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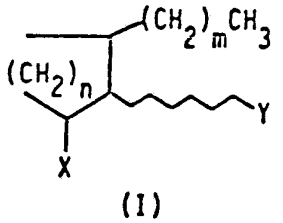

(I)

(57) Abstract

The compounds of formula (I), wherein: n = 2, 3; m = 4, 5, 6, 7; X = NHR, CH_2NHR, $NHNH_2$; R = H, a linear or branched (C_1-C_4)alkyl, a linear or branched (C_1-C_4)acyl; Y = CH_2NH_2, COOH, $CONH_2$ (with the exclusion of the compounds wherein n = 2, m = 5, X = NHR with R = H, a linear or branched (C_1-C_4)alkyl, a linear or branched (C_1-C_4)acyl; Y = COOH, $CONH_2$) including all optical and/or geometrical isomers, alone or in admixture, and their salts, which inhibit the platelet aggregation in the blood and which can be prepared for use as antiplatelet, antithrombotic agents.

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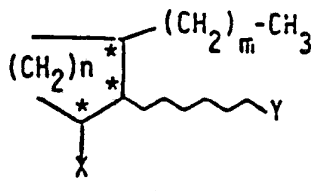
PROSTAGLANDIN-DERIVATIVES HAVING ANTITHROMBOTIC ACTIVITY

The instant invention refers to the activity and use of compounds having a prostaglandin-like structure as well as pharmaceutical compositions thereof, having platelet antiaggregating, antithrombotic activity.

It is known that substances such as ADP, collagen, thrombin , arachidonic acid , favour platelet aggregating phenomena causing the formation of thrombi which are mainly responsible for ischemic,cardio- and cerebro-vascular disorders,atherosclerotic peripheral arterial disorders and venous thrombosis. Thus, substances which are capable of antagonizing their effects are of considerable therapeutic interest.

In the course of studies carried out by the Applicants on prostaglandin-like compounds, possessing antiulcer activity, described in IT 1,190,400 filed on October 4,1985 and in IT 1,205,183 filed on June 25,1987 (corresponding to the PCT patent application No. IT88/00010 of February 10,1988), both owned by the Applicants, it has been discovered that some of the compounds, disclosed therein and corresponding to formula(I) of the instant application, possess antiplatelet, antithrombotic activity.

The compounds of formula (I)



(I)

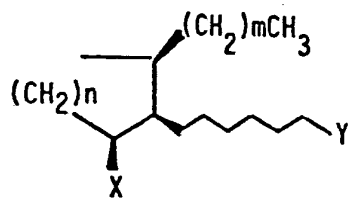
wherein:

n = 2,3; m = 4,5,6,7; X = NHR, CH_2NHR, $NHNH_2$, wherein R = H, a linear or branched (C_1-C_4)alkyl, a linear or branched (C_1-C_4)-acyl; Y = CH_2NH_2, COOH, $CONH_2$ (with the exclusion of the compounds wherein n = 2, m = 5, X = NHR with R = H, a linear or branched (C_1-C_4)alkyl, a linear or branched (C_1-C_4)acyl; Y = COOH, $CONH_2$) possess 3 asymmetric carbon atoms identified by an asterisc, wherefore 8 stereoisomers are possible.

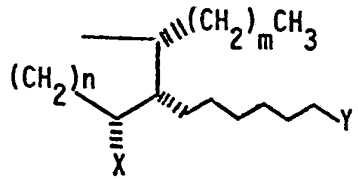
Therefore, when not otherwise specified, the above formula (I) includes all possible stereoisomers, all possible combinations of two or more such stereoisomers, of enanthiomers or mixtures of enanthiomers in any proportion.

The four pairs of possible enanthiomers indicated by the code Nos.IBI-P-(I)A, IBI-P-(I)B, IBI-P-(I)C, IBI-P-(I)D, are represented as follows:

IBI-P-(I)A

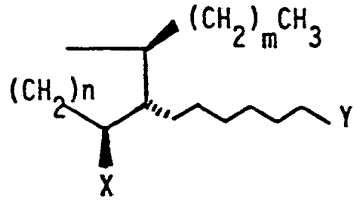


(cis-cis)

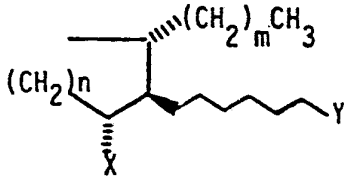


(cis-cis)

IBI-P-(I)B

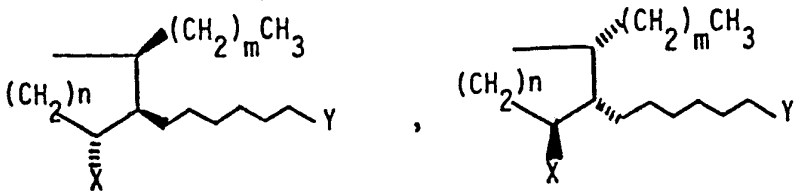


(trans-trans)



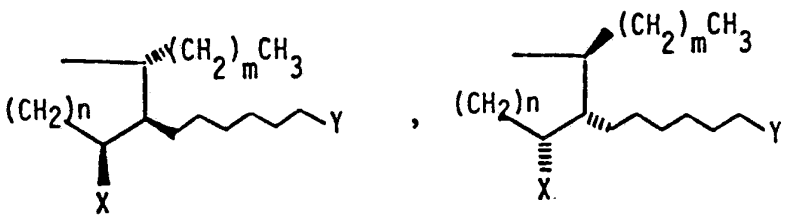
(trans-trans)

IBI-P-(I)C



(trans-cis) (trans-cis)

IBI-P-(I)D



(cis-trans) (cis-trans)

wherein, considering the planar or almost planar ring, lying in the horizontal plane of the sheet, as is customary in chemical literature, the broken lines indicate that a particular substituent lies below the molecular plane, while the full lines in the form of a wedge indicate that a particular substituent lies above the molecular plane. The prefices cis and trans are used to indicate the relative position of the substituents with respect to one another.

More particularly, the instant invention relates to prostanoic compounds of the above cited formula (I), useful for preparing pharmaceutical compositions having antiplatelet, antithrombot-

ic activity.

