

Description**Field of the invention**

The present invention relates to novel derivatives of tranexamic acid intended for use in medicine and therapeutically acceptable salts thereof; methods for their preparation; pharmaceutical compositions containing the compounds as active ingredient; and the use in medicine of the compounds, particularly for the treatment of ailments which are due to increased fibrinolysis, and for the treatment of hereditary angio-neurotic edema.

Background of the invention

Tranexamic acid, or trans-4-aminomethylcyclohexanecarboxylic acid:



is used clinically as an antifibrinolytic drug. The trans isomer is biologically active, while the cis-isomer is practically inactive. The normal route of administration of tranexamic acid is by oral administration, but it can also be administered parenterally, by infusion or by injection. However, because of the limited absorption of tranexamic acid when administered by the oral route — normally 35—40% of administered tranexamic acid is absorbed — fairly high dosages must be prescribed, typically from about 3 to about 6 grams per 24 hours. Such a large intake causes in some patients undesired side effects in the gastrointestinal tract, probably due to local irritation caused by not absorbed drug.

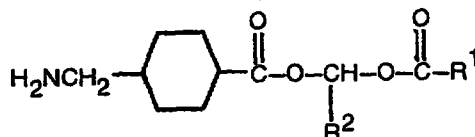
There is a need for orally active antifibrinolytic drugs with improved absorption properties after oral administration and with reduced undesired gastrointestinal effects. The present invention provides novel esters of tranexamic acid which possess such properties.

Prior art

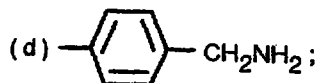
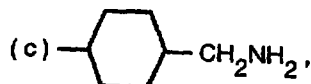
Tranexamic acid is disclosed for example in British patent no. 949,512. Esters of tranexamic acid are disclosed for example in Journal of Medicinal Chemistry 1972 volume 15 no. 3 pp. 247—255, and in the Derwent abstracts 27462 F, 31374 F, 67786 R, 06434 V, 80109 X, 56916 Y and 46818 A.

Detailed description of the invention

It has been found according to the present invention that the compounds of the formula

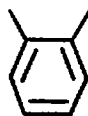


and therapeutically acceptable salts thereof, wherein R^1 is selected from the group consisting of
(a) alkyl groups containing 1—4 carbon atoms,
(b) alkoxy groups containing 1—4 carbon atoms,



R^2 is selected from the group consisting of

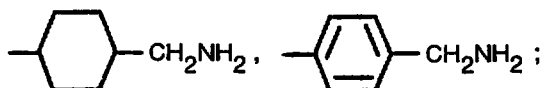
- (a) H,
 - (b) alkyl groups containing 1—4 carbon atoms,
 - (c) $-\text{COOR}^3$, wherein R^3 is an alkyl group containing 1—4 carbon atoms,
 - (d) $-\text{CONR}^4\text{R}^5$, wherein R^4 and R^5 are the same or different alkyl groups containing 1—3 carbon atoms;
- or wherein R^1 and R^2 represent together the radical



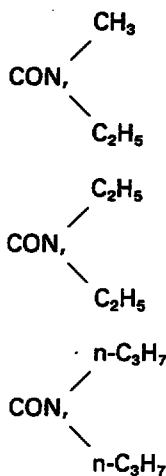
are antifibrinolytically active compounds which after oral administration are absorbed to a considerably higher degree than tranexamic acid as such. The compounds of the formula I are rapidly hydrolyzed in the organism whereby tranexamic acid is liberated and exerts its biological activity.

Illustrative examples of the radicals R^1 , R^2 , R^3 and R^4 are:

R^1 : CH_3 , C_2H_5 , $\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}(\text{CH}_3)_2$, n-butyl, iso-butyl, sec. butyl, tert. butyl, OCH_3 , OC_2H_5 , $\text{OCH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}(\text{CH}_3)_2$, n-butoxy, iso-butoxy, sec. butoxy, tert. butoxy



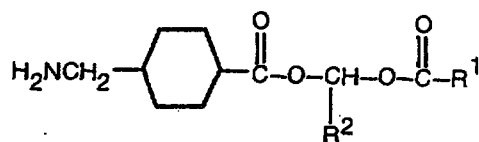
R^2 : H, CH_3 , C_2H_5 , $\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}(\text{CH}_3)_2$, n-butyl, iso-butyl, sec. butyl, tert. butyl, COOCH_3 , COOC_2H_5 , $\text{COO-n-C}_3\text{H}_7$, $\text{COO-n-C}_4\text{H}_9$, $\text{CON}(\text{CH}_3)_2$,

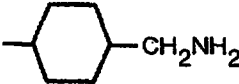
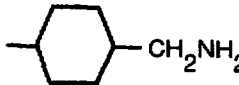


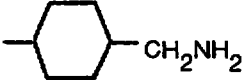
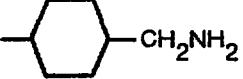
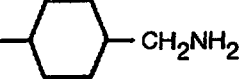
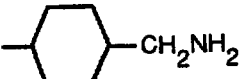
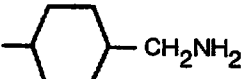
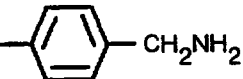
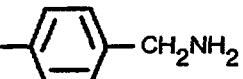
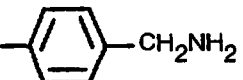
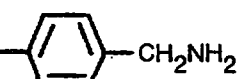
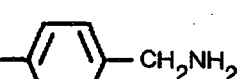
R_3 : CH_3 , C_2H_5 , $\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}(\text{CH}_3)_2$, n-butyl, isobutyl, sec. butyl, tert. butyl.

