(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 078 860**
A1

(12) # EUROPEAN PATENT APPLICATION

(21) Application number: **81109565.2**

(22) Date of filing: **07.11.81**

(51) Int. Cl.³: **C 07 D 333/38**
A 61 K 31/38
//C07D333/36

(43) Date of publication of application:
18.05.83 Bulletin 83/20

(84) Designated Contracting States:
AT BE CH FR GB IT LI LU NL SE

(71) Applicant: **A. Nattermann & Cie. GmbH**
Nattermannallee 1
D-5000 Köln 30(DE)

(72) Inventor: **Lautenschläger, Hans-Heiner, Dr.**
Neusser Gasse 50
D-5024 Pulheim-Stommeln(DE)

(72) Inventor: **Betzing, Hans, Dr.**
Heidestock 7
D-5014 Kerpen-Horrem(DE)

(72) Inventor: **Winkelmann, Johannes, Dr.**
Frankfurter Strasse 269
D-5000 Köln 90(DE)

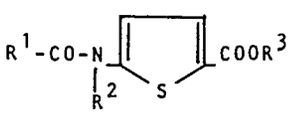
(72) Inventor: **Probst, Manfred, Dr.**
Widderstrasse 32
D-5020 Frechen 4(DE)

(72) Inventor: **Stoll, Brigitte**
Am Römerpfad 19
D-5024 Pulheim(DE)

(74) Representative: **Redies, Bernd, Dr. rer. nat. et al,**
Redies, Redies, Türk & Gille, Patentanwälte
Brucknerstrasse 20
D-4000 Düsseldorf 13(DE)

(54) **New 5-(N-alkyl-N-acyl-amino)-thiophen-2-carboxylic acid derivatives, process for producing the same and pharmaceutical compounds containing the same.**

(57) The present invention refers to new 5-(N-Alkyl-N-acylamino)-thiophen-2-carboxylic acid derivatives having the general formula I

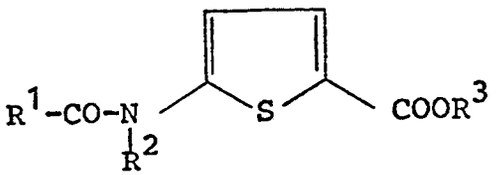


I

process for producing the same and pharmaceutical compounds containing the same as active ingredient.

EP 0 078 860 A1

The present invention is related to new 5-(N-alkyl-N-acyl)-amino-thiophen-2-carboxylic acid derivatives of the general formula I



I

wherein

R^1 is an alkyl group having from 1 to 5 carbon atoms,

R^2 is an alkyl group having from 12 to 18 carbon atoms,

R^3 is a hydrogen, an alkali ion or an alkyl group having from 1 to 3 carbon atoms,

as well as process for producing the same and pharmaceutical preparations containing the same as active ingredient.

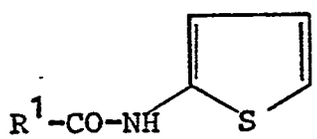
The hydrocarbon groups R^1, R^2 and R^3 may be straight or branched, saturated or unsaturated groups. R^1 preferably are straight or branched saturated hydrocarbon groups, in particular straight alkyl groups. R^2 preferably are straight saturated or such hydrocarbon groups with 12 to 18 carbon atoms having one olefine doublebond.

The compounds according to the present invention show interesting pharmacological properties. The new compounds have both anti-inflammatory and lipid decreasing properties. The acylamino thiophen carboxylic acids of the present invention have anti-inflammatory activity both in vitro and in vivo. They furthermore show an advantageous inhibation of the complement system. Furthermore, they decrease the platelet aggregation. These valuable pharmacological properties are furthermore supplemented by a significant plaques reduction in animals, a decrease of the total cholesterol, an increase of the α-lipoproteins and a reduction of the β-lipoproteins.