It is reiterated that the compounds of formula (I) are the subject matter of IT 1,190,400 filed on October 4,1985 and of IT 1,205,183 filed on June 25,1987, of which Applicants are the proprietors, wherein their activity as antiulcer agents and their use for preparing pharmaceutical compositions are described, and, therefore, they are not being claimed, per se, herein, whereas Applicants wish to protect their use as inhibitors of platelet aggregation and antithrombotic agents.

The compounds of formula (I) wherein n = 2, m = 5, X = NHR with R = H, a linear or branched (C_1-C_4)alkyl, a linear or branched (C_1-C_4)acyl, Y = COOH, $CONH_2$, fall within the scope of IT 1,060,366 filed on August 7,1974, owned by Applicants, which discloses their activity as inhibitors of platelet aggregation and hence such compounds are excluded from the present invention.

The present invention includes also the pharmaceutically acceptable cationic salts of the compounds of formula (I) when Y = COOH and, in general, the pharmaceutically acceptable anionic salts.

As used herein, the expression "pharmaceutically acceptable cationic salts" refers to the alkali and alkaline-earth metal salts such as, e.g. sodium, potassium, calcium, magnesium, or salts of aluminum, ammonium, zinc and of organic amines, including the amino acids such as, e.g. lysine,arginine, phenylalaline and proline, triethanol amine, inner salts and salts of basic resins.

As used herein, the expression "pharmaceutically acceptable anionic salts" refers to salts obtained by the addition of hydrochloric, hydrobromic, nitric, phosphoric, sulfuric,

benzenesulfonic, benzoic, citric, laurylsulfonic, fumaric,oxalic, maleic, methanesulfonic, tartaric, ascorbic, p-toluenesulfonic, salicylic and succinic acid.

With polybasic acids, the salt may include more than one mole of base per mole of acid. However, the salts obtained from one mole of acid per mole of the inventive compound are preferred.

The present invention, lastly, refers to pharmaceutical compositions containing a compound of formula (I) or a pharmaceutically acceptable anionic or cationic salt thereof.

The preparation of some of the compounds of formula (I) has already been described in IT 1,190,400 of October 4,1985 and IT 1,205,183 filed on June 25,1987.

For example, in said patents is described the preparation of the compounds of formula (I) wherein:

n = 2, m = 5, X = CH_2NH_2, Y = COOH (IBI-P-01058)

n = 2, m = 5, X = $NHNH_2$, Y = COOH (IBI-P-01062)

n = 2, m = 5, X = NH_2, Y = CH_2NH_2 (IBI-P-01068)

n = 3, m = 5, X = NH_2, Y = COOH (IBI-P-05006)

n = 3, m = 5, X = CH_2NH_2, Y = COOH (IBI-P-05011)

n = 3, m = 5, X = NH_2, Y = CH_2NH_2 (IBI-P-05012)

n = 2, m = 6, X = NH_2, Y = COOH (IBI-P-12004)

Here below is given, for illustrative purposes only, the preparation of the compounds of formula (I) wherein:

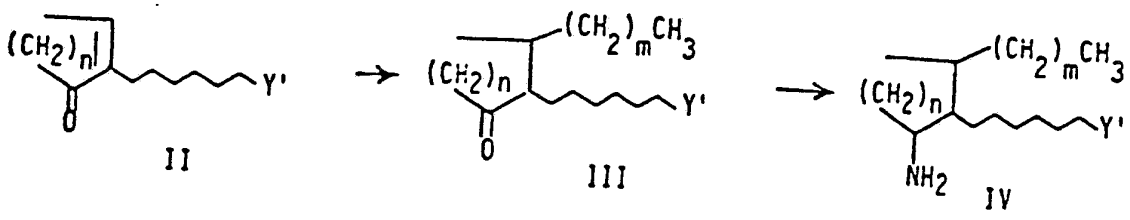
n = 2, m = 4, X = NH_2, Y = COOH (IBI-P-12003)

n = 2, m = 7, X = NH_2, Y = COOH (IBI-P-12005)

n = 3, m = 5, X = NH_2, Y = COOH (IBI-P-05006)

which may be prepared according to the reaction scheme I :

