R}^2$  is hydrogen into a corresponding therapeutically acceptable salt of an organic or inorganic base.



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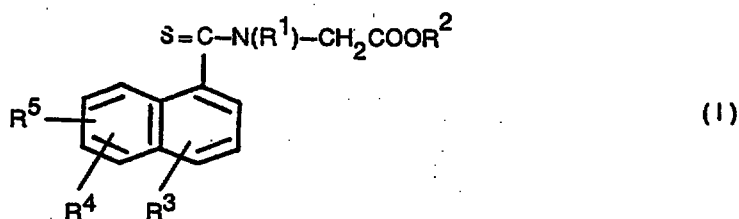
13. The process of claim 12 wherein the compound of formula II is obtained by coupling a compound of formula V



wherein  $R^3$ ,  $R^4$  and  $R^5$  are as defined therein with an aminoacid ester of the formula  $NH(R^1)-CH_2COOR$  wherein  $R^1$  and  $R$  are as defined therein.

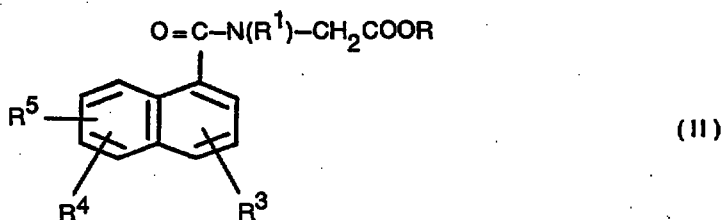
15 **Claims for the Contracting State: AT**

1. A process for preparing a compound of formula I



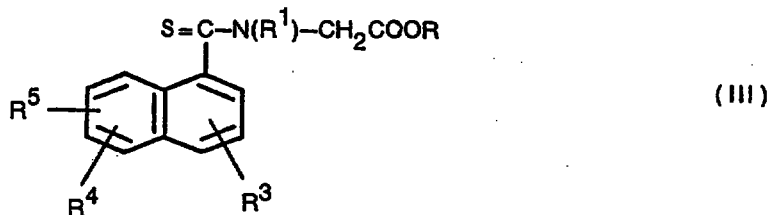
wherein  $R^1$  is hydrogen, lower alkyl, lower alkenyl or phenylmethyl;  $R^2$  is hydrogen or lower alkyl;  $R^3$  is hydrogen, a lower alkoxy at position 6 of the naphthalene ring, or a substituent at position 4, 5 or 8 of the naphthalene ring, the substituent being selected from the group consisting of lower alkyl, lower alkoxy, halo, cyano, nitro, trihalomethyl and trifluoromethylthio, and  $R^4$  and  $R^5$  each is hydrogen; or  $R^3$  and  $R^4$  each is a substituent at different positions selected from positions 3 to 7 of the naphthalene ring, the substituents being selected from the group consisting of lower alkyl, lower alkoxy, halo, trihalomethyl, trihalomethylthio, (lower)alkoxy(lower)alkoxy, phenylmethoxy and phenylmethoxy substituted on the phenyl portion with a lower alkyl, lower alkoxy, halo or trihalomethyl, and  $R^5$  is hydrogen; or  $R^3$ ,  $R^4$  and  $R^5$  each is a substituent at different positions selected from positions 4, 5 and 6 of the naphthalene ring, the substituent being selected from the group consisting of lower alkoxy, halo and trihalomethyl; or a therapeutically acceptable salt with an organic or inorganic base of the compound of formula I wherein  $R^2$  is hydrogen; which comprises:

(a) reacting an amidoester of formula II



wherein  $R^1$ ,  $R^3$ ,  $R^4$  and  $R^5$  are as defined herein and  $R$  is lower alkyl with phosphorus pentasulfide to obtain the corresponding compound of claim 1 wherein  $R^1$ ,  $R^3$ ,  $R^4$  and  $R^5$  are as defined herein and  $R^2$  is lower alkyl; or

(b) hydrolyzing the compound of formula III

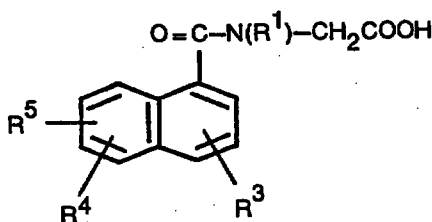


wherein  $R^1$ ,  $R^3$ ,  $R^4$  and  $R^5$  are as defined herein and  $R$  is lower alkyl or ar(lower)alkyl to obtain the corresponding compound of formula I wherein  $R^1$ ,  $R^3$ ,  $R^4$  and  $R^5$  are as defined herein and  $R^2$  is hydrogen; or



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(c) reacting an amidoacid of formula IV



(IV)

wherein  $R^1$ ,  $R^3$ ,  $R^4$  and  $R^5$  are as defined herein with phosphorus pentasulfide to obtain the corresponding compound of claim 1 wherein  $R^1$ ,  $R^3$ ,  $R^4$  and  $R^5$  are as defined herein and  $R^2$  is hydrogen; or

(d) transforming a compound of formula I wherein  $R^2$  is hydrogen into a corresponding therapeutically acceptable salt of an organic or inorganic base.

2. The process of claim 1, paragraph (a) or (b), wherein  $R^1$  is hydrogen, lower alkyl, 2-propenyl or phenylmethyl;  $R^2$  is hydrogen or lower alkyl;  $R^3$  is hydrogen, a lower alkoxy at position 6 of the naphthalene ring, or a substituent at positions 4, 5 or 8 of the naphthalene ring, the substituents being selected from the group consisting of lower alkyl, lower alkoxy, halo, cyano, nitro and trifluoromethyl, and  $R^4$  and  $R^5$  each is hydrogen; or  $R^3$  and  $R^4$  are a pair of substituents on the naphthalene ring, each substituent being at a different position of the ring, the pair of substituents being selected from the group consisting of 3-halo-4-lower alkoxy, 4,6-di(lower alkoxy), 5-halo-6-lower alkyl, 5-halo-6-lower alkoxy, 5,7-dihalo, 5-(trifluoromethyl)-6-lower alkoxy, 5-(trifluoromethylthio)-6-lower alkoxy, 5-halo-6-(lower)alkoxy(lower)alkoxy, 5-halo-6-[3-(trifluoromethyl)phenylmethoxy] and 5-halo-6-(4-chlorophenylmethoxy), and  $R^5$  is hydrogen; or  $R^3$ ,  $R^4$  and  $R^5$  each is a substituent on the naphthalene ring, each of the three substituents being at different positions on the ring, the three substituents being selected from the group of 4-lower alkoxy-5-halo-6-lower alkoxy and 4,6-di(lower alkoxy)-5-(trifluoromethyl).

3. The process of Claim 1, paragraph (a) or (b), wherein  $R^1$  is hydrogen, lower alkyl or phenylmethyl;  $R^2$  is hydrogen or lower alkyl;  $R^3$  is 4-halo or 5-halo and  $R^4$  and  $R^5$  each is hydrogen; or  $R^3$  and  $R^4$  are a pair of substituents on the naphthalene ring selected from the group of pairs consisting of 3-halo-4-lower alkoxy, 4,6-di(lower alkoxy), 5-halo-6-lower alkyl, 5-halo-6-lower alkoxy, 5,7-dihalo, 5-(trifluoromethyl)-6-lower alkoxy and 5-(trifluoromethylthio)-6-lower alkoxy, and  $R^5$  is hydrogen; or  $R^3$  is 4-lower alkoxy,  $R^4$  is 5-(trifluoromethyl) and  $R^5$  is 6-lower alkoxy.

4. The process of Claim 1, paragraph (b), wherein  $R^1$  is lower alkyl;  $R^2$  is hydrogen;  $R^3$  is 5-halo and  $R^4$  and  $R^5$  each is hydrogen; or  $R^3$  and  $R^4$  are a pair of substituents on the naphthalene ring selected from the group of pairs consisting of 3-halo-4-lower alkoxy, 5-halo-6-lower alkoxy, 5-(trifluoromethyl)-6-lower alkoxy and 5-(trifluoromethylthio)-6-lower alkoxy, and  $R^5$  is hydrogen; or  $R^3$  is 4-lower alkoxy,  $R^4$  is 5-(trifluoromethyl) and  $R^5$  is 6-lower alkoxy.

5. The process of Claim 1 wherein the compound of formula I which is prepared is N - [(5 - bromo - 1 - naphthalenyl)thioxomethyl] - N - methylglycine, N - [(5 - chloro - 1 - naphthalenyl)thioxomethyl] - N - methylglycine, N - [(5 - bromo - 1 - naphthalenyl)thioxomethyl]glycine, N - [(5 - bromo - 1 - naphthalenyl)thioxomethyl] - N - propylglycine, N - [(5 - bromo - 1 - naphthalenyl)thioxomethyl] - N - (2 - propenyl)glycine, N - [(5 - bromo - 1 - naphthalenyl)thioxomethyl] - N - ethylglycine, N - [(5 - bromo - 1 - naphthalenyl)thioxomethyl] - N - butylglycine, or N - [(5 - bromo - 1 - naphthalenyl)thioxomethyl] - N - (phenylmethyl)glycine, or the corresponding methyl ester thereof.

6. The process of Claim 1 wherein the compound of formula I which is prepared is N - [(5 - (trifluoromethyl) - 6 - methoxy - 1 - naphthalenyl)thioxomethyl] - N - methylglycine, N - [(5 - (trifluoromethylthio) - 6 - methoxy - 1 - naphthalenyl)thioxomethyl] - N - methylglycine, N - [(5 - (trifluoromethyl) - 1 - naphthalenyl)thioxomethyl] - N - methylglycine, or N - [(4,6 - dimethoxy - 5 - (trifluoromethyl) - 1 - naphthalenyl)thioxomethyl] - N - methylglycine, or the corresponding methyl ester thereof.

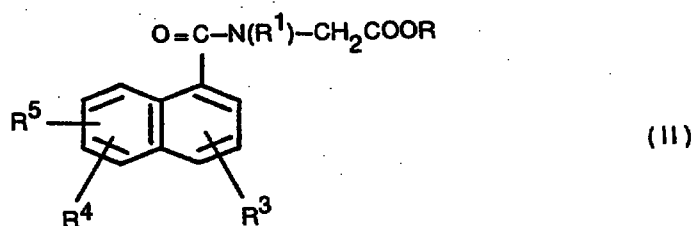
7. The process of Claim 1 wherein the compound of formula I which is prepared is N - [(3 - chloro - 4 - methoxy - 1 - naphthalenyl)thioxomethyl] - N - methylglycine, or N - [(3 - chloro - 4 - methoxy - 1 - naphthalenyl)thioxomethyl]glycine, or the corresponding methyl ester thereof.