Thus, the N-alkyl-N-acyl-amino-thiophen carboxylic acid derivatives may in particular be used for the treatment of inflammatory, arteriosclerotic and thrombotic diseases. Their use in dosages ranging from 1 to 5oo mg/kg, in particular 1o to 3oo mg/kg and most preferably from 2o to 2oo mg/kg.

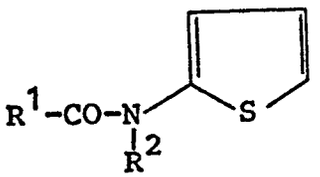
The acylamino thiophen carboxylic acid derivatives according to the present invention may be used as free acids or as the alkali salts thereof or as the esters of C_{1-3}-alcohols as active agent in pharmaceutical preprations together with usual carrier materials or dilluents. Esters of alcohols with 1 to 3 carbon atoms are particularly useful for oral administration.

The acylamino thiophen carboxylic acids and their derivatives are mostly produced by processes the chemical reaction whereof is known as such. The starting materials of the present process are the known carboxylic acid amides of the general formula II



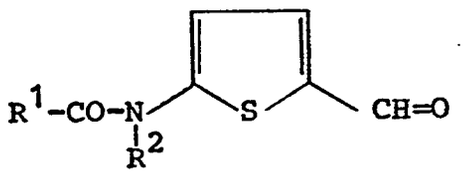
II

wherein R^1 has teh same meaning as in formula I. The compounds of formula II are alkylated at the nitrogen atom in accordance with the chemical reaction described by W. STEINKOFF, Liebigs Ann. vol. 4o3, p. 17. According to the present invention, the sodium there used is preferably substituted by sodium hydride and the reaction is carried out in a polar aprotic solvent such as methyl ethyl keton- or dimethylformamide. The addition of an alkali methyl iodide is preferred when using slowly reacting halogenides. The resulting product are compounds of the general formula III



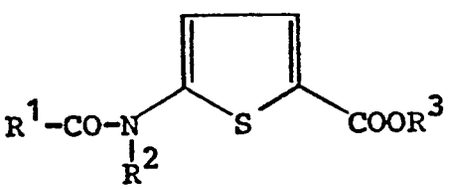
III

wherein R^1 and R^2 have the same meaning as in formula I. These compounds then are further converted into the aldehydes of the general formula IV



IV

wherein R^1 and R^2 have the same meaning as in formula I, applying reaction conditions usual for the FILSMEYER formylation. When oxydizing the aldehydes of formula IV with usual oxydizing agents such as potassium permanganate in an aqueous organic solvent, the new acids of formula I



I

wherein R^3 is hydrogen, are obtained.

The free acids of formula I (R^3 = H) may be converted to their alkali methyl salts wherein R^3 is alkali, by subjecting the acids to reaction with an alkali methyl hydroxide or carbonate in an aqueous or alcoholic-aqueous solvent and recovering the salts by evaporating the resulting solution.

The salts of formula I wherein R^3 is an alkali, may be converted into the corresponding esters of formula I with R^3 being an C_{1-3}-alkyl, by alkylating the salts with a alkyl

halide or a similar alkylating agent having the formula V

$$R^3—X \qquad V$$

wherein R^3 is a straight or branched C_{1-3}-alkyl group and X is a halogen such as Cl, Br, J or another usual group readily split of during alkylation, in a polar aprotic solvent. On the other side, esters of the formula I wherein R^3 is alkyl, may also be produced by subjecting the acids of formula I with R^3 being hydrogen or their alkali salts with R^3 being alkali, at first to reaction with thionyl chloride, possibly in an organic solvent, and further reaction with an alcohol of the formula R^3-OH, R^3 having the same meaning as in formula I.

Suitable substituted acid amides of formula II are for instance:

N-(2-thienyl)-acetamide,
N-(2-thienyl)-propionic acid amide,
N-(2-thienyl)-butyric acid amide,
N-(2-thienyl)-valerianic acid amide,
N-(2-thienyl)-capronic acid amide.