R^4 and R^5 : CH_3 , C_2H_5 , $\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}(\text{CH}_3)_2$.

Illustrative examples of compounds included in the formula I are given in the following table, where combinations of R^1 and R^2 are given:



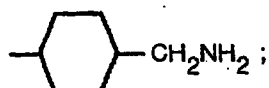
R ¹	R ²
CH ₃	H
C ₂ H ₅	H
CH ₂ CH ₂ CH ₃	H
CH(CH ₃) ₂	H
n-butyl	H
isobutyl	H
sec. butyl	H
tert. butyl	H
CH ₃	CH ₃
C ₂ H ₅	CH ₃
CH ₂ CH ₂ CH ₃	CH ₃
CH(CH ₃) ₂	CH ₃
n-butyl	CH ₃
isobutyl	CH ₃
sec. butyl	CH ₃
tert. butyl	CH ₃
CH ₃	C ₂ H ₅
C ₂ H ₅	C ₂ H ₅
CH(CH ₃) ₂	C ₂ H ₅
tert. butyl	C ₂ H ₅
	H
	CH ₃

R ¹	R ²
	C ₂ H ₅
	CON(CH ₃) ₂
	CON(C ₂ H ₅) ₂
	COOCH ₃
	COOC ₂ H ₅
	H
	CH ₃
	CON(CH ₃) ₂
	COOCH ₃
	COOC ₂ H ₅
OCH ₃	H
OC ₂ H ₅	H
OCH ₂ CH ₂ CH ₃	H
OCH(CH ₃) ₂	H
O-n-butyl	H
O-isobutyl	H
O-sec. butyl	H
O-tert. butyl	H
OCH ₃	CH ₃

R ¹	R ²
OC ₂ H ₅	CH ₃
OCH ₂ CH ₂ CH ₃	CH ₃
OC(CH ₃) ₂	CH ₃
O-n-C ₄ H ₉	CH ₃
O-isobutyl	CH ₃
O-sec. butyl	CH ₃
O-tert. butyl	CH ₃
OCH ₃	C ₂ H ₅
OC ₂ H ₅	C ₂ H ₅

Preferred meanings of the radicals R¹ and R² are:

- R¹: 1) alkyl groups containing 1—4 carbon atoms,
 2) alkoxy groups containing 1—4 carbon atoms,
 3) the radical

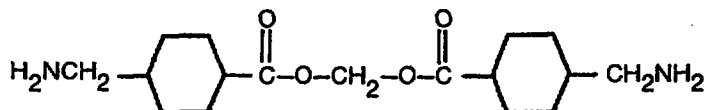
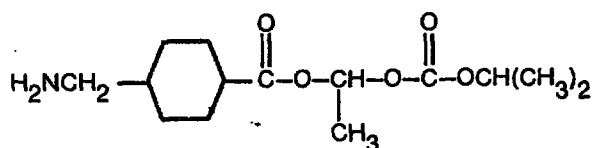
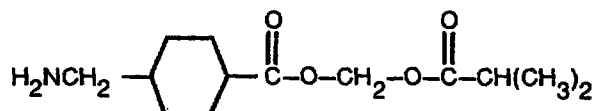
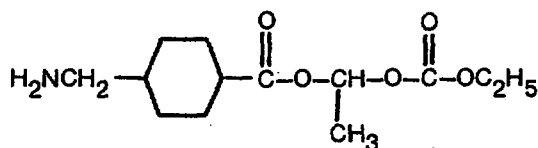


- R²: 1) H
 2) CH₃.

Preferred combinations of the radicals R¹ and R² are:

R ¹	R ²
alkyl group containing 1—4 carbon atoms	H
alkyl group containing 1—4 carbon atoms	CH ₃
alkoxy group containing 1—4 carbon atoms	H
alkoxy group containing 1—4 carbon atoms	CH ₃
<chem>*C1CCCCC1CN</chem>	H
<chem>*C1CCCCC1CN</chem>	CH ₃

Among the preferred compounds of the invention are:



An overriding aspect of the compound of the invention is that the trans-form of the compounds is preferred.

The compounds of the formula I will occur in cis- and trans-configuration. Compounds of both these configurations, as well as mixtures thereof, are included among the compounds of the present invention.

The compounds of trans-configuration are preferred. The cis- and trans-isomers can be separated by known methods.

The area of use of the compounds of the present invention is the same as for tranexamic acid. This means that the compounds will be used as antifibrinolytic agents, that is for combatting ailments in mammals and man which are due to increased fibrinolysis. Increased fibrinolysis may occur for instance during menstruation and also as a result of surgical operations.

Still another area of use for the compounds of the invention is in the treatment of peptic ulcers. At such treatment the compounds may be administered in an amount of from 100 to 2000 mg per day.

Still another area of use for the compounds of the present invention is in the treatment of hereditary angio-neurotic edema.

In clinical practice the compounds of the invention will normally be administered orally, by injection or topically in the form of a pharmaceutical preparation comprising the active ingredient in the form of the original compound or optionally in the form of pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier which may be a solid, semisolid or liquid diluent or an ingestible capsule, and such preparations comprise a further aspect of the invention. The compounds may also be used without carrier material. As examples of pharmaceutical preparations may be mentioned tablets, drops, gels, ointments, creams, eyedrops, nasal spray, etc. Usually the active substance will comprise between 0.05 to 99%, or between 0.1 to 99% by weight of the preparation, for example between 0.5 to 20% for preparations intended for injection and between 10 to 90% for preparations intended for oral administration.