8. The process of Claim 1 wherein the compound of formula I which is prepared is N - [(5 - bromo - 6 - methoxy - 1 - naphthalenyl)thioxomethyl] - N - methylglycine, N - [(5,7 - dichloro - 1 - naphthalenyl)thioxomethyl] - N - methylglycine, N - [(5 - bromo - 6 - pentyloxy - 1 - naphthalenyl)thioxomethyl] - N - methylglycine, N - [(5 - bromo - 6 - methyl - 1 - naphthalenyl)thioxomethyl] - N - methylglycine, N - [(5 - iodo - 6 - methoxy - 1 - naphthalenyl)thioxomethyl] - N - methylglycine, N - [(5 - bromo - 6 - (3 - methoxypropoxy) - 1 - naphthalenyl)thioxomethyl] - N - methylglycine, N - [(5 - bromo - 6 - [3 - (trifluoromethyl)phenylmethoxy] - 1 - naphthalenyl)thioxomethyl] - N - methylglycine, or N - [(5 - bromo - 6 - (4 - chlorophenylmethoxy) - 1 - naphthalenyl)thioxomethyl] - N - methylglycine, or the corresponding methyl ester thereof.

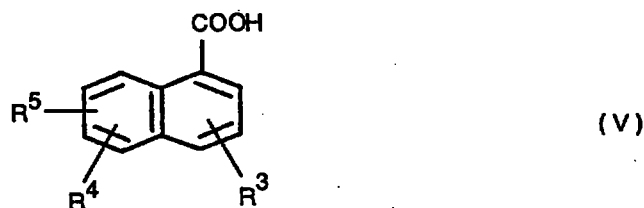
9. A process for preparing a pharmaceutical composition characterized in that a compound of formula I as defined in Claim 1, or when  $R^2$  is hydrogen a therapeutically acceptable acid addition salt thereof with an organic or inorganic base, is mixed with a pharmaceutically acceptable carrier.



10. A process for preparing a compound of formula II

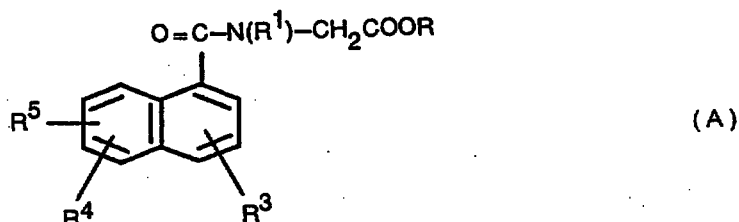


wherein  $\text{R}^1$ ,  $\text{R}^3$ ,  $\text{R}^4$  and  $\text{R}^5$  are as defined in claim 1 and R is lower alkyl or ar(lower)alkyl, which comprises coupling a compound of formula V



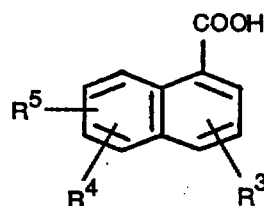
wherein  $\text{R}^3$ ,  $\text{R}^4$  and  $\text{R}^5$  are as defined therein with an amino ester of the formula  $\text{NH}(\text{R}^1)-\text{CH}_2\text{COOR}$  wherein  $\text{R}^1$  and R are as defined therein.

11. A process for preparing a compound of the formula



35 wherein  $\text{R}^1$  is lower alkyl, lower alkenyl or phenylmethyl;  $\text{R}^3$  is a substituent at position 4, 5 or 8 of the naphthalene ring, the substituent being selected from the group consisting of lower alkyl, lower alkoxy, halo, cyano, nitro and trihalomethyl, and  $\text{R}^4$  and  $\text{R}^5$  each is hydrogen; or  $\text{R}^3$  and  $\text{R}^4$  each is a substituent at different positions of the naphthalene ring, the positions selected from positions 3 to 7 and the substituents being selected from the group consisting of lower alkyl, lower alkoxy, halo, trihalomethyl, trihalomethylthio, (lower)alkoxy(lower)alkoxy, phenylmethoxy and phenylmethoxy substituted on the phenyl portion with a lower alkyl, lower alkoxy, halo or trihalomethyl and  $\text{R}^5$  is hydrogen; or  $\text{R}^3$ ,  $\text{R}^4$  and  $\text{R}^5$  each is a substituent at different positions selected from positions 4, 5 and 6 of the naphthalene ring, the substituent being selected from the group consisting of lower alkoxy, halo and trihalomethyl; and R is hydrogen or lower alkyl or a therapeutically acceptable salt with an organic or inorganic base of the compound wherein R is hydrogen, which process comprises

45 (a) coupling a compound of formula



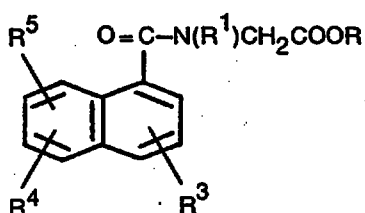
55 where  $\text{R}^3$ ,  $\text{R}^4$  and  $\text{R}^5$  are as defined above with an amino ester of formula



60 wherein  $\text{R}^1$  is as defined above and R is lower alkyl to give a compound of formula (A) in which  $\text{R}^1$ ,  $\text{R}^3$ ,  $\text{R}^4$  and  $\text{R}^5$  are as defined above and R is lower alkyl; or

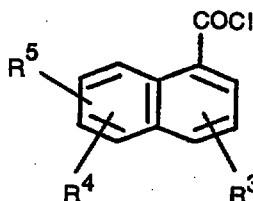


(b) hydrolysing an amidoester of formula



where  $R^1$ ,  $R^3$ ,  $R^4$  and  $R^5$  are as defined above and  $R$  is lower alkyl or ar(lower)alkyl to give a compound of formula A in which  $R^1$ ,  $R^3$ ,  $R^4$  and  $R^5$  are as defined above and  $R$  is hydrogen; or

(c) reacting a naphthalenecarboxylic acid chloride of formula



where  $R^3$ ,  $R^4$  and  $R^5$  are as defined above with an aminoacid of formula

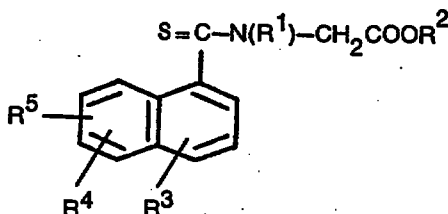


where  $R^1$  is as defined above, in presence of a base to give a compound of formula A wherein  $R^1$ ,  $R^3$ ,  $R^4$  and  $R^5$  are as defined above and  $R$  is hydrogen; or

(d) transforming a compound of formula A where  $R$  is hydrogen into a corresponding therapeutically acceptable salt of an organic or inorganic base.

Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

1. Eine Verbindung der Formel (I)



(I)

worin  $R^1$  Wasserstoff, nied.Alkyl, nied.Alkenyl oder Phenylmethyl ist;  $R^2$  Wasserstoff oder nied.Alkyl bedeutet;  $R^3$  Wasserstoff, nied.Alkoxy in Stellung 6 des Naphthalinringes oder ein Substituent in Stellung 4, 5 oder 8 des Naphthalinringes, wobei der Substituent ausgewählt ist aus der Gruppe bestehend aus nied.Alkyl, nied.Alkoxy, Halogen, Cyano, Nitro, Trihalogenmethyl und Trifluormethylthio, ist; und  $R^4$  und  $R^5$  jeweils Wasserstoff darstellen; oder  $R^3$  und  $R^4$  jeweils einen Substituenten an verschiedenen Stellungen ausgewählt sind aus den Stellungen 3 bis 7 des Naphthalinringes bedeuten, wobei die Substituenten ausgewählt sind aus der Gruppe bestehend aus nied.Alkyl, nied.Alkoxy, Halogen, Trihalogenmethyl, Trihalogenmethylthio, (nied).Alkoxy(nied.)alkoxy, Phenylmethoxy und Phenylmethoxy substituiert am Phenylteil mit nied.Alkyl, nied.Alkoxy, Halogen oder Trihalogenmethyl, und  $R^5$  Wasserstoff darstellt; oder  $R^3$ ,  $R^4$  und  $R^5$  jeweils einen Substituenten an verschiedenen Stellungen ausgewählt sind aus den Stellungen 4, 5 und 6 des Naphthalinringes bedeuten, wobei der Substituent ausgewählt ist aus der Gruppe bestehend aus nied.Alkoxy, Halogen und Trihalogenmethyl; oder ein therapeutisch annehmbares Salz mit einer organischen oder anorganischen Base der Verbindung der Formel (I), worin  $R^2$  Wasserstoff ist.

2. Eine Verbindung von Anspruch 1, worin  $R^1$  Wasserstoff, nied.Alkyl, 2-Propenyl oder Phenylmethyl ist;  $R^2$  Wasserstoff oder nied.Alkyl bedeutet;  $R^3$  Wasserstoff, nied.Alkoxy in Stellung 6 des Naphthalinringes oder ein Substituent in den Stellungen 4, 5 oder 8 des Naphthalinringes ist, wobei die Substituenten ausgewählt sind aus der Gruppe bestehend aus nied.Alkyl, nied.Alkoxy, Halogen, Cyano, Nitro und Trifluormethyl, und  $R^4$  und  $R^5$  jeweils Wasserstoff darstellen; oder  $R^3$  und  $R^4$  ein Substituentenpaar am Naphthalinring bedeuten, wobei jeder Substituent sich an einer anderen Stellung des Ringes befindet und das Substituentenpaar ausgewählt ist aus der Gruppe von Paaren bestehend aus 3-Halogen-4-nied.alloxy,



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4,6-Di(nied.alkoxy), 5-Halogen-6-nied.alkyl, 5-Halogen-6-nied.alkoxy, 5,7-Dihalogen, 5-(Trifluormethyl)-6-nied.alkoxy, 5-(Trifluormethylthio)-6-nied.alkoxy, 5-Halogen-6-(nied.)alkoxy(nied.)alkoxy, 5-Halogen-6-[3-(trifluormethyl)-phenylmethoxy] und 5-Halogen-6-(4-chlorphenylmethoxy), und  $R^5$  Wasserstoff darstellt; oder  $R^3$ ,  $R^4$  und  $R^5$  jeweils einen Substituenten am Naphthalinring bedeuten, wobei sich jeder der drei Substituenten an einer anderen Stellung des Ringes befindet und die drei Substituenten ausgewählt sind aus der Gruppe bestehend aus 4-nied.alkoxy-5-halogen-6-nied.alkoxy und 4,6-Di(nied.alkoxy)-5-(trifluormethyl); oder, wenn  $R^2$  Wasserstoff ist, ein therapeutisch annehmbares Salz hievon mit einer organischen oder anorganischen Base.