For preparing the compounds of formula III from the compounds of formula II there may be used as alkylating agent of formula R^2-X for instance:

bromododecane,bromotridecane, bromotetradecane, bromopentadecane, bromohexadecane, bromoheptadecane, bromooctadecane and the corresponding chloro and iodo compounds.

The full synthesis is further explained with some of the compounds III and IV and the resulting final compounds of formula I. Melting points given in the following examples

have been determined by means of a Büchi-51o-melting point determining apparatus and are not corrected melting points. IR-spectra have been determined by means of a Perkin-Elmer 257 and the mass spectra by means of a Varian MAT-311A (7oeV).

EXAMPLE 1

N-hexadecyl-N-(2-thienyl)-acetamide.
21 g N-(2-thienyl)-acetamide are dissolved in 15o cc. anhydrous methylethylketon. 3.6 g of sodium hydride are added to this solution. After termination of hydrogen formation, 38.9 g of chlorohexadecane and 44.7 g of dry sodiumiodide are added thereto and the reaction mixture is heated to boiling for 24 hours. The reaction mixture is evaporated in a vacuum and the residue is treturated with water and ether. The ethereal layer is separated, washed with water and dried over Na_2SO_4. The solvent is evaporated and the residue is purified chromatographically on a column of silicic acid gel using hexan/ethyl acetate as eluant. Yield: 28 g (51 % of the theoretical), m.p.: 34 - 36°C. IR (KBr): 1675 cm^{-1}

EXAMPLE 2

N-hexadecyl-N-(2-thienyl)-propionic acid amide.
7.9 g of sodium hydride are added to a solution of 46.5 g of N-(2-thienyl)-propionic acid amide in 6oo cc. of anhydrous dimethylformamide (DMF). The mixture is stirred until termination of hydrogen formation. Thereafter, 78 g of chlorohexadecane and 9 g of dry sodium iodide are added thereto and the reaction mixture is heated to 8o° C for 24 hours. After cooling, the reaction mixture is poured upon water, the mixture is extracted with ether and the

ethereal layer is washed with water and dried over Na_2SO_4. The ether is evaporated in a vacuum and the residue is purified chromatographically on a column of silicic acid gel using hexane/ethyl acetate as eluant.

Yield: 75 g (66 % of the theoretical), m.p.: 36°C.

IR (KBr): 1680 cm^{-1}

EXAMPLE 3

N-hexadecyl-N-(2-thienyl)-butyric acid amide.

8.6 g of sodium hydride are added to a solution of 55 g of N-(2-thienyl)-butyric acid amide dissolved in 600 cc. of anhydrous DMF. The mixture is stirred until termination of hydrogen formation. Thereafter, 84.7 g of chlorohexadecane and 9.7 g of sodium iodide are added thereto and the reaction mixture is heated to 80°C for 24 hours. After cooling, the reaction mixture is poured into water, the mixture is extracted with ether, the ethereal layer is separated, washed with water and dried over Na_2SO_4. The ether is evaporated in a vacuum and the residue is purified chromatographically on a column of silicic acid gel using hexan/ethyl acetate as eluant.

Yield: 78 g (61 % of the theoretical), m.p.: 36°C.

IR (KBr): 1675 cm^{-1}

EXAMPLE 4

N-(5-Formyl-thien-2-yl)-N-hexadecyl-acetamide.

27 g of N-Hexadecyl-N-(2-thienyl)-acetamide are dissolved in 22 cc. of anhydrous DMF and 14 g of phosphorus oxychloride are added dropwise thereto under cooling with ice, thereby avoiding increase of the temperature of the reaction mixture above 20°C. Stirring is continued for 1 hour at 20°C and the reaction mixture finally is stirred for 3 hours at

80°C. Ice is added to the reaction mixture and 5 N soda lye is added thereto until reaching a pH of 6. The resulting mixture is extracted with ether, the ethereal phase is separated, washed with water and dried over Na_2SO_4. The ether is separated and the residue is purified chromatographically on a column of silicic acid gel using hexane/ethyl acetate as eluant.
Yield: 25 g (86 % of the theoretical), m.p.: 53°C.