The new compounds according to the invention may be administered in the form of salts with physiologically acceptable acids. Suitable acids which may be used are, for example hydrochloric, hydrobromic, sulphuric, fumaric, citric, tartaric, maleic or succinic acid.

The invention further provides pharmaceutical compositions comprising as active ingredient at least one of the compounds according to the invention in association with a pharmaceutical carrier. Such compositions may be designed for example for oral, topical, rectal or parenteral administration.

To produce pharmaceutical preparations in the form of dosage units for oral application containing a compound of the invention in the form of the free base, or a pharmaceutically acceptable salt thereof, the active ingredient may be mixed with a solid, pulverized carrier, for example, lactose, saccharose, sorbitol, mannitol, a starch such as potato starch, corn starch, maize starch or amylopectin, a cellulose derivative or gelatin, and also may include lubricants such as magnesium or calcium stearate or a Carbowax or other

polyethylene glycol waxes and compressed to form tablets or centers for dragees. If dragees are required, the centers may be coated, for example, with concentrated sugar solutions which may contain gum arabic, talc and/or titanium dioxide, or alternatively with a lacquer dissolved in easily volatile organic solvents or mixtures of organic solvents. Dyestuffs can be added to these coatings. For the preparation of soft gelatin capsules (pearl-shaped closed capsules) consisting of gelatin and, for example, glycerol, or similar closed capsules, the active substance may be admixed with a Carbowax. Hard gelatin capsules may contain granulates of the active substance with solid, pulverized carriers such as lactose, saccharose, sorbitol, mannitol, starches (for example potato starch, corn starch, or amylopectin), cellulose derivatives or gelatin, and may also include magnesium stearate or stearic acid. Dosage units for rectal application may be in the form of suppositories comprising the active substance in admixture with a Carbowax or other polyethylene glycol waxes. Each dosage unit preferably contains 50 to 500 mg active ingredient.

Liquid preparations for oral application may be in the form of syrups, suspensions or emulsions, for example containing from about 0.1% to 20% by weight of active substance and also, if desired, such adjuvants as stabilizing agents, suspending agents, dispersing agents, flavouring agents and/or sweetening agents.

Liquid preparations for rectal administration may be in the form of aqueous solutions containing from about 0.1% to 2% by weight of active substance and also, if desired, stabilizing agents and/or buffer substances.

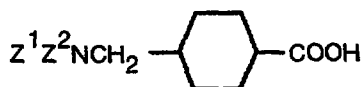
For parenteral application by injection the carrier may be a sterile, parenterally acceptable liquid, e.g. pyrogen-free water or an aqueous solution of polyvinylpyrrolidone, or a parenterally acceptable oil, e.g., arachis oil and optionally stabilizing agents and/or buffer substances. Dosage units of the solution may advantageously be enclosed in ampoules, each dosage unit preferably containing from 0.1 to 10 mg of active ingredient.

The dosage at which the active ingredients are administered may vary within a wide range and will depend on various factors such as for example the individual requirements of each patient. A suitable oral dosage range may be from 0.5 to 5 g per day.

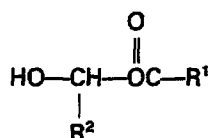
The pharmaceutical compositions containing the active ingredients may suitably be formulated so that they provide doses within these ranges either as single dosage units or as multiple dosage units.

The compounds of the invention can be prepared by known methods such as

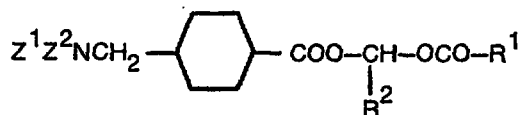
A. reacting a compound of the formula



wherein Z^1 and Z^2 are H or a protecting group, or a functionally equivalent derivative thereof with a compound of the formula

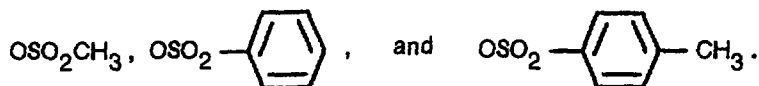


or a functionally equivalent derivative thereof, wherein R^1 and R^2 are as defined previously, whereby the possible amine substituent in R^1 also may be protected by protecting groups Z^1 and Z^2 , to the formation of a compound of the formula



whereafter if necessary protecting groups Z^1 and Z^2 are removed to the formation of a compound of the formula I.

Functionally equivalent derivatives of the hydroxy group in the compound III are for example halogen such as Cl or Br, or I, and sulphonates such as

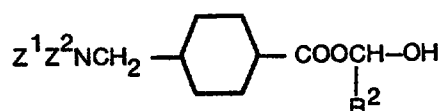


Functionally equivalent derivatives of the carboxyl group in the compound II are for example a carboxylic acid salt such as a metal salt, an ammonium salt or a salt with a substituted ammonium group, for example sodium, potassium, $(C_2H_5)_3N$, $(C_4H_9)_4N^+$, and pyridine salt, or an activated carboxyl group, for example an acid chloride, an alkyl ester, and acid anhydride or a mixed anhydride with formic esters or carboxylic acids, sulphonic or inorganic esters, or derivatives obtained by a reaction between a carboxylic acid and a carbodiimide or similarly functioning compounds such as N,N' -carbonyldiimidazole or N -ethyl-5-phenylisoxazolium-3'-sulphonate, the derivative of the carboxyl group being a carboxylic acid salt as defined above when the radical OH in the compound III has been replaced with halogen.

The protecting groups Z^1 and Z^2 are removed in known manner.

The protecting groups Z^1 and Z^2 are preferably a group which can be removed under neutral or acidic conditions or by hydrogenation, especially catalytic hydrogenation. Examples of such groups are tert. butoxycarbonyl, benzyloxycarbonyl, dibenzyl, triphenylmethyl, alkylcarbonyl and arylcarbonyl.