3. Eine Verbindung von Anspruch 1, worin  $R^1$  Wasserstoff, nied.alkyl oder Phenylmethyl ist;  $R^2$  Wasserstoff oder nied.alkyl bedeutet;  $R^3$  4-Halogen oder 5-Halogen ist und  $R^4$  und  $R^5$  jeweils Wasserstoff darstellen; oder  $R^3$  und  $R^4$  ein Substituentenpaar am Naphthalinring sind ausgewählt aus der Gruppe von Paaren bestehend aus 3-Halogen-4-nied.alkoxy, 4,6-Di(nied.alkoxy), 5-Halogen-6-nied.alkyl, 5-Halogen-6-nied.alkoxy, 5,7-Dihalogen, 5-(Trifluormethyl)-6-nied.alkoxy und 5-(Trifluormethylthio)-6-nied.alkoxy, und  $R^5$  Wasserstoff ist; oder  $R^3$  4-nied.alkoxy,  $R^4$  5-(Trifluormethyl) und  $R^5$  6-nied.alkoxy bedeuten; oder, wenn  $R^2$  Wasserstoff ist, ein therapeutisch annehmbares Salz hievon mit einer organischen oder anorganischen Base.

4. Eine Verbindung von Anspruch 1, worin  $R^1$  nied.alkyl ist;  $R^2$  Wasserstoff darstellt;  $R^3$  5-Halogen bedeutet und  $R^4$  und  $R^5$  jeweils Wasserstoff sind; oder  $R^3$  und  $R^4$  ein Substituentenpaar am Naphthalinring sind ausgewählt aus der Gruppe von Paaren bestehend aus 3-Halogen-4-nied.alkoxy, 5-Halogen-6-nied.alkoxy, 5-(Trifluormethyl)-6-nied.alkoxy und 5-(Trifluormethylthio)-6-nied.alkoxy und  $R^5$  Wasserstoff bedeutet; oder  $R^3$  4-nied.alkoxy,  $R^4$  5-(Trifluormethyl) und  $R^5$  6-nied.alkoxy sind; oder ein therapeutisch annehmbares Salz hievon mit einer organischen oder anorganischen Base.

5. Eine Verbindung von Anspruch 1, die N-[(5-Brom-1-naphthalenyl)-thioxomethyl]-N-methylglycin, N-[(5-Chlor-1-naphthalenyl)-thioxomethyl]-N-methylglycin, N-[(5-Brom-1-naphthalenyl)-thioxomethyl]-glycin, N-[(5-Brom-1-naphthalenyl)-thioxomethyl]-N-propylglycin, N-[(5-Brom-1-naphthalenyl)-thioxomethyl]-N-(2-propenyl)-glycin, N-[(5-Brom-1-naphthalenyl)-thioxomethyl]-N-äthylglycin, N-[(5-Brom-1-naphthalenyl)-thioxomethyl]-N-butylglycin oder N-[(5-Brom-1-naphthalenyl)-thioxomethyl]-N-(phenylmethyl)-glycin oder der entsprechende Methylester hievon ist.

6. Eine Verbindung von Anspruch 1, die N-[(5-(Trifluormethyl)-6-methoxy-1-naphthalenyl)-thioxomethyl]-N-methylglycin, N-[(5-(Trifluormethylthio)-6-methoxy-1-naphthalenyl)-thioxomethyl]-N-methylglycin, N-[(5-(Trifluormethyl)-1-naphthalenyl)-thioxomethyl]-N-methylglycin oder N-[(4,6-Dimethoxy-5-(trifluormethyl)-1-naphthalenyl)-thioxomethyl]-N-methylglycin oder der entsprechende Methylester hievon ist.

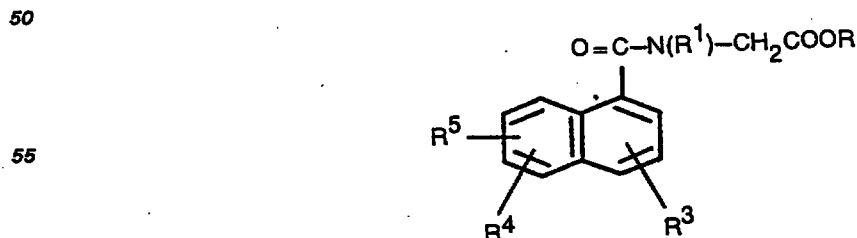
7. Eine Verbindung von Anspruch 1, die N-[(3-Chlor-4-methoxy-1-naphthalenyl)-thioxomethyl]-N-methylglycin oder N-[(3-Chlor-4-methoxy-1-naphthalenyl)-thioxomethyl]-glycin oder der entsprechende Methylester hievon ist.

8. Eine Verbindung von Anspruch 1, die N-[(5-Brom-6-methoxy-1-naphthalenyl)-thioxomethyl]-N-methylglycin, N-[(5,7-Dichlor-1-naphthalenyl)-thioxomethyl]-N-methylglycin, N-[(5-Brom-6-pentyloxy-1-naphthalenyl)-thioxomethyl]-N-methylglycin, N-[(5-Brom-6-methyl-1-naphthalenyl)-thioxomethyl]-N-methylglycin, N-[(5-Jod-6-methoxy-1-naphthalenyl)-thioxomethyl]-N-methylglycin, N-[(5-Brom-6-(3-methoxypropoxy)-1-naphthalenyl)-thioxomethyl]-N-methylglycin, N-[(5-Brom-6-[3-(trifluormethyl)-phenylmethoxy]-1-naphthalenyl)-thioxomethyl]-N-methylglycin oder N-[(5-Brom-6-(4-chlorphenylmethoxy)-1-naphthalenyl)-thioxomethyl]-N-methylglycin oder der entsprechende Methylester hievon ist.

9. Pharmazeutische Zusammensetzung zum Verhüten oder Erleichtern von diabetischen Komplikationen bei einem diabetischen Säugler, welche eine Verbindung, wie in einem der Ansprüche 1 bis 8 beansprucht, und einen pharmazeutisch annehmbaren Träger aufweist.

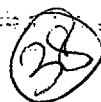
10. Eine Verbindung, wie in einem der Ansprüche 1 bis 8 beansprucht, zur Verwendung als Mittel zum Verhüten oder Erleichtern einer diabetischen Komplikation bei einem diabetischen Säugler.

11. Eine Verbindung der Formel



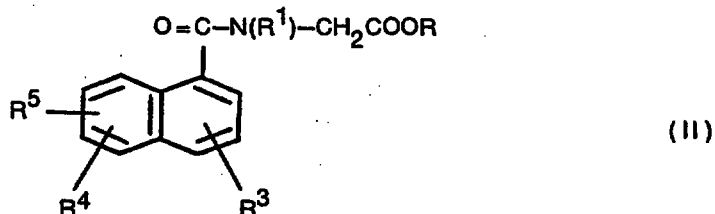
60 worin  $R^1$  nied.alkyl, nied.alkenyl oder Phenylmethyl ist;  $R^3$  ein Substituent in Stellung 4, 5 oder 8 des Naphthalinringes ist, wobei der Substituent ausgewählt ist aus der Gruppe bestehend aus nied.alkyl, nied.alkoxy, Halogen, Cyano, Nitro und Trihalogenmethyl und  $R^4$  und  $R^5$  jeweils Wasserstoff bedeuten; oder  $R^3$  und  $R^4$  jeweils einen Substituenten an verschiedenen Stellungen des Naphthalinringes darstellen, wobei die Stellungen unter den Stellungen 3 bis 7 gewählt sind und die Substituenten ausgewählt sind aus der Gruppe bestehend aus nied.alkyl, nied.alkoxy, Halogen, Trihalogenmethyl, Trihalogenmethylthio,

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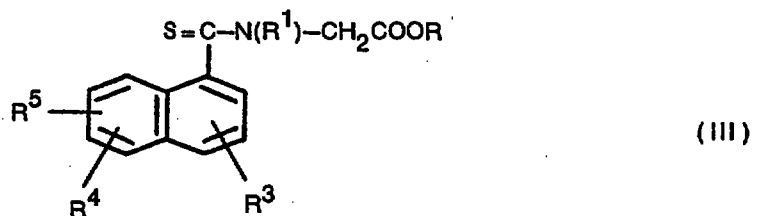
(nied.)Alkoxy(nied.)alkoxy, Phenylmethoxy und Phenylmethoxy, am Phenylteil substituiert mit nied.Alkyl, nied.Alkoxy, Halogen oder Trihalogenmethyl, und  $R^5$  Wasserstoff ist; oder  $R^3$ ,  $R^4$  und  $R^5$  jeweils einen Substituenten in verschiedenen Stellungen bedeuten ausgewählt aus den Stellungen 4, 5 und 6 des Naphthalinringes und der Substituent ausgewählt ist aus der Gruppe bestehend aus nied.Alkoxy, Halogen und Trihalogenmethyl; und R Wasserstoff oder nied.Alkyl bedeutet, oder ein therapeutisch annehmbares Salz mit einer organischen oder anorganischen Base der Verbindung, worin R Wasserstoff ist.