EXAMPLE 5

N-(5-Formyl-thien-2-yl)-N-hexadecyl-propionic acid amide.
75 g of N-hexadecyl-N-(2-thienyl)-propionic acid amide are dissolved in 59 cc. of anhydrous DMF and 36.7 g of phosphorus oxychloride are added thereto dropwise with ice cooling such that the temperature of the reaction mixture does not increase above 20°C. Stirring is continued for 1 hour and 20°C and the reaction mixture finally is heated 3 hours to 80°C. Ice is added to the reaction mixture and 5 N soda lye is added until reaching a pH of 6. The resulting mixture is extracted with ether, the ethereal layer is separated, washed with water and dried over Na_2SO_4. The desired final product crystallizes at low temperature from the ethereal solution.
Yield: 57.8 g (72 % of the theoretical), m.p.: 78°C.

EXAMPLE 6

N-(5-Formyl-thien-2-yl)-N-hexadecyl-butyric acid amide.
78 g of N-hexadecyl-N-(2-thienyl)-butyric acid amide are dissolved in 59 cc. of anhydrous DMF and 36.7 g of phosphorus oxychloride are added thereto with ice cooling such that the temperature of the reaction mixture does not rise above 20°C. Stirring is continued for 1 hour at 20°C and

the mixture is finally heated for 3 hours to 8o°C. Ice is added to the reaction mixture and 5 N soda lye is added until reaching a pH of 6. The mixture is extracted with ether, the ethereal layer is separated, washed with water and dried over Na_2SO_4. The desired final product crystallizes from the ethereal solution upon cooling to low temperature.

Yield: 58 g (7o % of the theoretical), m.p.: 66 - 67°C.

As described in Examples 4 to 6 there are further produced:

N-(5-formyl-thien-2-yl)-N-hexadecyl-valerianic acid amide,
N-(5-formyl-thien-2-yl)-N-hexadecyl-capronic acid amide.

EXAMPLE 7

N-Acetyl-N-hexadecyl-5-amino-thien-2-yl-carboxylic acid.

25 g of N-(5-formyl-thien-2-yl)-N-hexadecylacetamide are dissolved in 2o cc. of pyridine. A solution of 6.7 g of potassium permanganate in 9o cc. of pyridine and 4o cc. of water is added with stirring and cooling such that the temperature of the reaction mixture does not rise above -3°C. Stirring is continued until all of $KMnO_4$ has been reacted. Thereafter, the solvents are distilled off, the residue is triturated with dilute hydrochloric acid and the mixture is extracted with chloroform. The chloroform layer is separated, washed with water and dried over Na_2SO_4. The solvent is evaporated and the resulting crude product is purified chromatographically on a column of silicic acid gel using chloroform as eluant.

Yield: 8.4 g (32 % of the theoretical), m.p.: 82°C.

MS (m/e): 4o9 (42 %); 367 (1oo %); 156 (31 %); 43 (13 %).

EXAMPLE 8

N-Hexadecyl-N-propionyl-5-amino-thien-2-yl-carboxylic acid.

57.8 g of N-(5-formyl-thien-2-yl)-N-hexadecyl-propionic acid amide are dissolved in 300 cc. of pyridine. A solution of 14.6 g of $KMnO_4$ in 198 cc. of pyridine and 85 cc. of water is added with stirring and cooling such that the temperature of the reaction mixture does not rise above -3°C. Stirring is continued until all of $KMnO_4$ has been reacted. Thereafter, the solvent is distilled off, the residue is triturated with dillued acid and the mixture is extracted with chloroform. The chloroform layer is separated, washed with water and dried over Na_2SO_4. The solvent is evaporated and the resulting crude product is purified chromatographically on a column of silicic acid gel using chloroform as eluant. Yield: 14.5 g (24 % of the theoretical), m.p.: 88 - 89°C. MS (m/e): 423 (20 %); 367 (100 %); 156 (24 %).