B. reacting a compound of the formula



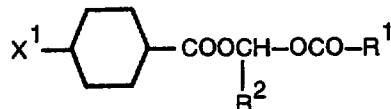
wherein Z^1 and Z^2 are H or a protecting group, or a functionally equivalent derivative thereof, with a compound of the formula



wherein R^1 is as defined above, or a functionally equivalent derivative thereof, whereby the possible amine substituent in R^1 also may be protected by protecting groups Z^1 and Z^2 , to the formation of a compound of the formula IV whereafter, if necessary, protecting groups Z^1 and Z^2 are removed to the formation of a compound of the formula I.

Examples of functionally equivalent derivatives of the compounds V and VI are the same derivatives which are described with regard to compounds II and III in method A.

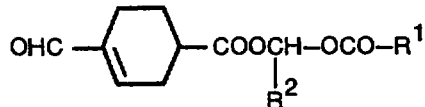
C. reduction of a compound of the formula



wherein R^1 and R^2 are as defined above and X^1 is $-\text{CN}$, $-\text{CH}_2\text{NO}_2$, $-\text{CH}_2\text{N}_3$, $-\text{CONH}_2$ or $-\text{CH}=\text{N}-\text{OH}$ to the formation of a compound of the formula I.

The reduction is carried out in known manner, for example by catalytical hydrogenation.

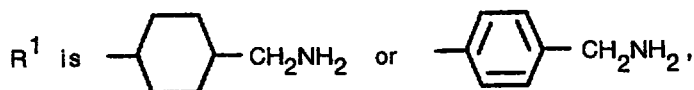
D. reduction of a compound of the formula



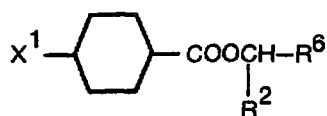
wherein R^1 and R^2 are as defined above, in the presence of NH_3 to the formation of a compound of the formula I.

The reduction may be carried out in known manner for example by catalytical hydrogenation. The NH_3 may be present in the form of NH_4OH .

E. for the preparation of compounds of the formula I wherein

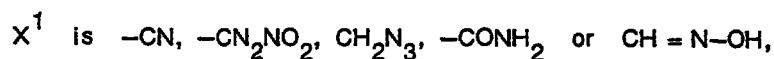
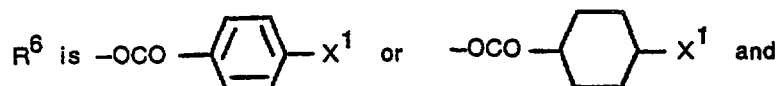


reduction of a compound of the formula

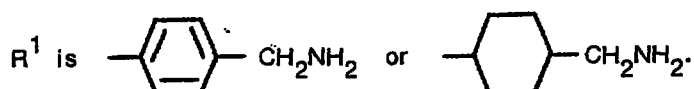


IX

wherein R^2 is as defined above,

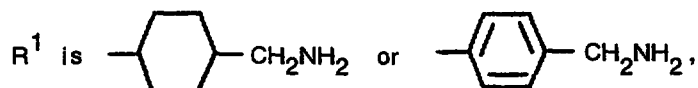


to the formation of a compound of the formula I wherein

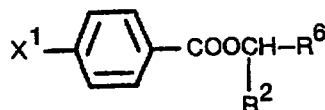


The reduction is carried out in known manner.

F. for the preparation of compounds of the formula I wherein

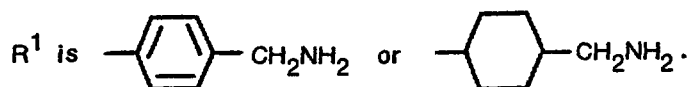


reduction of a compound of the formula



X

wherein R^2 , R^6 and X^1 are as defined above, to the formation of a compound of the formula I wherein

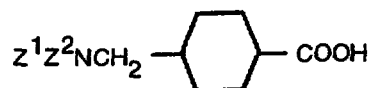


The reduction is carried out in known manner.

G. for the preparation of the compounds of the formula I wherein

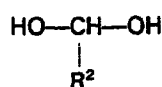


reacting a compound of the formula



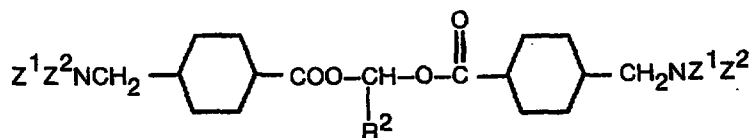
XI

wherein Z^1 and Z^2 are H or a protecting group as defined above, or a functionally equivalent derivative thereof, with a compound of the formula



XII

wherein R^2 is as defined above, or a functionally equivalent derivative thereof, to give a compound of the formula

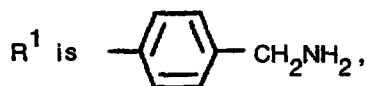


XIII

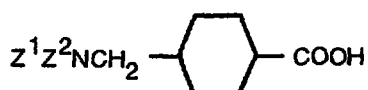
whereafter if necessary protecting groups Z^1 and Z^2 are removed.

Examples of groups which are functionally equivalent with the carboxyl and hydroxy groups in the formula XI and XII are for example the groups mentioned in Method A above.