SCHEME I

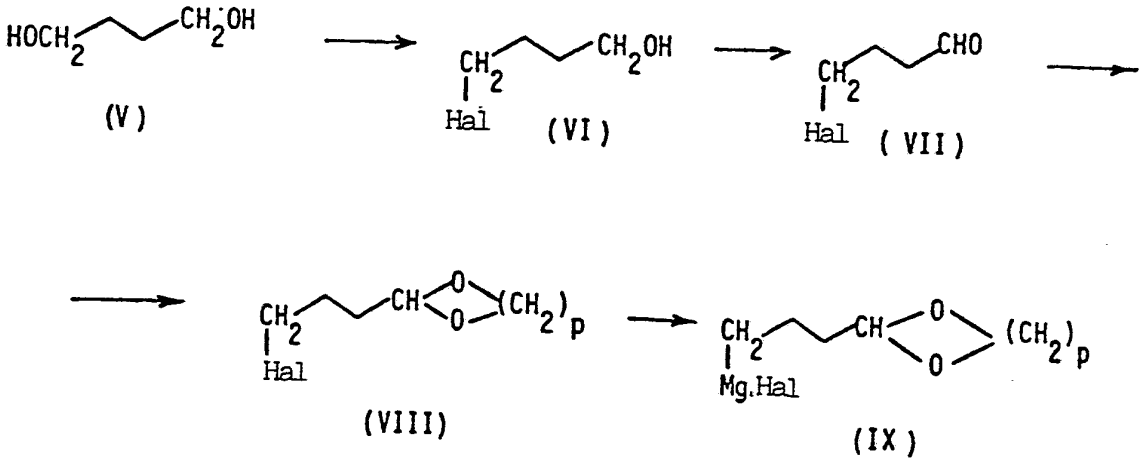


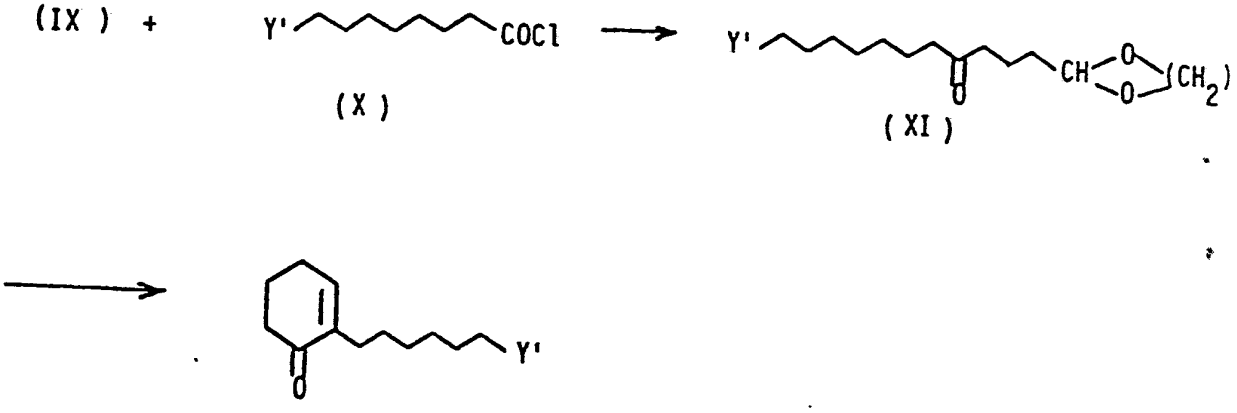
wherein Y' = CH_2NH_2, $CONH_2$, COOR' and R' = a linear or branched $H(C_1-C_4)$alkyl.

The cycloalkenone of formula (II), when n = 2, may be prepared as described in IT patent application 19043 A/84 of January 5,1984 (continuation-in-part U.S.S.N. 117669 of November 5, 1987 of U.S. application S.N. 744406 of June 13,1985) owned by Applicants.

It has now been found that when n = 3, Y' = $COOCH_3$, the cycloalkenone of formula (II) may be prepared according to the following reaction scheme II:

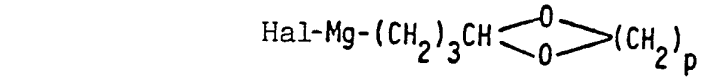
SCHEME II





(II) with n = 3;Y = $COOCH_3$; Hal = Cl,Br,I.

The monochloride of 8-carbomethoxy-octanoic acid (X)(prepared as disclosed in IT patent application 19043 A/84) is condensed as a Grignard compound of formula (IX)



(IX)

wherein Hal = Cl,Br,I; p = 2, 3
in inert polar solvents such as, e.g. tetrahydrofuran, ethyl ether, butyl ether, dioxane, dimethylformamide.

The acetal of the 1,5-dicarbonyl compound(XI),prepared by Grignard condensation, can be cyclized by acid catalyzed,intramolecular crotonic condensation, in a suitable solvent, yielding the desired compound of formula (II).

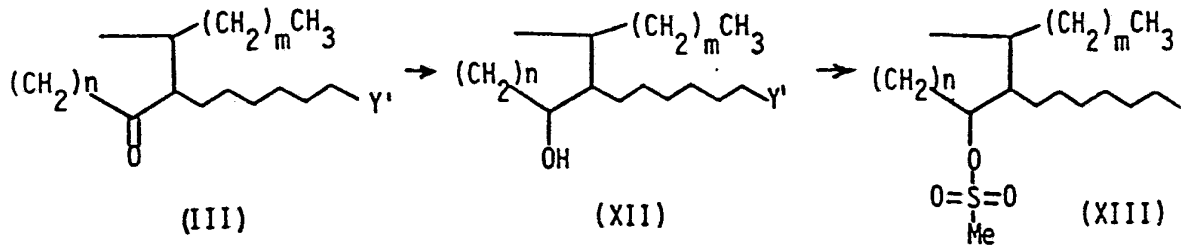
The compounds of formula (IX) may be prepared according to methods known from the literature, for example by monohalogenation of the 1,4-butanediol (V) performed as described by Suk-Ku-Kang in Synthesis,1161 (1985),oxydation of the aldehyde (VII) of the ω-halobutanol (VI) with a catalytic process employing sodium hypochlorite as the oxydizing agent and the free radical 2,2,6,6-tetramethyl-piperidinyl-1-oxyl as the catalyst, as described by P.L.Anelli,C.Biffi, F.Montanari in J.Org.Chem.52,2559 (1987) and the subsequent protection of the carbonyl group of the compounds of formula (VII), with ethylene glycol or with 1,3-propanediol, and the subsequent transformation into a Grignard reagent, viz. the compound of formula (IX).

As described in IT 1,205,183 filed on June 25,1987, the cycloalkenone of formula (II) may be transformed into the cycloalkanone of formula (III) wherein m = 4,5,6 and 7, using a Grignard reagent such as, e.g. $CH_3(CH_2)_m$ MgHal (Hal= Cl,B,I) in the presence of copper salts such as,e.g. CuCl, $Cu(OAc)_2$,CuCN, CuI,$CuCl_2$. Polar

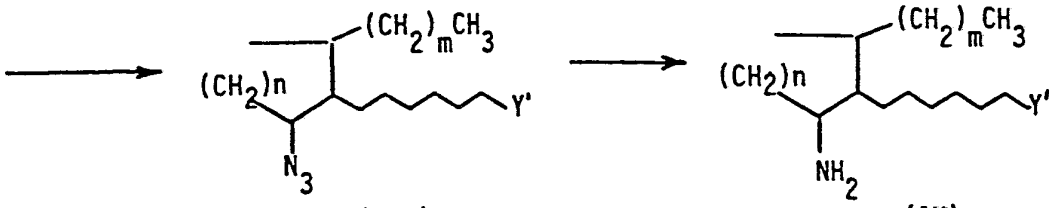
and inert solvents are generally used such as, e.g. tetrahydrofuran, dimethyl-formamide, ethyl ether, butyl ether.