12. Verfahren zum Herstellen einer Verbindung, wie in Anspruch 1 beansprucht, welches umfaßt:  
(a) das Umsetzen eines Amidoesters der Formel (II)



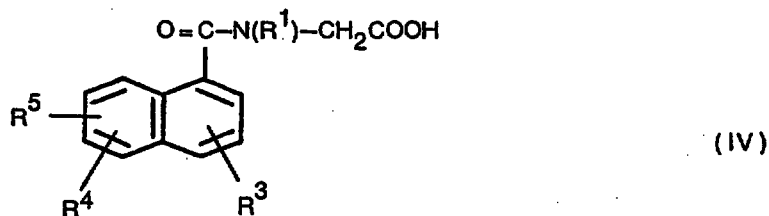
worin  $R^1$ ,  $R^3$ ,  $R^4$  und  $R^5$  wie in Anspruch 1 definiert sind und R nied.Alkyl ist, mit Phosphorpentasulfid zur Erzielung der entsprechenden Verbindung von Anspruch 1, worin  $R^1$ ,  $R^3$ ,  $R^4$  und  $R^5$  wie hier definiert sind und  $R^2$  nied.Alkyl ist; oder

(b) das Hydrolysieren der Verbindung der Formel (III)



worin  $R^1$ ,  $R^3$ ,  $R^4$  und  $R^5$  wie in Anspruch 1 definiert sind und R nied.Alkyl oder Ar(nied.)alkyl bedeutet, zum Erzielen der entsprechenden Verbindung der Formel (I), worin  $R^1$ ,  $R^3$ ,  $R^4$  und  $R^5$  wie hier definiert sind und  $R^2$  Wasserstoff bedeutet; oder

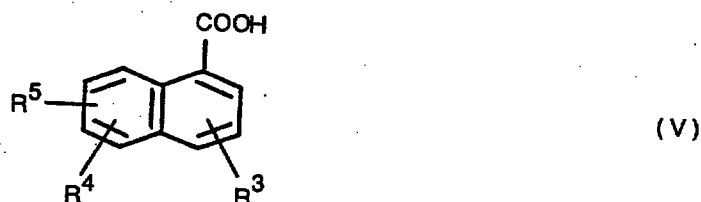
(c) das Umsetzen einer Amidosäure der Formel (IV)



worin  $R^1$ ,  $R^3$ ,  $R^4$  und  $R^5$  wie in Anspruch 1 definiert sind, mit Phosphorpentasulfid zur Erzielung der entsprechenden Verbindung von Anspruch 1, worin  $R^1$ ,  $R^3$ ,  $R^4$  und  $R^5$  wie hier definiert sind und  $R^2$  Wasserstoff bedeutet; und

(d) wenn erforderlich, Überführen der Verbindung der Formel (I), worin  $R^2$  Wasserstoff ist in ein entsprechendes therapeutisch annehmbares Salz einer organischen oder anorganischen Base.

13. Verfahren nach Anspruch 12, worin die Verbindung der Formel (II) durch Koppeln einer Verbindung der Formel (V)

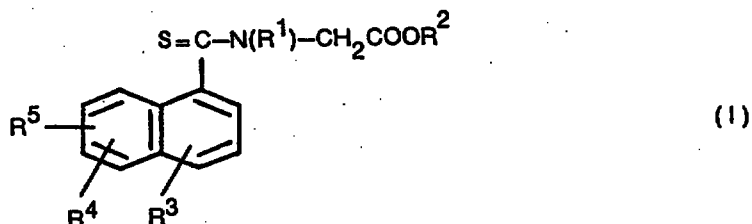


worin  $R^3$ ,  $R^4$  und  $R^5$  wie hier definiert sind, mit einem Aminosäureester der Formel  $\text{NH}(\text{R}^1)-\text{CH}_2\text{COOR}$ , worin  $R^1$  und R wie hier definiert sind, erhalten wird.



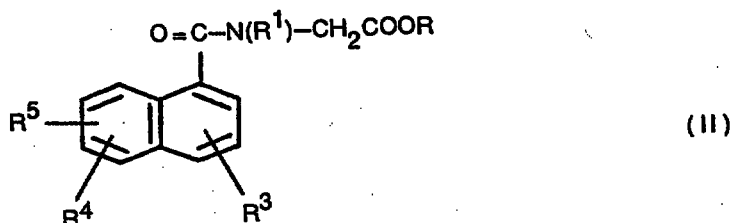
# Patentansprüche für den Vertragsstaat: AT

## 1. Verfahren zum Herstellen einer Verbindung der Formel (I)



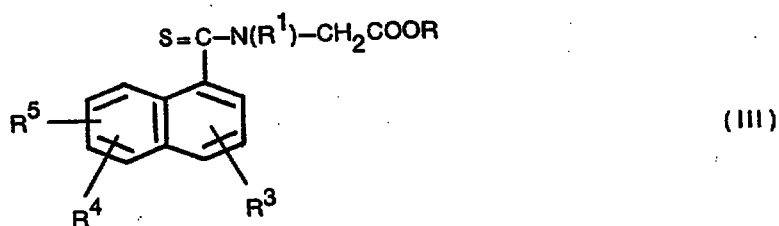
15 worin  $\text{R}^1$  Wasserstoff, nied.Alkyl, nied.Alkenyl oder Phenylmethyl ist;  $\text{R}^2$  Wasserstoff oder nied.Alkyl bedeutet;  $\text{R}^3$  Wasserstoff, nied.Alkoxy in Stellung 6 des Naphthalinringes oder ein Substituent in Stellung 4, 5 oder 8 des Naphthalinringes, wobei der Substituent ausgewählt ist aus der Gruppe bestehend aus nied.Alkyl, nied.Alkoxy, Halogen, Cyano, Nitro, Trihalogenmethyl und Trifluormethylthio, ist; und  $\text{R}^4$  und  $\text{R}^5$  jeweils Wasserstoff darstellen; oder  $\text{R}^3$  und  $\text{R}^4$  jeweils einen Substituenten an verschiedenen Stellungen ausgewählt sind aus den Stellungen 3 bis 7 des Naphthalinringes bedeuten, wobei die Substituenten ausgewählt sind aus der Gruppe bestehend aus nied.Alkyl, nied.Alkoxy, Halogen, Trihalogenmethyl, 20 Trihalogenmethylthio, (nied.)Alkoxy(nied.)alkoxy, Phenylmethoxy und Phenylmethoxy substituiert am Phenylteil mit nied.Alkyl, nied.Alkoxy, Halogen oder Trihalogenmethyl, und  $\text{R}^5$  Wasserstoff darstellt; oder  $\text{R}^3$ ,  $\text{R}^4$  und  $\text{R}^5$  jeweils einen Substituenten an verschiedenen Stellungen ausgewählt aus den Stellungen 4, 5 und 6 des Naphthalinringes bedeuten, wobei der Substituent ausgewählt ist aus der Gruppe bestehend aus nied.Alkoxy, Halogen und Trihalogenmethyl; oder eines therapeutisch annehmbaren Salzes mit einer 25 organischen oder anorganischen Base der Verbindung der Formel (I), worin  $\text{R}^2$  Wasserstoff ist, welches umfaßt:

(a) das Umsetzen eines Amidoesters der Formel (II)



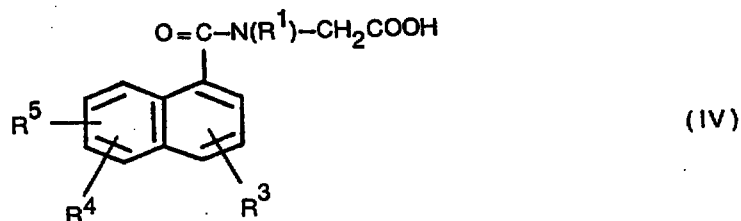
40 worin  $\text{R}^1$ ,  $\text{R}^3$ ,  $\text{R}^4$  und  $\text{R}^5$  wie hier definiert sind und  $\text{R}$  nied.Alkyl bedeutet, mit Phosphorpentasulfid zum Erzielen der entsprechenden Verbindung von Anspruch 1, worin  $\text{R}^1$ ,  $\text{R}^3$ ,  $\text{R}^4$  und  $\text{R}^5$  wie hier definiert sind und  $\text{R}^2$  nied.Alkyl bedeutet; oder

(b) das Hydrolysieren der Verbindung der Formel (III)



55 worin  $\text{R}^1$ ,  $\text{R}^3$ ,  $\text{R}^4$  und  $\text{R}^5$  wie hier definiert sind und  $\text{R}$  nied.Alkyl oder Ar(nied.)alkyl bedeutet, zum Erzielen der entsprechenden Verbindung der Formel (I), worin  $\text{R}^1$ ,  $\text{R}^3$ ,  $\text{R}^4$  und  $\text{R}^5$  wie hier definiert sind und  $\text{R}^2$  Wasserstoff bedeutet; oder

(c) das Umsetzen einer Amidosäure der Formel (IV)



65 worin  $\text{R}^1$ ,  $\text{R}^3$ ,  $\text{R}^4$  und  $\text{R}^5$  wie hier definiert sind, mit Phosphorpentasulfid zum Erzielen der entsprechenden



Verbindung von Anspruch 1, worin  $R^1$ ,  $R^2$ ,  $R^4$  und  $R^5$  wie hier definiert sind und  $R^2$  Wasserstoff bedeutet; oder

(d) das Überführen einer Verbindung der Formel (I), worin  $R^2$  Wasserstoff ist, in ein entsprechendes therapeutisch annehmbares Salz einer organischen oder anorganischen Base.

- 5 2. Verfahren nach Anspruch 1, Abs. (a) oder (b), worin  $R^1$  Wasserstoff, nied.Alkyl, 2-Propenyl oder Phenylmethyl ist;  $R^2$  Wasserstoff oder nied.Alkyl bedeutet;  $R^3$  Wasserstoff, nied.Alkoxy in Stellung 6 des Naphthalinringes oder ein Substituent in den Stellungen 4, 5 oder 8 des Naphthalinringes ist, wobei die Substituenten ausgewählt sind aus der Gruppe bestehend aus nied.Alkyl, nied.Alkoxy, Halogen, Cyano, Nitro und Trifluormethyl, und  $R^4$  und  $R^5$  jeweils Wasserstoff darstellen; oder  $R^3$  und  $R^4$  ein Substituenten-
- 10 paar am Naphthalinring bedeuten, wobei jeder Substituent sich an einer anderen Stellung des Ringes befindet und das Substituentenpaar ausgewählt ist aus der Gruppe bestehend aus 3-Halogen-4-nied.alloxy, 4,6-Di(nied.alloxy), 5-Halogen-6-nied.alloxy, 5-Halogen-6-nied.alloxy, 5,7-Dihalogen, 5-(Trifluormethyl)-6-nied.alloxy, 5-(Trifluormethylthio)-6-nied.alloxy, 5-Halogen-6-(nied.alloxy), 5-Halogen-6-[3-(trifluormethyl)-phenylmethoxy] und 5-Halogen-6-(4-chlorphenylmethoxy), und  $R^5$  Wasserstoff darstellt; oder  $R^3$ ,  $R^4$  und  $R^5$  jeweils einen Substituenten am Naphthalinring bedeuten, wobei sich jeder der drei Substituenten an einer anderen Stellung des Ringes befindet und die drei Substituenten ausgewählt sind aus der Gruppe 4-nied.Alkoxy-5-halogen-6-nied.alloxy und 4,6-Di(nied.alloxy)-5-(trifluormethyl).