H. for the preparation of compounds of the formula I wherein

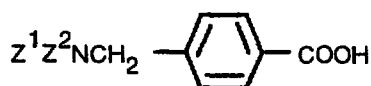


reacting a compound of the formula



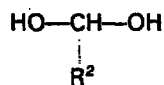
XI

and a compound of the formula



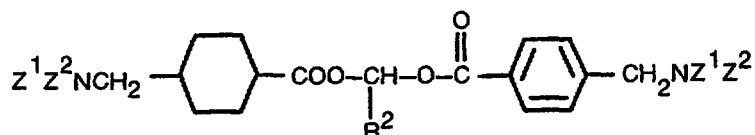
XIV

in which formulas Z^1 and Z^2 are H or a protecting group as defined above, or a functionally equivalent derivative thereof with a compound of the formula



XII

wherein R^2 is as defined above, or a functionally equivalent derivative thereof, to give a compound of the formula

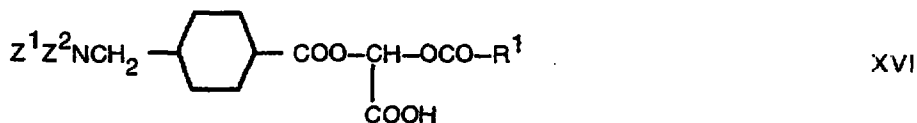


XV

whereafter if necessary protecting groups Z^1 and Z^2 are removed.

Examples of groups which are functionally equivalent with the carboxyl and hydroxy groups in the formula XI, XIV and XII are for example the groups mentioned in Method A above.

In Method H, the protecting groups Z in compound XI and compound XIV are suitably different.
 I. For the preparation of a compound of the formula I wherein R² is COOR³, reacting a compound of the formula



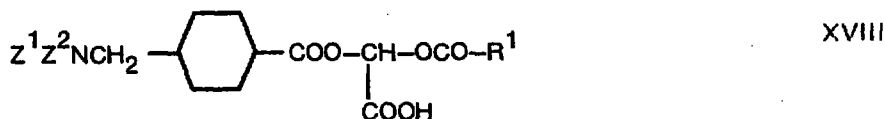
wherein Z¹ and Z² are H or a protecting group as defined in Method A and R¹ is as defined above, whereby the possible amine substituent in R¹ also may be protected by protecting groups Z¹ and Z², or a functionally equivalent derivative thereof, with a compound of the formula



wherein R³ is as defined above, or a functionally equivalent derivative thereof, whereafter, if necessary, protecting groups Z¹ and Z² are removed, to the formation of a compound of the formula I wherein R² is COOR³.

Examples of groups which are functionally equivalent with the carboxyl and hydroxy groups in the formula XVI and XVII are for example the groups mentioned in Method A above.

J. for the preparation of a compound of the formula I wherein R² is CONR⁴R⁵, reacting a compound of the formula



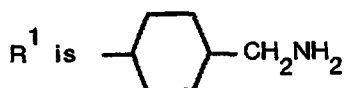
wherein R¹ is as defined above, or a functionally equivalent derivative thereof, with a compound of the formula



wherein R⁴ and R⁵ are as defined above, or a functionally equivalent derivative thereof, whereafter, if necessary, protecting groups Z¹ and Z² are removed, to the formation of a compound of the formula I wherein R² is CONR⁴R⁵.

Functionally equivalent derivatives of the carboxyl group in compound XVIII are for example an activated carboxyl group such as an acid halide, an alkyl ester, an acid anhydride, a mixed anhydride with formic ester or carboxylic esters, sulphonic or inorganic acids, or derivatives obtained by a reaction between a carboxylic acid and a carbodiimide or similarly functioning compounds such as N,N'-carbonyldiimidazole or N-ethyl-5-phenyl-isoxazolium-3'-sulphonate.

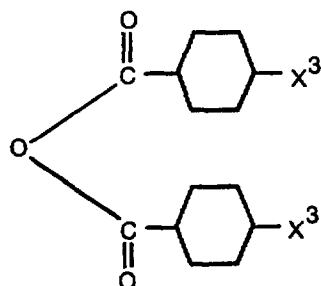
K. for the preparation of compounds wherein



60 reacting a compound of the formula



65 wherein R² is as defined above, with a compound of the formula



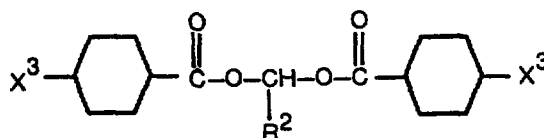
XXI

wherein X^3 is

(a) $CH_2NZ^1Z^2$

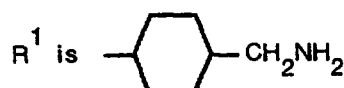
wherein Z^1 and Z^2 are protecting groups as defined in method A, or

(b) CN , CH_2NO_2 , CH_2N_3 , $CONH_2$ or $CH=N-OH$,
to the formation of a compound of the formula

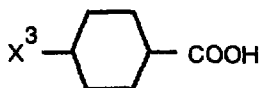


XXII

whereafter each of the groups X^3 are converted to CH_2NH_2 by removal of the protecting groups Z^1 and Z^2 or by reduction of the groups CN , CH_2NO_2 , CH_2N_3 , $CONH_2$, $CH=N-OH$ to the formation of a compound of the formula I wherein

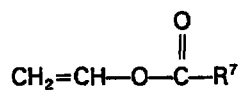


L. for the preparation of compounds of the formula I wherein R^1 is an alkyl group containing 1—4 carbon atoms, and R^2 is CH_3 , reacting a compound of the formula



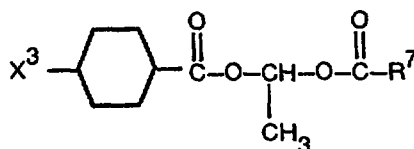
XXIII

wherein X^3 is as defined in Method K, with a compound of the formula



XXIV

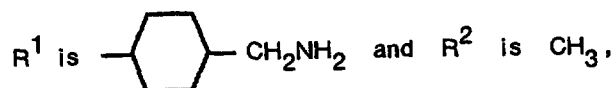
wherein R^7 is an alkyl group containing 1—4 carbon atoms, to the formation of a compound of the formula



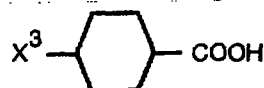
XXV

wherein X^3 and R^7 are as defined above, whereafter X^3 is converted to CH_2NH_2 as described in Method K to the formation of a compound of the formula I wherein R^1 is an alkyl group containing 1—4 carbon atoms and wherein R^2 is CH_3 .