The compounds of formula (IV) can be prepared from the corresponding cycloalkanones (III) by using per se known reactions such as e.g. reductive aminations with ammonia, hydrogen and metal catalysts, in alcoholic solvents, at a temperature of from 30° to 100°C and at a pressure of from 1 to 20 atms according to reaction scheme I, or according to methods known from the technical literature, according to scheme III:

SCHEME III



(III) (XII) (XIII)



(XIV) (IV)

through reduction of the cycloalkanones of formula (III) to the alcohols (XII) with hydrides selected among lithium aluminum hydride, sodium boronhydride, lithium tri-sec-butyl boronhydride, lithium dicyclohexyl-tert-butyl boronhydride, lithium di-sec-

butyl hexyl boronhydride, lithium diisobutyl-tert-butyl boronhydride; preparation of the mesilate (XIII),substitution of the mesilate with sodium azide to yield the compounds of formula(XIV) and subsequent reduction with metal catalysts and hydrogen. As disclosed in IT 1,205,183 filed on June 25,1987, the compounds of formula (IV) can subsequently be converted into the compounds of formula (I), e.g. wherein Y = COOH and X = NH_2, in aqueous, or aqueous alcoholic, or alcoholic solutions, of bases such as,e.g. NaOH,KOH, K_2CO_3, which are capable of hydrolizing the carbalcoxy group.

The compounds of formula (I) prepared according to the processes of the instant invention, when not otherwise specified, generally consist of mixtures of the stereoisomers in ratios depending on the route of synthesis, on the reagents used and the experimental conditions.

The desired enanthiomer pairs can be prepared by separating the stereoisomeric mixtures by methods known to the man skilled in the art.

It is, for example, possible to isolate chromatographically a pair of enanthiomers from a mixture containing all the stereoisomers of the compounds of formula (I) or of formula (IV); as stationary phase one can use e.g. acid alumina, neutral alumina, basic alumina, cellulose, charcoal, silica, Amberlite XAD 2 (Fluka), Amberlite IRC 50 (Fluka); and as eluent it is possible to use a solvent or a solvent mixture selected among e.g.ethanol, methanol, ethyl acetate, acetone, ethyl ether,methylene chloride, chloroform, hexane, petrol ether, per se or in admixture with bases such as e.g. diethylamine, isopropylamine, triethylamine and ammonium hydroxide. The thus separated enanthiomer pairs of the compounds of formula (IV) yield the corresponding enanthiomer

pairs of formula (I), by saponification with suitable bases, in alcoholic or hydroalcoholic solvents.

It is possible to prepare an enthiometer pair of formula(I) by fractional crystallization of salts of stereoisomer mixtures of the compounds of formula (I) or of formula (IV), prepared by addition of inorganic or organic acids selected e.g. among the following acids: hydrochloric, hydrobromic, nitric, phosphoric, sulfuric, benzenesulfonic, p-toluenesulfonic, methanesulfonic, acetic, trifluoroacetic,oxalic, maleic, benzoic, in solvents or solvent mixtures selected among e.g. isopropanol, ethanol, methanol, ethyl ether, diisopropyl ether, dioxane, tetrahydrofuran, chloroform, methylene chloride, benzene, toluene, at a temperature of from -20° and +40°C and subsequent reaction with bases to yield the desired enanthiomer pairs in their free form.

It is furthermore possible to prepare each enanthiomer pair of the compounds of formula (I) by chromatographically separating the mixture of the stereoisomer alcohols (XII) prepared by reduction with stereoselective reducing agents as described by C.H.Brown, S.Kirishnamurthy in J.Am.Chem.Soc. 7159 (1972), or by reduction with reducing agents having a low steric demand (Scheme III) of the compounds of formula (III) and subsequent conversion into the corresponding mesilate, substitution with sodium azide and reduction with hydrogen and metal catalysts.

The instant invention shall now be further described by the following examples illustrating the preparation of the compounds of formula (I), of the intermediates of formula (I) as well as of the enanthiomer pairs.

Example 1

2-(6'-carbomethoxy-n-hexyl)-2-cyclohexene-1-one (a derivative of formula(II) wherein n = 3 and Y' = $COOCH_3$).

a) A suspension of magnesium (19.6 g) in tetrahydrofuran (220 ml) is added with a solution of 2-(4-bromobutyl)-1,3-dioxolane (prepared according to reaction scheme II) in tetrahydrofuran (1600 ml) keeping the temperature at 20-25°C, at the end of which the reaction mixture is kept under stirring for further 60 min. The reaction mixture is cooled to -45°C and added with the monochloride of 8-carbomethoxy-octanoic acid (prepared according to the method disclosed in IT patent application 19043 A/84 of January 5,1984), keeping the temperature between -40° and -45°C. The reaction mixture is stirred for 5 hrs at -15°C, at the end of which a 15% solution of sodium chloride(120 ml) and ethyl ether (120 ml) is added thereto.

The organic phase is separated, washed to neutrality with a sodium chloride aqueous solution; it is then anhydrated on sodium sulfate and the solvent is evaporated under reduced pressure yielding 125 g of crude 2-(11-carbomethoxy)4-oxo-n-undecyl)-1,3-dioxolane which is used without any further purification.

b) A solution of the compound (125 g) prepared according to the preceding step (a) dissolved in tetrahydrofuran (1000 ml) is reacted 16 hrs at room temperature with 6N hydrochloric acid (300 ml).

At the end, the reaction mixture is extracted with methylene chloride (2 x 300 ml), and the organic phase is washed to neutrality with a 10% brine solution.

It is then anhydrated over Na_2SO_4 and the solvent is distilled off under reduced pressure. The thus obtained crude material

contains, as the main by-product, 2-(6'-carboxy-n-hexyl)-cyclohexene-2-one which is converted into the title compound by reaction with methanol and p-toluenesulfonic acid. The thus prepared compound is distilled at 0.3 mmHg whereby the fraction having a b.p. of 140°-142°C is collected; 60 g of the title compound is obtained.

Analytical Data

B.p. : 140°-142°C at 0.3 mmHg

I.R. (ν max) = 1740 cm^{-1}, 1675 cm^{-1}

NMR (δ) = 6.75 (m,1H); 3.7(s,3H); 2.2 (m,8H); 1.5 (m,10H)

Calculated : C = 70.56% H = 9.30%

Found : C = 70.47% H = 9.21%

Example 2

2-(6'-carbomethoxy-n-hexyl)-3-n-hexyl-cyclohexanone (a derivative of formula (III) wherein n = 3, Y' = $COOCH_3$).