- 20 3. Verfahren nach Anspruch 1, Abs. (a) oder (b), worin  $R^1$  Wasserstoff, nied.Alkyl oder Phenylmethyl ist;  $R^2$  Wasserstoff oder nied.Alkyl bedeutet;  $R^3$  4-Halogen oder 5-Halogen ist und  $R^4$  und  $R^5$  jeweils Wasserstoff darstellen; oder  $R^3$  und  $R^4$  ein Substituentenpaar am Naphthalinring sind ausgewählt aus der Gruppe von Paaren bestehend aus 3-Halogen-4-nied.alloxy, 4,6-Di(nied.alloxy), 5-Halogen-6-nied.alloxy, 5-Halogen-6-nied.alloxy, 5,7-Dihalogen, 5-(Trifluormethyl)-6-nied.alloxy und 5-(Trifluormethylthio)-6-nied.alloxy, und  $R^5$  Wasserstoff ist; oder  $R^3$  4-nied.Alkoxy,  $R^4$  5-(Trifluormethyl) und  $R^5$  6-nied.Alkoxy
- 25 bedeuten.

4. Verfahren nach Anspruch 1, Abs.(b), worin  $R^1$  nied.Alkyl ist;  $R^2$  Wasserstoff darstellt;  $R^3$  5-Halogen bedeutet und  $R^4$  und  $R^5$  jeweils Wasserstoff sind; oder  $R^3$  und  $R^4$  ein Substituentenpaar am Naphthalinring sind ausgewählt aus der Gruppe von Paaren bestehend aus 3-Halogen-4-nied.alloxy, 5-Halogen-6-nied.alloxy, 5-(Trifluormethyl)-6-nied.alloxy und 5-(Trifluormethylthio)-6-nied.alloxy und  $R^5$  Wasserstoff
- 30 bedeutet; oder  $R^3$  4-nied.Alkoxy,  $R^4$  5-(Trifluormethyl) und  $R^5$  6-nied.Alkoxy sind.

5. Verfahren nach Anspruch 1, worin die Verbindung der Formel (I), die hergestellt wird, N - [(5 - Brom - 1 - naphthalenyl) - thioxomethyl] - N - methylglycin, N - [(5 - Chlor - 1 - naphthalenyl) - thioxomethyl] - N - methylglycin, N - [(5 - Brom - 1 - naphthalenyl) - thioxomethyl] - glycyl, N - [(5 - Brom - 1 - naphthalenyl) - thioxomethyl] - N - propylglycin, N - [(5 - Brom - 1 - naphthalenyl) - thioxomethyl] - N - (2 - propenyl) - glycyl, N - [(5 - Brom - 1 - naphthalenyl) - thioxomethyl] - N - äthylglycin, N - [(5 - Brom - 1 - naphthalenyl) - thioxomethyl] - N - butylglycin oder N - [(5 - Brom - 1 - naphthalenyl) - thioxomethyl] - N - (phenylmethyl) - glycyl oder der entsprechende Methylester hievon
- 35 ist.

6. Verfahren nach Anspruch 1, worin die Verbindung der Formel (I), die hergestellt wird, N - [(5 - (Trifluormethyl) - 6 - methoxy - 1 - naphthalenyl) - thioxomethyl] - N - methylglycin, N - [(5 - (Trifluormethylthio) - 6 - methoxy - 1 - naphthalenyl) - thioxomethyl] - N - methylglycin, N - [(5 - (Trifluormethyl) - 1 - naphthalenyl) - thioxomethyl] - N - methylglycin oder N - [(4,6 - Dimethoxy - 5 - (trifluormethyl) - 1 - naphthalenyl) - thioxomethyl] - N - methylglycin oder der entsprechende Methylester hievon ist.
- 40

7. Verfahren nach Anspruch 1, worin die Verbindung der Formel (I), die hergestellt wird, N - [(3 - Chlor - 4 - methoxy - 1 - naphthalenyl) - thioxomethyl] - N - methylglycin oder N - [(3 - Chlor - 4 - methoxy - 1 - naphthalenyl) - thioxomethyl] - glycyl oder der entsprechende Methylester hievon ist.
- 45

8. Verfahren nach Anspruch 1, worin die Verbindung der Formel (I), die hergestellt wird, N - [(5 - Brom - 6 - methoxy - 1 - naphthalenyl) - thioxomethyl] - N - methylglycin, N - [(5,7 - Dichlor - 1 - naphthalenyl) - thioxomethyl] - N - methylglycin, N - [(5 - Brom - 6 - pentyloxy - 1 - naphthalenyl) - thioxomethyl] - N - methylglycin, N - [(5 - Brom - 6 - methyl - 1 - naphthalenyl) - thioxomethyl] - N - methylglycin, N - [(5 - Jod - 6 - methoxy - 1 - naphthalenyl) - thioxomethyl] - N - methylglycin, N - [(5 - Brom - 6 - (3 - methoxypropoxy) - 1 - naphthalenyl) - thioxomethyl] - N - methylglycin, N - [(5 - Brom - 6 - [3 - (trifluormethyl) - phenylmethoxy] - 1 - naphthalenyl) - thioxomethyl] - N - methylglycin
- 50 oder N - [(5 - Brom - 6 - (4 - chlorphenylmethoxy) - 1 - naphthalenyl) - thioxomethyl] - N - methylglycin oder der entsprechende Methylester hievon ist.

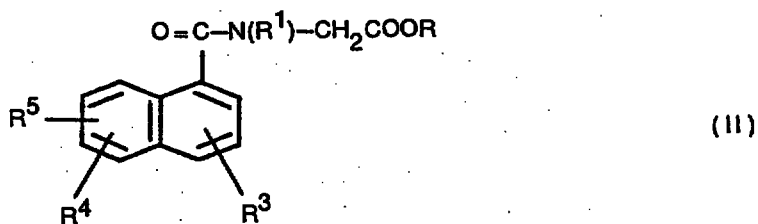
9. Verfahren zum Herstellen einer pharmazeutischen Zusammensetzung, dadurch gekennzeichnet, daß eine Verbindung der Formel (I), wie in Anspruch 1 definiert, oder, wenn  $R^2$  Wasserstoff ist, ein therapeutisch annehmbares Säureadditionssalz hievon mit einer organischen oder anorganischen Base
- 55 mit einem pharmazeutisch annehmbaren Träger gemischt wird.
- 60



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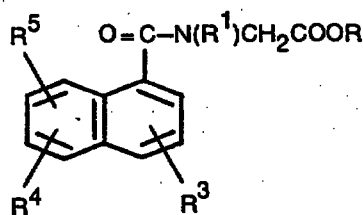
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10. Verfahren zum Herstellen einer Verbindung der Formel (II)



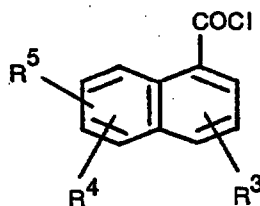


(b) das Hydrolysieren eines Amidoesters der Formel

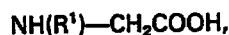


worin  $R^1$ ,  $R^3$ ,  $R^4$  und  $R^5$  wie oben definiert sind und R nied. Alkyl oder Ar(nied.)alkyl bedeutet, wobei eine Verbindung der Formel (A) erhalten wird, worin  $R^1$ ,  $R^3$ ,  $R^4$  und  $R^5$  wie oben definiert sind und R Wasserstoff ist; oder

(c) das Umsetzen eines Naphthalincarbonsäurechlorids der Formel



worin  $R^3$ ,  $R^4$  und  $R^5$  wie oben definiert sind, mit einer Aminosäure der Formel

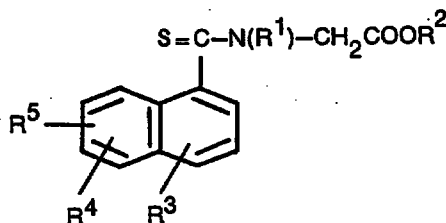


worin  $R^1$  wie oben definiert ist, in Anwesenheit einer Base, wobei eine Verbindung der Formel (A) erhalten wird, worin  $R^1$ ,  $R^3$ ,  $R^4$  und  $R^5$  wie oben definiert sind und R Wasserstoff ist; oder

(d) das Überführen einer Verbindung der Formel (A), worin R Wasserstoff ist, in ein entsprechendes therapeutisch annehmbares Salz einer organischen oder anorganischen Base.

Revendications pour les Etats contractants: BE CH DE FR GB IT LI LU NL SE

1. Composé de formule I



(I)

dans laquelle  $R^1$  est l'hydrogène, un groupe alkyle inférieur, alcényle inférieur ou phénylméthyle;  $R^2$  est l'hydrogène ou un groupe alkyle inférieur;  $R^3$  est l'hydrogène, un groupe alkoxy inférieur en position 6 du noyau de naphthalène, ou un substituant en position 4, 5 ou 8 du noyau de naphthalène, le substituant étant choisi dans le groupe formé de radicaux alkyle inférieurs, alkoxy inférieurs, halogéno, cyano, nitro, trihalogénométhyle et trifluorométhylthio, et  $R^4$  et  $R^5$  représentent chacun un atome d'hydrogène, ou bien  $R^3$  et  $R^4$  représentent chacun un substituant en des positions différentes choisies entre les positions 3 à 7 du noyau de naphthalène, les substituants étant choisis dans le groupe formé des radicaux alkyle inférieurs, alkoxy inférieurs, halogéno, trihalogénométhyle, trihalogénométhylthio, (alkoxy inférieur)-alkoxy inférieur, phénylméthoxy et phénylméthoxy substitués sur la portion phényle avec un radical alkyle inférieur, alkoxy inférieur, halogéno ou trihalogénométhyle, et  $R^5$  est l'hydrogène; ou bien  $R^3$ ,  $R^4$  et  $R^5$  représentent chacun un substituant en des positions différentes choisies entre les positions 4, 5 et 6 du noyau de naphthalène, le substituant étant choisi dans le groupe comprenant des substituants alkoxy inférieurs, halogéno et trihalogénométhyle; ou un sel thérapeutiquement acceptable avec une base organique ou inorganique du composé de formule I dans laquelle  $R^2$  est l'hydrogène.