M. for the preparation of compounds of the formula I wherein



reacting a compound of the formula



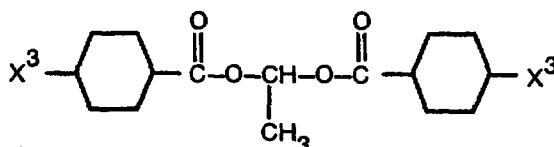
XXIII

15 wherein X^3 is as defined in Method K, with a compound of the formula



XXVI

20 to the formation of a compound of the formula



XXVII

30 wherein X^3 is as defined above, whereafter X^3 is converted to CH_2NH_2 as described in Method K to the formation of a compound of the formula I.

If desired, the compound of the formula I obtained by the processes A—M may be converted in known manner to a therapeutically acceptable salt. The compound of the formula I, or a therapeutically acceptable salt thereof, may also if necessary be separated in known manner in its cis- and trans-isomers. As noted above, the main biological activity will reside in the trans-isomer.

Example 1

Preparation of pivaloyloxymethyl trans-4-aminomethylcyclohexanecarboxylate hydrochloride (Method A)

40 Chloromethyl pivalate (33.2 g; 0.22 mol) was added to a suspension of sodium bromide (22.4 g; 0.22 mol) in dimethylformamide. After 2 h a solution of trans-4-(tert.-butoxycarbonylaminoethyl)cyclohexanecarboxylic acid in triethylamine (24 g; 0.24 mol) and dimethylformamide was added. The mixture was stirred overnight at room temperature. The solvent was distilled off and water (1 L) and dichloromethane was added. The organic layer was separated, washed, dried and evaporated to yield 55 g. This product was dissolved in ethyl acetate and cooled. A solution of hydrochloric acid in ethyl acetate was added. After 1 h ether was added. The precipitate was filtered, washed and dried to yield 30.2 g, m.p. 165°C after crystallisation from acetone.

Calculated for

$C_{14}H_{26}ClNO_4$:

C 54.6	H 8.51	N 4.55	O 20.8	Cl 11.5
found 54.7	8.38	4.51	21.1	11.7

Example 2

Preparation of phthalidyl trans-4-aminomethylcyclohexanecarboxylate hydrochloride (Method A)

55 A solution of 3-bromophthalide (70.5 g; 0.33 mol) in dimethylformamide (65 ml) was added dropwise to a cold solution of trans-4-(tert.-butoxycarbonylaminoethyl)cyclohexanecarboxylic acid (77.1 g; 0.3 mol) in triethylamine (36.4 g; 0.36 mol) and dimethylformamide (195 ml). After 18 h the solvent was evaporated, water (1.5 L) and ethyl acetate (1.5 L) were added. The ethyl acetate extract was washed, dried and evaporated to give 122 g. This was dissolved in ethyl acetate (400 ml) and ethyl acetate/hydrochloric acid was added at ice bath temperature. After 2 h at room temperature, the precipitate was filtered, washed and dried to yield 63.8 g. This substance was dissolved in methanol, filtered through charcoal and precipitated with diethyl ether. Yield 54.4 g (56%), m.p. 212°C.

Calculated for

$C_{26}H_{20}ClNO_4$:

C 59.0	H 6.19	N 4.30	O 19.64	Cl 10.88
found 59.1	6.18	4.13	19.65	11.15

Example 3

Preparation of 1-(ethyloxycarbonyloxy)ethyl trans-4-aminomethylcyclohexanecarboxylate hydrochloride (Method A)

- A solution of trans-4-(tert.-butoxycarbonylaminoethyl)cyclohexanecarboxylic acid (25.7 g; 0.1 mol) and tetrabutylammonium hydrogen sulfate (34 g; 0.1 mol) in 2N sodium hydroxide (100 ml) was extracted with ethanolfree chloroform. The chloroform solution was dried and evaporated to give 50 g. This was dissolved in trichloroethylene (200 ml) and ethyl (1-chloroethyl) carbonate (16.8 g; 0.11 mol) was added. After refluxing for 3 h the solution was washed with dilute sulphuric acid, sodium bicarbonate solution and water. After evaporation of chloroform the residue was dissolved in ethyl acetate cooled to 0°C. To this solution a cold solution of hydrochloric acid in ethyl acetate was added. After 3 h at ice bath temperature the solvent was evaporated to give 23 g. This was dissolved in isopropyl alcohol and precipitated with diisopropyl ether. Yield 15 g (49%), m.p. 139°C.