EXAMPLE 9

N-Butyryl-N-hexadecyl-5-amino-thien-2-yl-carboxylic acid.

58 g of N-(5-formyl-thien-2-yl)-N-hexadexyl-butyric acid amide are dissolved in 300 cc. of pyridine. A solution of 13.9 g of $KMnO_4$ in 177 cc. of pyridine and 82 cc. of water are added thereto dropwise with stirring and cooling such that the temperature of the reaction mixture does not rise above -3°C. Stirring is continued until all of $KMnO_4$ has been reacted. The solvents are distilled off, the residue is trituated with dillued hydrochloric acid and the reaction mixture is extracted with chloroform. The chloroform layer is separated, washed with water and dried over Na_2SO_4. The solvent is evaporated and the remaining crude product is purified chromatographically on a column of silicic acid

gel using chloroform as eluant.
Yield: 1o.o g (17 % of the theoretical), m.p.: 79 - 81°C.
MS (m/e): 437 (14 %); 367 (1oo %); 156 (17 %); 71 (16 %).

As described in Examples 7 to 9 there are further more produced:

N-Hexadecyl-N-valeryl-5-amino-thien-2-yl-carboxylic acid,
N-Hexadecyl-N-hexanoyl-5-amino-thien-2-yl-carboxylic acid.

EXAMPLE 1o

Sodium salt of N-acetyl-N-hexadecyl-5-amino-thien-2-yl-carboxylic acid.

N-Acetyl-N-hexadecyl-5-amino-thien-2-yl-carboxylic acid as dissolved in ethanol and neutralized with alcoholic soda lye. The mixture is evaporated to dryness in a vacuum and the solid residue is powdered.
IR (KBr): 1575, 167o cm^{-1}.

As described in Example 1o there are produced the sodium salt of the following acids:

N-Hexadecyl-N-propionyl-5-amino-thien-2-yl-carboxylic acid,
N-Butyryl-N-hexadecyl-5-amino-thien-2-yl-carboxylic acid,
N-Hexadecyl-N-valeryl-5-amino-thien-2-yl-carboxylic acid,
N-Hexadecyl-N-hexanoyl-5-amino-thien-2-yl-carboxylic acid.

EXAMPLE 11

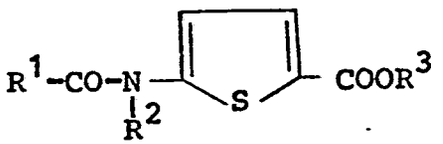
N-Hexadecyl-N-propionyl-5-amino-thien-2-yl-carboxylic acid methyl ester.

1 g of the sodium salt of N-hexadecyl-N-propionyl-5-amino-thien-2-yl-carboxylic acid are suspended in 20 cc. of acetone. 0.8 g of methyl iodide are added dropwise thereto. The mixture is refluxed for 5 hours, the solvent is distilled off and the residue is dissolved in chloroform. The chloroform solution is washed consecutively with an aqueous solution of $NaHCO_3$ and water and thereafter is dried over Na_2SO_4. The solvent is distilled off and the residue is purified chromatographically on a column of silicic acid gel using hexane/ethyl acetate as eluant.

Yield: 0.2 g (20 % of the theoretical), m.p.: 52°C.
IR (KBr): 1710 and 1665 cm^{-1}.
MS (m/e): 437 (23 %); 406 (1 %); 381 (100 %); 170 (25 %).

PATENT CLAIMS:

1. 5-(N-Alkyl-N-acyl-amino)-thiophen-2-carboxylic acid derivatives having the general formula I



I

wherein

R^1 is an alkyl group having from 1 to 5 carbon atoms,

R^2 is an alkyl group having from 12 to 18 carbon atoms,

R^3 is hydrogen, alkali or an alkyl group having from 1 to 3 carbon atoms.