2. Composé suivant la revendication 1, dans lequel  $R^1$  est l'hydrogène, un radical alkyle inférieur, 2-propényle ou phénylméthyle;  $R^2$  est l'hydrogène ou un radical alkyle inférieur;  $R^3$  est l'hydrogène ou un radical alkoxy inférieur en position 6 du noyau de naphthalène, ou un substituant en positions 4, 5 ou 8 du noyau de naphthalène, les substituants étant choisis dans le groupe comprenant des substituants alkyle inférieurs, alkoxy inférieurs, halogéno, cyano, nitro et trifluorométhyle, et  $R^4$  et  $R^5$  représentent chacun



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l'hydrogène; ou bien R<sup>3</sup> et R<sup>4</sup> représentent une paire de substituants sur le noyau de naphthalène, chaque substituant occupant une position différente sur le noyau, la paire de substituants étant choisie dans le groupe des paires formées de radicaux 3-halogéno-4-alkoxy inférieurs, 4,6-di-(alkoxy inférieurs), 5-halogéno-6-alkyle inférieurs, 5-halogéno-6-alkoxy inférieurs, 5,7-dihalogéno, 5-(trifluorométhyl)-6-alkoxy inférieurs, 5-(trifluorométhylthio)-6-alkoxy inférieurs, 5-halogéno-6-(alkoxy inférieur)-alkoxy inférieurs, 5-halogéno-6-[3-(trifluorométhyl)phénylméthoxy] et 5-halogéno-6-(4-chlorophénylméthoxy), et R<sup>5</sup> est l'hydrogène; ou bien R<sup>3</sup>, R<sup>4</sup> et R<sup>5</sup> représentent chacun un substituant sur le noyau de naphthalène, chacun des trois substituants occupant une position différente sur le noyau, les trois substituants étant choisis dans le groupe de substituants 4-(alkoxy inférieur)-5-halogéno-6-alkoxy inférieurs et 4,6-di-(alkoxy inférieur)-5-(trifluorométhyle); ou bien lorsque R<sup>2</sup> est l'hydrogène, un sel thérapeutiquement acceptable de ce composé avec une base organique ou inorganique.

3. Composé suivant la revendication 1, dans lequel R<sup>1</sup> est l'hydrogène, un groupe alkyle inférieur ou phénylméthyle; R<sup>2</sup> est l'hydrogène ou un groupe alkyle inférieur; R<sup>3</sup> est un radical 4-halogéno ou 5-halogéno et R<sup>4</sup> et R<sup>5</sup> représentent chacun un atome d'hydrogène; ou bien R<sup>3</sup> et R<sup>4</sup> forment une paire de substituants sur le noyau de naphthalène choisie dans le groupe des paires formées de substituants 3-halogéno-4-alkoxy inférieurs, 4,6-di-(alkoxy inférieurs), 5-halogéno-6-alkyle inférieurs, 5-halogéno-6-alkoxy inférieurs, 5,7-dihalogéno, 5-(trifluorométhyl)-6-alkoxy inférieurs et 5-(trifluorométhylthio)-6-alkoxy inférieurs, et R<sup>5</sup> est l'hydrogène; ou bien R<sup>3</sup> est un radical 4-alkoxy inférieur, R<sup>4</sup> est un radical 5-(trifluorométhyle) et R<sup>5</sup> est un radical 6-alkoxy inférieur; ou bien lorsque R<sup>2</sup> est l'hydrogène, un sel thérapeutiquement acceptable de ce composé avec une base organique ou inorganique.

4. Composé suivant la revendication 1, dans lequel R<sup>1</sup> est un radical alkyle inférieur; R<sup>2</sup> est l'hydrogène; R<sup>3</sup> est un radical 5-halogéno et R<sup>4</sup> et R<sup>5</sup> représentent chacun un atome d'hydrogène; ou bien R<sup>3</sup> et R<sup>4</sup> représentent une paire de substituants sur le noyau de naphthalène choisie dans le groupe des paires formées de substituants 3-halogéno-4-alkoxy inférieurs, 5-halogéno-6-alkoxy inférieurs, 5-(trifluorométhyl)-6-alkoxy inférieurs et 5-(trifluorométhylthio)-6-alkoxy inférieurs, et R<sup>5</sup> est l'hydrogène; ou bien R<sup>3</sup> est un radical 4-alkoxy inférieur, R<sup>4</sup> est un radical 5-(trifluorométhyle) et R<sup>5</sup> est un radical 6-alkoxy inférieur; ou un sel thérapeutiquement acceptable de ce composé avec une base organique ou inorganique.

5. Composé suivant la revendication 1, que est la N - [(5 - bromo - 1 - naphthalényl)thioxométhyl] - N - méthylglycine, la N - [(5 - chloro - 1 - naphthalényl)thioxométhyl] - N - méthylglycine, la N - [(5 - bromo - 1 - naphthalényl)thioxométhyl]glycine, la N - [(5 - bromo - 1 - naphthalényl)thioxométhyl] - N - (2 - propényl)glycine, la N - [(5 - bromo - 1 - naphthalényl)thioxométhyl] - N - éthylglycine, la N - [(5 - bromo - 1 - naphthalényl)thioxométhyl] - N - butylglycine ou la N - [(5 - bromo - 1 - naphthalényl)thioxométhyl] - N - (phénylméthyl)glycine ou son ester méthylique correspondant.

6. Composé suivant la revendication 1, que est la N - [(5 - (trifluorométhyl) - 6 - méthoxy - 1 - naphthalényl)thioxométhyl] - N - méthylglycine, la N - [(5 - (trifluorométhylthio) - 6 - méthoxy - 1 - naphthalényl)thioxométhyl] - N - méthylglycine, la N - [(5 - (trifluorométhyl) - 1 - naphthalényl)thioxométhyl] - N - méthylglycine ou la N - [(4,6 - diméthoxy - 5 - (trifluorométhyl) - 1 - naphthalényl)thioxométhyl] - N - méthylglycine ou son ester méthylique correspondant.

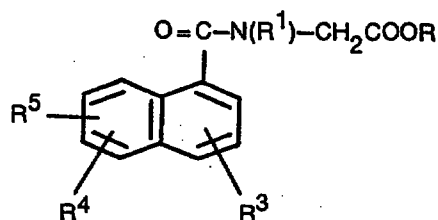
7. Composé suivant la revendication 1, que est la N - [(3 - chloro - 4 - méthoxy - 1 - naphthalényl)thioxométhyl] - N - méthylglycine ou la N - [(3 - chloro - 4 - méthoxy - 1 - naphthalényl)thioxométhyl]glycine ou son ester méthylique correspondant.

8. Composé suivant la revendication 1, qui est la N - [(5 - bromo - 6 - méthoxy - 1 - naphthalényl)thioxométhyl] - N - méthylglycine, la N - [(5,7 - dichloro - 1 - naphthalényl)thioxométhyl] - N - méthylglycine, la N - [(5 - bromo - 6 - pentyloxy - 1 - naphthalényl)thioxométhyl] - N - méthylglycine, la N - [(5 - bromo - 6 - méthyl - 1 - naphthalényl)thioxométhyl] - N - méthylglycine, la N - [(5 - iodo - 6 - méthoxy - 1 - naphthalényl)thioxométhyl] - N - méthylglycine, la N - [(5 - bromo - 6 - (3 - méthoxypropoxy) - 1 - naphthalényl)thioxométhyl] - N - méthylglycine, la N - [(5 - bromo - 6 - (3 - (trifluorométhyl)phénylméthoxy) - 1 - naphthalényl)thioxométhyl] - N - méthylglycine, ou la N - [(5 - bromo - 6 - (4 - chlorophénylméthoxy) - 1 - naphthalényl)thioxométhyl] - N - méthylglycine ou son ester méthylique correspondant.

9. Composition pharmaceutique destinée à prévenir ou à combattre des complications diabétiques chez un mammifère atteint de diabète, qui comprend un composé suivant l'une quelconque des revendications 1 à 8 et un support pharmaceutiquement acceptable.

10. Composé suivant l'une quelconque des revendications 1 à 8, destiné à être utilisé comme agent préventif ou curatif vis-à-vis d'une complication diabétique chez un mammifère atteint de diabète.

11. Composé de formule



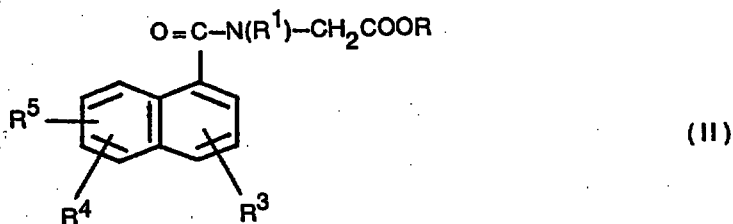


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dans laquelle  $R^1$  est un radical alkyle inférieur, alcényle inférieur ou phénylméthyle;  $R^3$  est un substituant en position 4, 5 ou 8 du noyau de naphthalène, le substituant étant choisi dans le groupe des substituants alkyle inférieurs, alkoxy inférieurs, halogéno, cyano, nitro et trihalogénométhyle, et  $R^4$  et  $R^5$  représentent chacun un atome d'hydrogène; ou bien  $R^3$  et  $R^4$  représentent chacun un substituant dans des positions différentes du noyau de naphthalène, les positions étant choisies parmi les positions 3 à 7 et les substituants étant choisis dans le groupe des substituants alkyle inférieurs, alkoxy inférieurs, halogéno, trihalogénométhyle, trihalogénométhylthio, (alkoxy inférieur)-alkoxy inférieurs, phénylméthoxy et phénylméthoxy substitué sur la portion phényle avec un radical alkyle inférieur, alkoxy inférieur, halogéno ou trihalogénométhyle et  $R^5$  est l'hydrogène; ou bien  $R^3$ ,  $R^4$  et  $R^5$  représentent chacun un substituant dans des positions différentes choisies entre les positions 4, 5 et 6 du noyau de naphthalène, le substituant étant choisi dans le groupe des substituants alkoxy inférieurs, halogéno et trihalogénométhyle; et R représente l'hydrogène ou un radical alkyle inférieur, ou un sel thérapeutiquement acceptable avec une base organique ou inorganique du composé dans lequel R est l'hydrogène.