This derivative is prepared according to the process disclosed in IT Pat.Appln. 19043 A/84 filed on January 5,1984, by reacting 2-(6'-carbomethoxy-hexyl)-2-cyclohexene-1-one) (41 g) with bromohexane (52 g) and CuI (3.3 g); 48.3 g of the title compound is obtained.

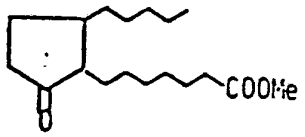
Analytical Data

I.R. (ν max) : 1740 cm^{-1}, 1710 cm^{-1}

NMR (δ) = 3.7 (s, 3H);3.6-1.1 (m, 30H); 0.95 (s, 3H)

Example 3

2-(6'-carbomethoxy-hexyl)-3-pentyl-cyclopentanone



This derivative is prepared, as described in example 2, by react-

ing 2-(6'-carbomethoxy-hexyl)-2-cyclopentene-1-one (67 g) with Mg (14.4 g), bromopentane (96.6 g) and CuI (5.7 g) yielding 73 g of the title compound.

I.R. (ν max) : 1740 cm^{-1}

Example 4

2-(6'-carboxyhexyl)-3-pentyl-cyclopentanone

The compound of example 3 is dissolved in methanol (300 ml) and treated with a solution of NaOH (24 g) in water (300 ml).

The reaction mixture is refluxed under stirring to completion of the reaction. Then it is cooled, acidified to pH 2, extracted with methylene chloride (250 ml) and washed with water to neutrality. The reaction mixture is anhydrated and the solvent is distilled off; 68 g of the title compound is obtained.

Example 5

2-(6'-carboxyhexyl)-3-pentyl-cyclopentylamine (a derivative of formula (I) wherein n = 2, m = 4, X = NH_2, Y = COOH(IBI-P-12003)

The compound of example 4(68 g) is reacted with methanol (1000 ml), ammonia (200 g), PtO_2 (3 g), at a temperature of from 40 - 60°C, in an autoclave, and left for 3 days under hydrogen pressure, yielding 42 g of a solid white compound.

Analytical data:

m.p. = 166°-168°C

I.R. (ν max) : 3300 cm^{-1}, 1560 cm^{-1}

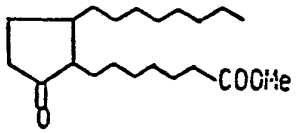
NMR (δ) = 4.6 (s, 3H); 2.8 (m, 1H); 1.2(m, 26H); 0.9(t,3H)

Titer (as base) = 96%

Calculated:	C = 72.08%	H = 11.66%	N = 4.95%
Found :	C = 71.92%	H = 11.72%	N = 4.98%

Example 6

2-(6'-carbomethoxy-hexyl)-3-octyl-cyclopentanone



This derivative is prepared in an analogous manner to that described in example 3, using as the starting material 2-(6'-carbomethoxy-hexyl)-2-cyclopentene-1-one (67 g); yield : 78 g of the title compound.

I.R. (ν max) : 1740 cm^{-1}

Example 7

2-(6'-carboxyhexyl)-3-octyl-cyclopentylamine (a derivative of formula (I) wherein n= 2,m = 7, X = NH_2, Y = COOH (IBI-P-12005)

This derivative is prepared in analogous manner to that described in example 5, using as the starting material 2-(6'-carboxyhexyl)-3-octyl-cyclopentanone (75 g). Finally, 34 g of a solid white material is yielded.

Analytical Data

m.p. = 152° - 154°C

I.R. (ν max) : 3300 cm^{-1}, 1560 cm^{-1}

NMR (δ) = 4.6 (s,3H); 2.8 (m,1H); 1.2 (m,32H); 0.9 (t,3H)

Titer (as base) = 98%

Example 8

2-(6'-carbomethoxy-hexyl)-3-n-hexyl-cyclohexylamine

A suspension of 2-(6'-carboxyhexyl)-3-n-hexyl-cyclohexylamine (200 g) (IBI-P-05006, a compound disclosed in IT 1,205,183 filed on June 25,1987), in methanol (100 ml), is added with p-toluenesulfonic acid.

The reaction mixture is refluxed three hours, cooled to room temperature, then the solvent is concentrated under reduced pressure and the reaction mixture is added with a 1N NaOH aqueous solution (1000 ml) and extracted with ethyl ether (2x300 ml).

The organic phase is washed to neutrality with a 20% brine and anhydrated over Na_2SO_4, the solvent is distilled off under

reduced pressure, yielding 203 g of a colorless oil.

Analytical Data

I.R. (ν max) : 1745 cm^{-1}, 1670 cm^{-1}

Calculated : C = 73.85% H = 12.00% N = 4.31%

Found : C = 73.90% H = 12.11% N = 4.27%

Example 9

R,S-cis-2-(6'-carbomethoxy-hexyl)-cis-3-n-hexyl-cyclohexylamine

A solution of 2-(6'-carboxymethoxy-hexyl)-3-n-hexyl-cyclohexylamine(100 g)in methanol(500 g)is added with p-toluenesulfonic acid (61.4 g) and stirred for 15 min at room temperature, whereupon the solvent is distilled off under reduced pressure: a white solid material is obtained.

The thus obtained solid material is suspended in ethyl ether (500 ml) and stirred for 60 min at room temperature.

The reaction mixture is filtered on a Büchner funnel and the solid material is dessicated, yielding 104 g R,S-cis-2-(6'-carbomethoxy-hexyl)-cis-3-n-hexyl-cyclohexylamine p-toluenesulfonate.

The thus obtained solid is treated with water (250 ml) and with a 1N NaOH aqueous solution (250 ml),stirred 10 min and extracted with ethyl ether (500 ml): the organic phase is then washed to neutrality with a 20% brine,anhydrated over Na_2SO_4 and the solvent is distilled off under reduced pressure.

Yield: 43.5 g of a colorless oil.