Calculated for					
$C_{13}H_{24}ClNO_5$:	C 50.4	H 7.81	N 4.51	O 25.8	Cl 11.5
found	50.4	7.82	4.80	25.4	11.7

Example 4

Preparation of 1-(isopropylloxycarbonyloxy)ethyl trans-4-aminomethylcyclohexanecarboxylate hydrochloride (Method A)

- Isopropyl (1-chloroethyl) carbonate (22 g; 0.3 mol) was added to sodium bromide (13.5 g; 0.13 mol) in dimethylformamide (120 ml). This mixture was stirred for 3 h and then added to trans-4-(tert.-butoxycarbonylaminoethyl)cyclohexanecarboxylic acid (30.8 g; 0.12 mol), dissolved in dimethylformamide (450 ml) and triethylamine (24 g; 0.24 mol). This mixture was stirred at 120°C for 60 h. The solvent was distilled off and the residue partitioned between ether and water. The ether layer was washed, dried and evaporated to give 9 g of an oil. This oil was dissolved in ethyl acetate and treated with hydrochloric acid in ethyl acetate. After evaporation of the solvent and recrystallization from acetone 3.3 g of product, m.p. 158°C was obtained.

Calculated for					
$C_{14}H_{26}ClNO_5$:	C 51.9	H 8.09	N 4.33	O 24.7	Cl 11.0
found	51.8	8.09	4.13	24.2	11.1

- The isopropyl (1-chloroethyl) carbonate used as starting material was prepared as follows. 1-chloroethyl chloroformate (28.5 g; 0.2 mol) was mixed with isopropyl alcohol (13.2 g; 0.22 mol) and heated to 90°C. After cooling to room temperature the product was washed with water and sodium bicarbonate solution and dried. 30 g was obtained. NMR spectrum ($CDCl_3$) 1.40 (CH_3)₂C; δ 1.85 CH_3 C; δ 5.10 C—CH—C; δ 6.45 OCH(C)Cl.

Example 5

Preparation of 1-(acetyloxy)ethyl trans-4-aminomethylcyclohexanecarboxylate (Method A)

- 1-(acetyloxy)ethyl chloride (24.5 g; 0.2 mol) was mixed with sodium bromide (21 g; 0.2 mol) in dimethylformamide (400 ml). To this mixture after 2 h of stirring trans-4-(tert.-butoxycarbonylaminoethyl)cyclohexanecarboxylic acid (64.3 g; 0.25 mol) and triethylamine (50 g; 0.5 mol) were added. This mixture was stirred for 24 h at 35°C. Water and diethyl ether was added. The organic phase was washed, dried and evaporated to give 8.5 g. This product was dissolved in ethyl acetate, cooled and mixed with ethylacetate containing hydrochloric acid. Diethyl ether was added after 3 h and the precipitate was filtered off, washed and dried. 5 g was obtained which after recrystallization from an isopropyl alcohol/isopropyl ether mixture yielded 4.5 g, m.p. 126°C.

Calculated for					
$C_{12}H_{22}ClNO_4$:	C 51.5	H 7.93	N 5.01	O 22.9	Cl 12.7
found	51.4	7.93	4.41	23.2	12.8

Example 6

Preparation of isobutyryloxymethyl trans-4-aminomethylcyclohexanecarboxylate (Method A)

- Sodium bromide (3.8 g; 0.037 mol) and isobutyryloxymethyl chloride (5.1 g; 0.037 mol) was mixed with dimethylformamide (40 ml) and stirred for 3 h at room temperature. Trans-4-(tert.-butoxycarbonylaminoethyl)cyclohexanecarboxylic acid (15.4 g; 0.06 mol) dissolved in dimethylformamide (100 ml) and triethylamine (12 g; 0.12 mol) was added and the stirring continued for 100 h at room temperature. The solvent was evaporated and water and diethylether were added. The ether layer was washed, dried and evaporated to give 6.1 g. This product was dissolved in ethyl acetate and ethyl acetate/hydrochloric acid was added. After 3 h at room temperature ether was added and the precipitate collected. Yield 3.5 g, m.p. 100°C.

- The product was dissolved in chloroform. Some undissolved material was filtered off and the solution was evaporated. M.p. 104°C.

Calculated for
C₁₃H₂₄ClNO₄:
found

C 53.2	H 8.23	N 4.77	O 21.8	Cl 12.1
53.5	7.78	4.65	21.2	12.1

- 5 The isobutyryloxymethyl chloride used as starting material was prepared as follows:
Isobutyryl chloride (53 g; 0.5 mol) was mixed with paraformaldehyde (15 g; 0.5 mol) and treated to 90°C. The reaction was started by adding a catalytical amount of zinc chloride. After 3 h the mixture was extracted with pentane. The pentane solution was washed, dried and evaporated to yield 44 g. This product was distilled at 44—48°C at 0.5 kPa.

10

Example 7

Preparation of 1-(isobutyryloxy)ethyl trans-4-aminomethylcyclohexanecarboxylate (Method A)

- 15 Sodium bromide (13.5 g; 0.132 mol) and 1-(isobutyryloxy)ethyl chloride (19.9 g; 0.132 mol) were added to dimethylformamide (120 ml). After 3 h at room temperature a solution of trans-4-(tert.-butoxycarbonyl-aminomethyl)cyclohexanecarboxylic acid (30.8 g; 0.12 mol) and triethylamine (24 g; 0.24 mol) in dimethylformamide (200 ml) was added. The mixture was stirred at room temperature for 60 h and then the solvent was evaporated. Water and diethylether were added and the ether layer was separated, washed, dried and evaporated to yield 13 g of an oil. The oil was dissolved and ethyl acetate and ethyl acetate/hydrochloric acid was added. Diethyl ether was added after 3 h and the precipitate was collected. Yield 2.5 g, m.p. 100°C.