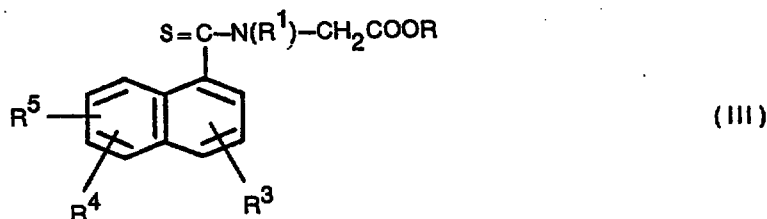
12. Procédé de préparation d'un composé suivant la revendication 1, qui consiste:

(a) à faire réagir un amidoester de formule II



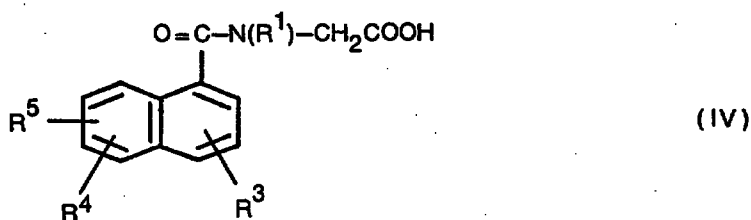
dans laquelle  $R^1$ ,  $R^3$ ,  $R^4$  et  $R^5$  ont les définitions données dans la revendication 1 et R est un radical alkyle inférieur, avec le pentasulfure de phosphore pour obtenir le composé correspondant de la revendication 1, dans lequel  $R^1$ ,  $R^3$ ,  $R^4$  et  $R^5$  ont les définitions données ici et  $R^2$  est un radical alkyle inférieur; ou bien

(b) à hydrolyser le composé de formule III



dans laquelle  $R^1$ ,  $R^3$ ,  $R^4$  et  $R^5$  ont les définitions données dans la revendication 1 et R est un radical alkyle inférieur ou ar(alkyl inférieur) pour obtenir le composé correspondant de formule I dans laquelle  $R^1$ ,  $R^3$ ,  $R^4$  et  $R^5$  ont les définitions données ici et  $R^2$  est l'hydrogène; ou bien

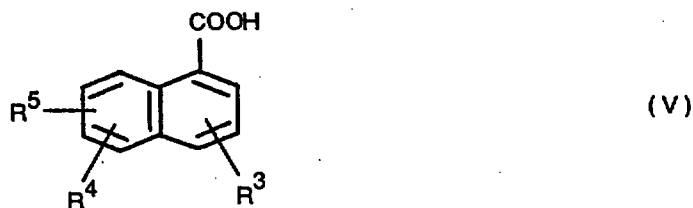
(c) à faire réagir un amidoacide de formule (IV)



dans laquelle  $R^1$ ,  $R^3$ ,  $R^4$  et  $R^5$  ont les définitions données dans la revendication 1, avec le pentasulfure de phosphore pour obtenir le composé correspondant de la revendication 1, dans lequel  $R^1$ ,  $R^3$ ,  $R^4$  et  $R^5$  ont les définitions données ici et  $R^2$  est l'hydrogène; et

(d) le cas échéant, à transformer le composé de formule I dans lequel  $R^2$  est l'hydrogène, en un sel thérapeutiquement acceptable correspondant d'une base organique ou inorganique.

13. Procédé suivant la revendication 12, dans lequel le composé de formule II est obtenu par combinaison d'un composé de formule V



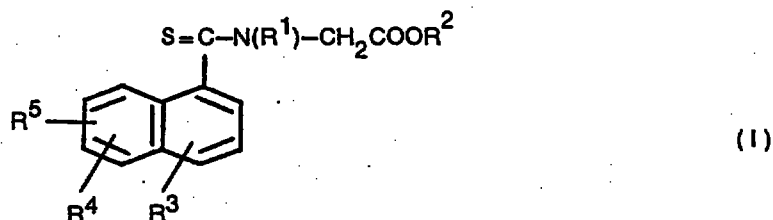


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dans laquelle  $R^3$ ,  $R^4$ , et  $R^5$  sont tels que définis dans ladite revendication, avec un ester d'acide aminé de formule  $NH(R^1)-CH_2COOR$  dans laquelle  $R^1$  et  $R$  sont tels que définis dans ladite revendication.

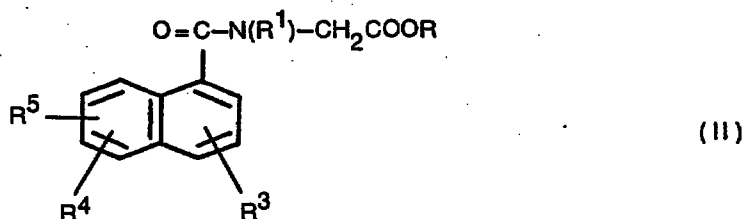
# Revendications pour l'Etat contractant: AT:

## 1. Procédé de préparation d'un composé de formule I



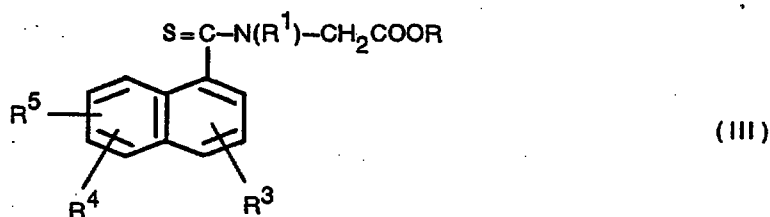
dans laquelle  $R^1$  est l'hydrogène, un groupe alkyle inférieur, alcényle inférieur ou phénylméthyle;  $R^2$  est l'hydrogène ou un groupe alkyle inférieur;  $R^3$  est l'hydrogène, un groupe alkoxy inférieur en position 6 du noyau de naphthalène, ou un substituant en position 4, 5 ou 8 du noyau de naphthalène, le substituant étant choisi dans le groupe formé de radicaux alkyle inférieurs, alkoxy inférieurs, halogéno, cyano, nitro, trihalogénométhyle et trifluorométhylthio, et  $R^4$  et  $R^5$  représentent chacun un atome d'hydrogène, ou bien  $R^3$  et  $R^4$  représentent chacun un substituant en des positions différentes choisies entre les positions 3 à 7 du noyau de naphthalène, les substituants étant choisis dans le groupe formé des radicaux alkyle inférieurs, alkoxy inférieurs, halogéno, trihalogénométhyle, trihalogénométhylthio, (alkoxy inférieur)-alkoxy inférieurs, phénylméthoxy et phénylméthoxy substitués sur la portion phényle avec un radical alkyle inférieur, alkoxy inférieur, halogéno ou trihalogénométhyle, et  $R^5$  est l'hydrogène; ou bien  $R^3$ ,  $R^4$  et  $R^5$  représentent chacun un substituant en des positions différentes choisies entre les positions 4, 5 et 6 du noyau de naphthalène, le substituant étant choisi dans le groupe comprenant des substituants alkoxy inférieurs, halogéno et trihalogénométhyle; ou d'un sel thérapeutiquement acceptable avec une base organique ou inorganique du composé de formule I dans laquelle  $R^2$  est l'hydrogène; qui consiste;

(a) à faire réagir un amidoester de formule II



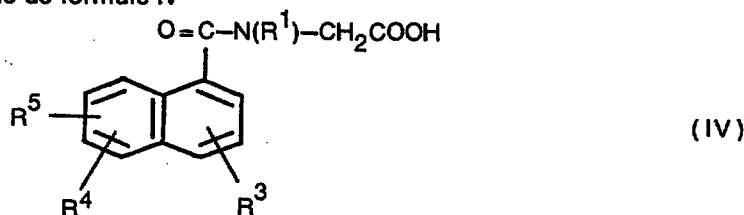
dans laquelle  $R^1$ ,  $R^3$ ,  $R^4$  et  $R^5$  ont les définitions données ici et  $R$  est un radical alkyle inférieur, avec le pentasulfure de phosphore pour obtenir le composé correspondant de la revendication 1, dans lequel  $R^1$ ,  $R^3$ ,  $R^4$  et  $R^5$  sont tels que définis ici et  $R^2$  est un radical alkyle inférieur; ou

(b) à hydrolyser le composé de formule III



dans laquelle  $R^1$ ,  $R^3$ ,  $R^4$  et  $R^5$  sont tels que définis ici et  $R$  est un radical alkyle inférieur ou ar(alkyle inférieur) pour obtenir le composé correspondant de formule I dans laquelle  $R^1$ ,  $R^3$ ,  $R^4$  et  $R^5$  sont tels que définis ici et  $R^2$  est l'hydrogène; ou bien

(c) à faire réagir un amidoacide de formule IV



dans laquelle  $R^1$ ,  $R^3$ ,  $R^4$  et  $R^5$  sont tels que définis ici, avec le pentasulfure de phosphore pour obtenir le



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composé correspondant de la revendication 1, dans lequel  $R^1$ ,  $R^3$ ,  $R^4$  et  $R^5$  sont tels que définis ici et  $R^2$  est l'hydrogène; ou

(d) à transformer un composé de formule I dans laquelle  $R^2$  est l'hydrogène en un sel thérapeutiquement acceptable correspondant d'une base organique ou inorganique.

5 2. Procédé suivant le paragraphe (a) ou (b) de la revendication 1, dans lequel  $R^1$  est l'hydrogène ou un radical alkyle inférieur, 2-propényle ou phénylméthyle;  $R^2$  est l'hydrogène ou un radical alkyle inférieur;  $R^3$  est l'hydrogène, un radical alkyle inférieur en position 6 du noyau de naphthalène ou un substituant en positions 4, 5 ou 8 du noyau de naphthalène, les substituants étant choisis dans le groupe de substituants alkyle inférieurs, alkoxy inférieurs, halogéno, cyano, nitro et trifluorométhyle, et  $R^4$  et  $R^5$  représentent  
10 chacun l'hydrogène; ou bien  $R^3$  et  $R^4$  sont une paire de substituants sur le noyau de naphthalène, chaque substituant occupant une position différente sur le noyau, la paire de substituants étant choisie dans le groupe de paires comprenant des substituants 3-halogéno-4-alkoxy inférieurs, 4,6-di-(alkoxy inférieurs), 5-halogéno-6-alkyle inférieurs, 5-halogéno-6-alkoxy inférieurs, 5,7-dihalogéno, 5-(trifluorométhyl)-6-alkoxy inférieurs, 5-(trifluorométhylthio)-6-alkoxy inférieurs, 5-halogéno-6-(alkoxy inférieur)-alkoxy inférieurs 5-  
15 halogéno-6-[3-(trifluorométhyl)phénylméthoxy] et 5-halogéno-6-(4-chlorophénylméthoxy), et  $R^5$  est l'hydrogène; ou bien  $R^3$ ,  $R^4$  et  $R^5$  représentent chacun un substituant sur le noyau de naphthalène, chacun des trois substituants occupant une position différente sur le noyau, les trois substituants étant choisis dans le groupe de substituants 4-(alkoxy inférieur)-5-halogéno-6-alkoxy inférieurs et 4,6-di-(alkoxy inférieur)-5-(trifluorométhyle).