Elemental Data

I.R. (ν max) : 1745 cm^{-1}, 1675 cm^{-1}

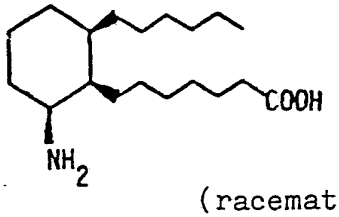
NMR (δ): 3.6 (s,3H); 2.69 (m,1H); 2.27 (t, 2H); 1.6-0.9(broad, 30H); 0.85 (t, 3H)

Calculated: C = 73.85% H = 12.00% N = 4.31%

Found : C = 73.79% H = 11.95% N = 4.37%

Example 10

R,S-cis-2-(6-carboxyhexyl)-cis-3-n-hexyl-cyclohexylamine (IBI-P-05006A)



(racemate)

The compound (40 g) of example 9 is dissolved in methanol(400 ml) and added with a potassium carbonate (34.2g) water (60 ml) solution. The reaction mixture is refluxed three hours; it is then cooled and the solvent is distilled off under reduced pressure. The reaction mixture is then added with water (250 ml),acidified to pH 5.6-5.8 with a 3N HCl solution, filtered off, washed with water, acetone, and dessicated under reduced pressure yielding 36 g of a white solid compound.

Analytical data

m.p. = 208°-210°C

Titer (as base) = 98.67%

Calculated :	C = 73.31%	H = 11.90%	N = 4.50%
Found :	C = 73.41%	H = 12.00%	N = 4.61%

Example 11

R,S-cis-2-(6'-carbomethoxy-hexyl)-cis-3-n-hexyl-cyclohexanol

a) 2-(6'-carboxyhexyl)-3-n-hexyl-cyclohexanol (125 g) is reacted with a 1N lithium-tri-sec-butylboronhydride solution in THF (800 ml) according to the method described by H.C.Brown et al in J.Am.Chem.Soc. 7159 (1972),yielding 130 g of an oily material essentially consisting of a mixture of R,S-cis-2-(6'-carboxyhexyl)-cis-3-n-hexyl-cyclohexanol and of R,S-cis-2-(6'-carboxyhexyl)-trans-3-n-hexyl-cyclohexanol.

Analytical data:

I.R. (ν max) : 3400 cm^{-1}, 1710 cm^{-1}

b) The thus obtained compound is dissolved in methanol (750 ml) and added with p-toluenesulfonic acid (12.5 g).
The reaction mixture is refluxed 90 min, cooled and the methanol is concentrated under reduced pressure; the reaction mixture is then added with water (600 ml) and ethyl ether (400 ml).
The organic phase is washed with a 20% brine, anhydrated over Na_2SO_4 and the solvent is distilled off under reduced pressure, yielding a yellow oil (124.3 g) consisting of a mixture of R,S-cis-2-(6'-carbomethoxyhexyl)-cis-3-n-hexyl-cyclohexanol and of R,S-cis-2-(6'-carbomethoxyhexyl)-trans-3-n-hexyl-cyclohexanol.
Chromatographing the stereoisomer mixture by silica T.L.C., using as the eluent a 7:3 hexane:ethyl acetate mixture, the cis-cis enanthiomer pair gives a R.f. = 0.50 whereas the cis-trans enanthiomer pair gives a R.f. = 0.59.
The stereoisomer mixture is chromatographed on silica gel column using as the eluent a 7:3 hexane:ethyl acetate mixture, recovering the enanthiomer pair having a R.f. = 0.50.
Yield: 70 g of the title compound.

Analytical Data

I.R. (ν max): 3450 cm^{-1}, 1742 cm^{-1}

NMR (δ): 3.70 (m, 1H); 3.68 (s,3H), 2.3 (t,2H); 1.8-1(broad, 29H); 0.87 (t,3H).

Calculated: C = 73.61% H = 11.66%

Found : C = 73.55% H = 11.71%

Example 12

R,S-trans-2-(6'-carbomethoxyhexyl)-cis-3-n-hexyl-cyclohexyl-azide

A solution of R,S-cis-2-(6'-carbomethoxyhexyl)-cis-3-hexyl-

cyclohexanol (70 g) in methylene chloride (350 ml) is added with triethylamine (51.7 ml) and methanesulfonyl chloride (34.3 g) is added dropwise, at a temperature of from 0° to 5°C; the reaction mixture is reacted 30 min at the same temperature and at the end it is poured into water (600 ml). The various phases are separated; the organic phase is washed to neutrality with a 10% brine, anhydrated over Na_2SO_4 and the solvent is distilled off under reduced pressure, whereby 93.9 g of a clear oil is obtained. (I.R. (ν max): 1740 cm^{-1}, 1340 cm^{-1}, 1170 cm^{-1}). That residue is taken up with water (850 ml), added with NaN_3 (37.4 g), hexadecyltributylphosphonium bromide (12.22 g) and stirred 4 hours at 65°C.

At the end, the reaction mixture is cooled and extracted with ethyl ether (500 ml). The organic phase is then washed with a 20% brine, anhydrated over Na_2SO_4, and the solvent is distilled off under reduced pressure, yielding 96 g of an orange oil. The material is purified by silica gel chromatography, eluting with 95:5 hexane:ethyl acetate.

Yield: 42 g of the title compound.

Analytical Data

I.R. (ν mx) : 2100 cm^{-1}, 1745 cm^{-1}

Example 13

R,S-trans-2-(6'-carbomethoxyhexyl)-cis-3-n-hexyl-cyclohexyl-amine

A solution of R,S-trans-2(6'-carbomethoxyhexyl)-cis-3-n-hexyl-cyclohexylazide (42 g) in methanol (400 ml) ethyl ether (200 ml) is added with 5% Pd/C (4 g).

The reaction mixture is then shaken 5 hours under hydrogen atmosphere, then the catalyst is filtered off and the solvent is distilled off under reduced pressure; the residue is chromato-

graphed on silica gel using an 80:20:0.5 hexane:acetone:ammonia mixture as the eluent.

Yield: 9.6 g of an oily material consisting essentially of the title compound.

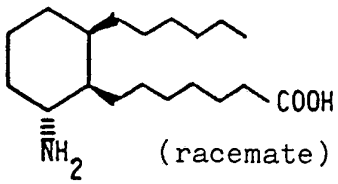
Analytical Data

I.R. (ν max): 1745 cm^{-1}, 1675 cm^{-1}

NMR (δ) : 3.65 (s,3H); 2.65 (m,1H); 2.25 (t,2H); 1.7-1(broad, 30H); 0.82 (t, 3H)

Example 14

R,S-trans-2-(6'-carboxyhexyl)-cis-3-n-hexyl-cyclohexylamine (IBI-P-05006C)



(racemate)

9.6 g of R,S-trans-2-(6'-carbomethoxyhexyl)-cis-3-n-hexyl-cyclohexylamine is treated in the same way as described in example 10.