2. 5-(N-Acetyl-N-hexadecyl)-amino-thien-2-yl carboxylic acid and the pharmaceutically compatible salts and esters thereof according to claim 1.

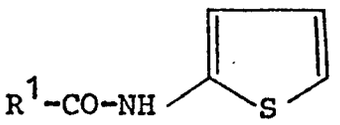
3. 5-(N-Hexadecyl-N-propionyl)-amino-thien-2-yl carboxylic acid and the pharmaceutically compatible salts and esters thereof according to claim 1.

4. 5-(N-Butyryl-N-hexadecyl)-amino-thien-2-yl carboxylic acid and the pharmaceutically compatible salts and esters thereof according to claim 1.

5. 5-(N-Hexadecyl-N-valeryl)-amino-thien-2-yl carboxylic acid and the pharmaceutically compatible salts and esters thereof according to claim 1.

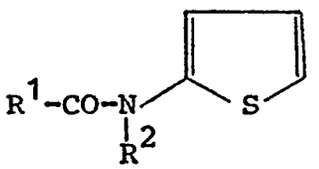
6. 5-(N-Hexadecyl-N-hexanoyl)-amino-thien-2-yl carboxylic acid and the pharmaceutically compatible salts and esters thereof according to claim 1.

7. Process for the production of the 5-acylamino-thiophen-2-carboxylic acid derivatives according to claims 1 to 6, wherein a N-(2-thienyl)-carboxylic acid amide of the general formula II



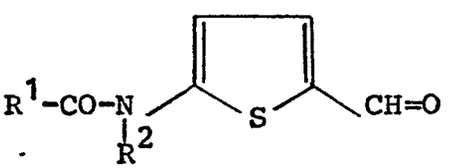
II

wherein R^1 has the same meaning as in formula I, is subjected to reaction with an N-alkylating agent and the resulting N-alkyl-N-(2-thienyl)-carboxylic acid amide of the general formula III



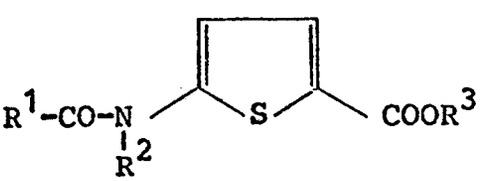
III

wherein R^1 and R^2 have the same meaning as in formula I, is subjected to formylation in the 2-position of the thiophen ring and the resulting aldehyde of formula IV



IV

wherein R^1 and R^2 have the same meaning as in formula I, is subjected to oxydation to the corresponding carboxylic acid of formula I



I

wherein R^3 is hydrogen and, if desired, the resulting 5-acylamino-thiophen-2-carboxylic acid is converted into its alkali salt or ester of formula I.

8. Pharmaceutical preparations comprising a compound according to claims 1 to 6 as active agent desides usual inert carrier materials and/or diluents.

European Patent Office

EUROPEAN SEARCH REPORT

0078860
Application number

EP 81 10 9565

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
A	EP - A - 0 003 663 (AMERICAN CYANAMID) * page 285, example 1520 *	1,7
A	GB - A - 1 548 398 (LILLY IND. LTD.) * pages 12,13; examples 45,46; claims *	1,8

CLASSIFICATION OF THE APPLICATION (Int. Cl. 3)

C 07 D 333/38
A 61 K 31/38//
C 07 D 333/36

TECHNICAL FIELDS SEARCHED (Int.Cl. 3)

C 07 D 333/00
A 61 K 31/00

CATEGORY OF CITED DOCUMENTS

X: particularly relevant if taken alone
Y: particularly relevant if combined with another document of the same category
A: technological background
O. non-written disclosure
P. intermediate document
T: theory or principle underlying the invention
E: earlier patent document, but published on, or after the filing date
D: document cited in the application
L: document cited for other reasons

&: member of the same patent family, corresponding document

X The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	04-06-1982	CHOULY

EPO Form 1503.1 06.78