20 3. Procédé suivant le paragraphe (a) ou (b) de la revendication 1, dans lequel  $R^1$  est l'hydrogène, un radical alkyle inférieur ou phénylméthyle;  $R^2$  est l'hydrogène ou un radical alkyle inférieur;  $R^3$  est un radical 4-halogéno ou 5-halogéno et  $R^4$  et  $R^5$  représentent chacun l'hydrogène; ou bien  $R^3$  et  $R^4$  représentent une paire de substituants sur le noyau de naphthalène, choisie dans le groupe des paires de substituants 3-halogéno-4-alkoxy inférieurs, 4,6-di(alkoxy inférieurs), 5-halogéno-6-alkyle inférieurs, 5-halogéno-6-alkoxy inférieurs, 5,7-dihalogéno, 5-(trifluorométhyl)-6-alkoxy inférieurs et 5-(trifluorométhylthio)-6-alkoxy inférieurs, et  $R^5$  est l'hydrogène; ou bien  $R^3$  est un radical 4-alkoxy inférieur,  $R^4$  est un radical 5-(trifluorométhyle) et  $R^5$  est un radical 6-alkoxy inférieur.

4. Procédé suivant le paragraphe (b) de la revendication 1, dans lequel  $R^5$  est un radical alkyle inférieur;  $R^2$  est l'hydrogène;  $R^3$  est un radical 5-halogéno et  $R^4$  et  $R^5$  représentent chacun l'hydrogène; ou bien  $R^3$  et  $R^4$  forment une paire de substituants sur le noyau de naphthalène choisie dans le groupe des paires comprenant des substituants 3-halogéno-4-alkoxy inférieurs, 5-halogéno-6-alkoxy inférieurs, 5-(trifluorométhyl)-6-alkoxy inférieurs et 5-(trifluorométhylthio)-6-alkoxy inférieurs, et  $R^5$  est l'hydrogène; ou bien  $R^3$  est un radical 4-alkoxy inférieur,  $R^4$  est un radical 5-(trifluorométhyle) et  $R^5$  est un radical 6-alkoxy inférieur.

5. Procédé suivant la revendication 1, dans lequel le composé de formule I qui est préparé est la N -  
35 [(5 - bromo - 1 - naphthalényl)thioxométhyl] - N - méthylglycine, la N - [(5 - choro - 1 - naphthalényl)thioxométhyl] - N - méthylglycine, la N - [(5 - bromo - 1 - naphthalényl)thioxométhyl] - N - propylglycine, la N - [(5 - bromo - 1 - naphthalényl)thioxométhyl] - N - (2 - propényl)glycine, la N - [(5 - bromo - 1 - naphthalényl)thioxométhyl] - N - éthylglycine, la N - [(5 - bromo - 1 - naphthalényl)thioxométhyl] - N - butylglycine ou la N - [(5 - bromo - 1 - naphthalényl)thioxométhyl] - N - (phénylméthyl)glycine ou son ester méthylique correspondant.

6. Procédé suivant la revendication 1, dans lequel le composé de formule I qui est préparé est la N -  
[(5 - (trifluorométhyl) - 6 - méthoxy - 1 - naphthalényl) - thioxométhyl] - N - méthylglycine, la N - [(5 - (trifluorométhylthio) - 6 - méthoxy - 1 - naphthalényl)thioxométhyl] - N - méthylglycine, la N - [(5 - (trifluorométhyl) - 1 - naphthalényl)thioxométhyl] - N - méthylglycine ou la N - [(4,6 - diméthoxy - 5 - (trifluorométhyl) - 1 - naphthalényl)thioxométhyl] - N - méthylglycine ou son ester méthylique correspondant.

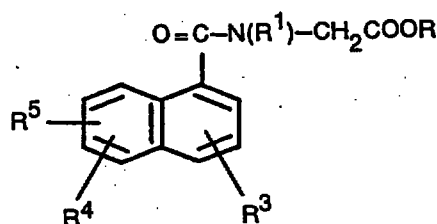
7. Procédé suivant la revendication 1, dans lequel le composé de formule I qui est préparé est la N -  
[(3 - chloro - 4 - méthoxy - 1 - naphthalényl)thioxométhyl] - N - méthylglycine ou la N - [(3 - chloro - 4 - méthoxy - 1 - naphthalényl)thioxométhyl]glycine ou son ester méthylique correspondant.

8. Procédé suivant la revendication 1, dans lequel le composé de formule I qui est préparé est la N -  
[(5 - bromo - 6 - méthoxy - 1 - naphthalényl)thioxométhyl] - N - méthylglycine, la N - [(5,7 - dichloro - 1 - naphthalényl)thioxométhyl] - N - méthylglycine, la N - [(5 - bromo - 6 - pentyloxy - 1 - naphthalényl)thioxométhyl] - N - méthylglycine, la N - [(5 - iodo - 6 - méthoxy - 1 - naphthalényl)thioxométhyl] - N - méthylglycine, la N - [(5 - bromo - 6 - (3 - méthoxypropoxy) - 1 - naphthalényl)thioxométhyl] - N - méthylglycine, la N - [(5 - bromo - 6 - [3 - (trifluorométhyl)phénylméthoxy] - 1 - naphthalényl)thioxométhyl] - N - méthylglycine, ou la N - [(5 - bromo - 6 - (4 - chlorophénylméthoxy) - 1 - naphthalényl)thioxométhyl] - N - méthylglycine ou son ester méthylique correspondant.

9. Procédé de préparation d'une composition pharmaceutique, caractérisé en ce qu'un composé de formule I tel que défini dans la revendication 1 ou bien, lorsque  $R^2$  est l'hydrogène, un sel d'addition d'acide pharmaceutiquement acceptable de ce composé avec une base organique ou inorganique, est mélangé avec un support pharmaceutiquement acceptable.

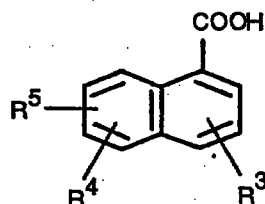


## 10. Procédé de préparation d'un composé de formule II



(II)

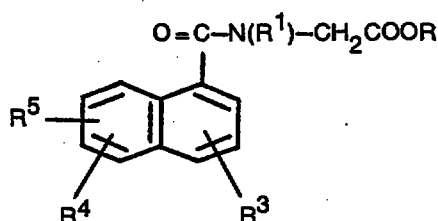
dans laquelle  $\text{R}^1$ ,  $\text{R}^3$ ,  $\text{R}^4$  et  $\text{R}^5$  ont les définitions données dans la revendication 1 et R est un radical alkyle inférieur ou ar(alkyle inférieur), qui consiste à combiner un composé de formule V



(V)

dans laquelle  $\text{R}^3$ ,  $\text{R}^4$  et  $\text{R}^5$  ont les définitions données dans ladite revendication, avec un aminoester de formule  $\text{NH}(\text{R}^1)-\text{CH}_2\text{COOR}$  dans laquelle  $\text{R}^1$  et R ont les définitions données dans ladite revendication.

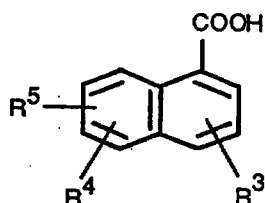
## 11. Procédé de préparation d'un composé de formule



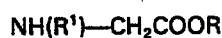
(A)

dans laquelle  $\text{R}^1$  est un radical alkyle inférieur, alcényle inférieur ou phénylméthyle;  $\text{R}^3$  est un substituant en positions 4, 5 ou 8 du noyau de naphthalène, le substituant étant choisi dans le groupe des substituants alkyle inférieurs, alkoxy inférieurs, halogéno, cyano, nitro et trihalogénométhyle, et  $\text{R}^4$  et  $\text{R}^5$  représentent chacun l'hydrogène; ou bien  $\text{R}^3$  et  $\text{R}^4$  représentent chacun un substituant dans des positions différentes du noyau de naphthalène, les positions étant choisies parmi les positions 3 à 7 et les substituants étant choisis dans le groupe des substituants alkyle inférieurs, alkoxy inférieurs, halogéno, trihalogénométhyle, trihalogénométhylthio, (alkoxy inférieur)-alkoxy inférieurs, phénylméthoxy et phénylméthoxy substitué sur la portion phényle avec un radical alkyle inférieur, alkoxy inférieur, halogéno ou trihalogénométhyle et  $\text{R}^5$  est l'hydrogène; ou bien  $\text{R}^3$ ,  $\text{R}^4$  et  $\text{R}^5$  représentent chacun un substituant dans des positions différentes choisies entre les positions 4, 5 et 6 du noyau de naphthalène, le substituant étant choisi dans le groupe des substituants alkoxy inférieurs, halogéno et trihalogénométhyle; et R est l'hydrogène ou un radical alkyle inférieur, ou un sel thérapeutiquement acceptable avec une base organique ou inorganique du composé dans lequel R est l'hydrogène, procédé qui consiste

(a) à combiner un composé de formule



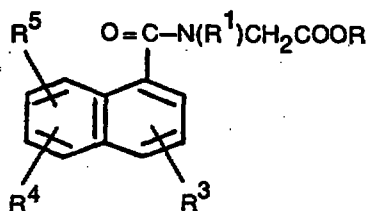
dans laquelle  $\text{R}^3$ ,  $\text{R}^4$  et  $\text{R}^5$  ont les définitions données ci-dessus, avec un aminoester de formule



dans laquelle  $\text{R}^1$  a la définition donnée ci-dessus et R est un radical alkyle inférieur, pour former un composé de formule (A) dans laquelle  $\text{R}^1$ ,  $\text{R}^3$ ,  $\text{R}^4$  et  $\text{R}^5$  ont les définitions données ci-dessus et R est un radical alkyle inférieur; ou bien

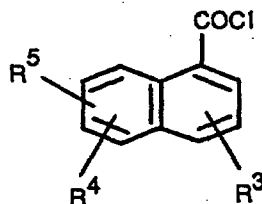


(b) à hydrolyser un amidoester de formule



dans laquelle  $R^1$ ,  $R^3$ ,  $R^4$  et  $R^5$  ont les définitions données ci-dessus et  $R$  est un radical alkyle inférieur ou ar(alkyle inférieur) pour donner un composé de formule A dans laquelle  $R^1$ ,  $R^3$ ,  $R^4$  et  $R^5$  ont les définitions données ci-dessus et  $R$  est l'hydrogène; ou bien

(c) à faire réagir un chlorure d'acide naphtalène-carboxylique de formule



dans laquelle  $R^3$ ,  $R^4$  et  $R^5$  ont les définitions données ci-dessus, avec un aminoacide de formule



dans laquelle  $R^1$  a la définition donnée ci-dessus, en présence d'une base pour former un composé de formule A dans laquelle  $R^1$ ,  $R^3$ ,  $R^4$  et  $R^5$  ont les définitions données ci-dessus et  $R$  est l'hydrogène; ou bien

(d) à transformer un composé de formule A dans laquelle  $R$  est l'hydrogène en un sel thérapeutiquement acceptable correspondant d'une base organique ou inorganique.