Yield: 5.2 g of the title compound as a white solid.

Analytical Data

m.p. = 154°-156°C.

I.R. (ν max): 1580 cm^{-1}

Calculated:	C = 73.31%	H = 11.90%	N = 4.5%
Found :	C = 73.28%	H = 11.97%	N = 4.45%

Titer (as base) 99.3%

The activity of the inventive compounds as platelet aggregation inhibitors and as antithrombotic agents has been investigated in vitro determining the percent inhibition of the platelet aggregation induced by ADP, collagen, arachidonic acid and thrombin using platelet-rich plasma (hereinafter referred to as PRP) of mammals according to G.V.R.Born: Nature 194, 927-929 (1962) and G.V.R.Born and M.J.Cross:Physiol.168,178-195(1963).

1) Inhibition of platelet aggregation by added ADP with rat PRP

The tests are conducted with rat PRP (500,000 platelets/mm^3) adding a compound of formula (I) or a pharmacologically acceptable salt thereof so that its plasma concentration be 10^{-4} M incubating 9 min at room temperature; whereupon as aggregating agent ADP (3 /uM) is added and the percent inhibition of the platelet aggregation is measured using the turbidimetric method of Born and Cross (Table 1).

2) Inhibition of platelet aggregation by added collagen with rat PRP

The test is carried out as described sub 1) (inhibition of platelet aggregation by added ADP), using collagen (3 mcg/ml) as the aggregating agent (Table 1).

3) Inhibition of platalet aggregation by added arachidonic acid with rat PRP

The test is carried out as described sub 1) (inhibition of platelet aggregation by added ADP), using arachidonic acid (200 /uM) as the aggregating agent (Table 1).

4) Inhibition of the platalet aggregation by added thrombin with rat PRP

The test is carried out as described sub 1) (inhibition of platelet aggregation by added ADP), using thrombin (0.1 U/ml) as the aggregating agent. The transmittance measurements have been effected with a Chromo-Log or Elvi 840 aggregometer.

TABLE 1

COMPOUND	Percentage of inhibition of platelet aggregation with rat PRP, with added:			
	ADP	Collagen	Arachidonic acid	Thrombin
2-(6'-carboxyhexyl)-3-hexyl-aminomethyl-cyclopentane (IBI-0-01058)	18	26	96	95
/2-(6'-carboxyhexyl)/-3-hexyl-cyclopentyl hydrazine chloride (IBI-P-01062)	35,6	82	62	47
2-(7'-aminoheptyl)-2-hexyl-cyclopentyl-amine (IBI-P-01068)	100	100	100	100
2-(6'-carboxyhexyl)-3-hexyl-cyclohexyl-amine (IBI-P-05006)	10	100	100	67,5
2-(6'-carboxyhexyl)-3-hexyl-aminomethyl-cyclohexane (IBI-P-05011)	11,6	69,7	100	100
2-(7'-aminoheptyl)-3-hexyl-cyclohexyl-amine (IBI-P-05012)	100	---	98	---
2-(6'-carboxyhexyl)-3-pentyl-cyclopentylamine (IBI-P-12003)	10	73	66	10
2-(6'-carboxyhexyl)-3-heptylcyclopentyl-amine (IBI-P-12004)	24	93	100	96,6
2-(6'-carboxyhexyl)-3-octyl-cyclopentyl-amine (IBI-P-12005)	13,5	70	100	100
R,S-cis-2-(6'-carboxyhexyl)-cis-3-n-hexyl-cyclohexylamine (IBI-P-05006 A)	<10	100	100	15
R,S-trans-2-(6'-carboxyhexyl)-cis-3-n-hexyl-cyclohexylamine (IBI-P-05006 C)	<10	100	100	45,5

The compounds of formula (I) wherein n = 2, m = 5, X = NHR with R = H, a linear or branched (C_1-C_4)alkyl, a linear or branched (C_1-C_4)acyl; Y = COOH ,$CONH_2$ disclosed in IT 1,060,366 filed on August 7,1974 of which Applicants are the owner, have shown a very low inhibition of platelet function, antithrombotic activity.

Table 2 illustrates the percent inhibition of platelet function with rat PRP, determined under the same conditions and at the same compound concentrations (10^{-3}M) as well as at the same concentration of the aggregation favoring agent as used in the above described tests of platelet function, for example for the compounds according to the above referred formula (I) wherein :

n = 2, m = 5, X = NH_2, Y = COOH (IBI-P-01009)

n = 2, m = 5, X = $NHCOCH_3$, Y = COOH (IBI-P-01012)

n = 2, m = 5, X = $NHCH_3$, Y = COOH (IBI-P-01013)

n = 2, m = 5, X = $NHCH(CH_3)_2$, Y = COOH (IBI-P-01015

n = 2, m = 5, X = NH_2, Y = $CONH_2$ (IBI-P-013036).

TABLE 2

(COMPARISON)

COMPOUNDS OF IT 1,060,366 EXCLUDED FROM THE INSTANT INVENTION	Percentage of inhibition of the platelet aggregation with rat PRP, added with			
	ADP	Collagen	Arachidonic Acid	Thrombin
2-(6'-carboxyethyl)-3-hexyl-cyclopentylamine	<10	15,4	75,6	---
N-/2-(6'-carboxyhexyl)-3-hexyl-cyclopentyl/acetamide	<10	inactive	---	---
N-/2-(6'-carboxyhexyl)-3-hexyl-cyclopentyl/-N'-methylamine	<10	61	16,3	---
N-/2-(6'-carboxyhexyl)-3-hexyl-cyclopentyl/-N'-isopropylamine	<10	inactive	12	---
2-(6'-carbamoylhexyl)-3-hexyl-cyclopentylamine	25	60	65	45

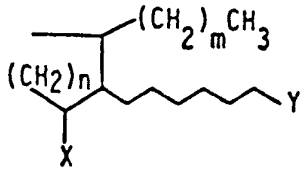
It therefore can be seen that the compounds subject of the instant invention show an antiplatelet, antithrombotic activity which is surprisingly higher(more than 10 times)over that of the compounds disclosed in IT 1,060,366 filed on August 7,1984.

The compounds of the instant invention are preferably administered as pharmaceutical compositions in admixture with one or more pharmacologically acceptable diluents and/or carriers.

Within the scope of the instant invention the expression "pharmacologically acceptable diluents and/or carriers" refers to substances such as e.g. starch and derivatives thereof (e.g. maize starch, STA RX 1500®, which is a registered tradename of Colacon Ltd., Orpington, Kent, rice starch,carboxymethyl starch); cellulose and derivatives thereof (e.g. Avicel®, registered tradename of FMC Corporation, Philadelphia, U.S.A., and methyl cellulose, ethyl cellulose, hydroxypropylmethyl cellulose); silicates and silica oxides (e.g.talc,hydrated calcium silicate,Mg and Al silicates, Aerosil®, registered tradename of Wacker-Chemie GmbH, Munich, Fed.Repub.of Germany, Syloid®, registered tradename of W.R.Grace & Co., New York, U.S.A.); ionic solid surfactants (e.g.sodium laurylsulfate) and non-ionic surfactants (e.g. fatty acid esters of saccharose); acrylic derivatives and polymers thereof; alkali and alkaline-earth metal sulfates, carbonates and phosphates; polyvinyl pyrrolidone and derivatives thereof. Preferably, the inventive compounds are administered orally (e.g. as tablets, capsules, granules, syrups) or parenterally (i.v. or i.m.). Although the dosages may vary according to the symptoms, sex, body weight and conditions of the patient as well as to the frequency of the route of administration, the inventive compounds can be administered orally to an adult at a daily dose of from 1 to 2000 mg, preferably of from 10 to 1000 mg, per single dose, or in doses subdivided over a period of 24 hours.

C L·A I M S

1. The use of a compound of formula (I)



(I)

including all possible opticical and/or geometrical isomers wherein:

n = 2,3; m = 4,5,6,7; X = NHR, CH_2NHR, $NHNH_2$, wherein R = H, a linear or branched (C_1-C_4)alkyl, a linear or branched (C_1-C_4)-acyl, Y = CH_2NH_2, COOH, $CONH_2$, with the exclusion of the compounds according to formula (I) wherein n = 2, m = 5, X = NHR with R = H, a linear or branched (C_1-C_4)alkyl, a linear or branched (C_1-C_4)acyl, Y = COOH, $CONH_2$; or a pharmaceutically acceptable salt thereof for preparing pharmaceutical compositions having antiplatelet, antithrombotic activity, in human and veterinary medicine.

2. A process for preparing R,S-cis-2-(6'-carboxyhexyl)-cis-3-n-hexyl-cyclohexylamine characterized in that the compound obtained by addition of an equivalent of p-toluenesulfonic acid to a mixture containing all the stereoisomers of 2-(6'-carbomethoxyhexyl)-3-n-hexyl-cyclohexylamine is crystallized with ethyl ether, whereby the R,S-cis-2-(6'-carbomethoxyhexyl)-cis-3-n-hexyl-cyclohexylamine p-toluenesulfonate thus obtained is treated with a base thereby yielding R,S-cis-2-(6'-carboxyhexyl)-cis-3-n-hexyl-cyclohexylamine.

3. A process for preparing R,S-trans-2-(6'-carboxyhexyl)-cis-3-n-hexyl-cyclohexylamine characterized in that 2-(6'-carboxyhexyl)-3-n-hexyl-cyclohexanone is reacted with lithium-tri-

sec-butylboronhydride in THF at -70°C thereby yielding a mixture of R,S-cis-2-(6'-carboxyhexyl)-cis-3-n-hexyl-cyclohexanol and R,S-cis-2-(6'-carboxyhexyl)-trans-3-n-hexyl-cyclohexanol, the thus obtained mixture is then treated with methanol and p-toluenesulfonic acid and chromatographed on silica gel using a 7:3 mixture of hexane: ethyl acetate as the eluent, whereby R,S-cis-2-(6'-carbomethoxyhexyl)-cis-3-n-hexyl-cyclohexanol is separated which, after subsequent transformation into the corresponding mesilate and after substitution with sodium azide and reduction with a metal catalyst and hydrogen and subsequent saponification yields R,S-trans-2-(6'-carboxyhexyl)-cis-3-n-hexyl-cyclohexylamine.

4. The use of a compound of formula (I) according to Claim 1 or a pharmacologically acceptable salt thereof for preparing pharmaceutical compositions having antiplatelet, antithrombotic activity, in human and veterinary medicine, characterized in that in said formula :

n = 2, m = 5, X = CH_2NH_2, Y = COOH;

n = 2, m = 5, X = $NHNH_2$, Y = COOH;

n = 2, m = 5, X = NH_2, Y = CH_2NH_2;

n = 3, m = 5, X = NH_2, X = COOH:

n = 3, m = 5, X = CH_2NH_2, Y = COOH;

n = 3, m = 5, X = NH_2, Y = CH_2NH_2;

n = 2, m = 4, X = NH_2, Y = COOH;

n = 2, m = 6, X = NH_2, Y = COOH;

n = 2, m = 7, X = NH_2, Y = COOH.

5. The use of R,S-cis-2-(6'-carboxyhexyl)-cis-3-n-hexyl-cyclohexylamine, a compound of formula (I) according to Claim 1, and a pharmacologically acceptable salt thereof having antiplatelet , antithrombotic activity, in human and veterinary medicine.

6. The use of R,S-trans-2-(6'-carboxyhexyl)-cis-3-n-hexyl-cyclohexylamine, a compound of formula (I) according to Claim 1 and a pharmacologically acceptable salt thereof having antiplatelet, antithrombotic activity, in human and veterinary medicine.

7. A pharmaceutical composition having antiplatelet, antithrombotic activity,characterized in that it contains, as the active ingredient, a compound of formula (I) according to Claim 1 or a pharmacologically acceptable salt thereof.

8. A pharmaceutical composition having antiplatelet, antithrombotic activity containing, as its active ingredient, a compound according to one of the Claims 4 to 6 or a pharmacologically acceptable salt thereof.