20

Calculated for
C₁₄H₂₆ClNO₄:
found

C 54.6	H 8.51	N 4.55	O 20.8	Cl 11.5
54.4	8.53	4.31	20.1	11.7

25

Example 8

Preparation of 1-(pivaloyloxy)ethyl trans-4-aminomethylcyclohexanecarboxylate hydrochloride (Method C)

- 30 A solution of (1-pivaloyloxy)ethyl trans-4-cyanocyclohexanecarboxylate (4.4 g; 1.5 mmol) in ethyl alcohol and chloroform was hydrogenated using platinumoxide (0.5 g) as a catalyst. After 20 h at room temperature catalyst was filtered off and the solvent evaporated. The product was recrystallized from a mixture of isopropyl alcohol and diisopropyl ether. Yield 1.7 g, m.p. 85°C.

Calculated for
C₁₅H₂₈ClNO₄:
found

C 56.0	H 8.77	N 4.35	O 19.9	Cl 11.0
56.0	8.94	4.45	19.7	11.3

35

In the same manner as described in Example 8 the following compounds were prepared:

Example 9

- 40 Preparation of 1-(ethyloxycarbonyloxy)ethyl trans-4-aminomethylcyclohexanecarboxylate hydrochloride
The title compound, m.p. 139°C was obtained from 1-(ethyloxycarbonyloxy)ethyl trans-4-cyanocyclohexanecarboxylate.

Example 10

- 45 Preparation of isobutyryloxymethyl trans-4-aminomethylcyclohexanecarboxylate
The title compound, m.p. 104°C was obtained from isobutyryloxymethyl trans-4-cyanocyclohexanecarboxylate, m.p. 33—35°C.

Example 11

- 50 Preparation of methandiol bis-(trans-4-aminomethylcyclohexanecarboxylate) dihydrochloride (Method E)
To a solution of methandiol bis-(trans-4-cyanocyclohexanecarboxylate) (8.5 g) in 200 ml glacial acetic acid, was added a catalyst (5% palladium on carbon) 1 g, and this mixture was hydrogenated in a Parr-apparatus for 5 h at 0.4 MPa. The catalyst was filtered off and the solvent was evaporated. The residue was dissolved in a mixture of ethyl acetate, isopropyl alcohol and hydrochloric acid dissolved in ethyl acetate was added. The crystalline precipitate was crystallized from isopropyl alcohol. Yield 3.2 g, mp. 270°C.

55

Calculated for
C₁₇H₃₂N₂O₄Cl:
found

C 51.2	H 8.08	N 7.02	O 16.0	Cl 17.8
49.4	8.09	7.11	15.8	17.9

60

The methandiol bis-(trans-4-cyanocyclohexanecarboxylate) used as starting material was prepared as follows:

- 65 A solution of trans-4-cyanocyclohexanecarboxylate (7.7 g; 0.05 mol) in tetrabutylammonium hydrogen sulfate in 2N sodium hydroxide was extracted three times with methylene dichloride. The combined organic solution was dried and refluxed for 120 h. The solution was washed with diluted sulphuric acid,

water and diluted sodium hydrogen carbonate solution, dried and evaporated. Yield 6.8 g, m.p. 94°C after crystallization from isopropyl alcohol.

Calculated for

5	$C_{17}H_{22}N_2O_4$:	C 64.1	H 6.97	N 8.80	O 20.1
	found	64.2	6.97	8.66	20.5

Example 12

Preparation of 1,1-ethandiol bis-(4-aminomethylcyclohexanecarboxylate) dihydrochloride (Method F)

- 10 A solution of 1,1-ethandiol trans-4-cyanocyclohexanecarboxylate-4-cyanobenzoate (4.4 g; 0.0134 mol) in absolute ethanol and chloroform was hydrogenated for 20 h at 22°C in a Parr-apparatus at 3.4 MPa with platinum oxide as a catalyst. The catalyst was filtered off and the solvent evaporated to yield 5.0 g. After recrystallization from 2-propanol containing methanol 2.5 g of the title compound was obtained, m.p. 260°C.

Calculated for

15	$C_{18}H_{34}N_2O_4Cl_2$:	C 52.3	H 8.29	N 6.78	O 15.5	Cl 17.2
	found	52.1	8.22	6.55	15.5	16.9

- 20 The starting material used in Example 12 was prepared as follows.

a) 1-(trans-4-cyanocyclohexanoyloxy)ethyl chloride

- trans-4-cyanocyclohexanecarboxylic acid (7.7 g; 0.05 mol) and thionyl chloride (8.0 g; 0.066 mol) was mixed and refluxed for 30 min. Excess thionyl chloride was evaporated in vacuum. Paraldehyde (2.5 g; 0.062 mol) and a catalytic amount of zinc chloride were added and the mixture was heated at 90°C for 1½ h with stirring. The cooled mixture was extracted with ether, washed with sodium bicarbonate solution, dried and evaporated, the product was distilled at 112°C/1 Pa. Yield 6.5 g of an oil.

b) 1,1-Ethandiol trans-4-cyanocyclohexylcarboxylate 4-cyano benzoate

- 30 A solution of 4-cyanobenzoic acid (11 g; 0.075 mol) and tetrabutylammonium hydrogensulfate (25.5 g; 0.075 mol) dissolved in 2 M sodium hydroxide (80 ml) was extracted with ethanolfree chloroform. The solvent was dried and evaporated. The residue was dissolved in 600 ml trichloroethylene and 1-(trans-4-cyanocyclohexanoyloxy)ethyl chloride (10.8 g; 0.05 mol) was added and the solution was refluxed for 8 h. The solution was washed, dried and the solvent was evaporated to yield 15.8 g, m.p. 105°C after crystallization from ethanol.

Calculated for

40	$C_{18}H_{18}N_2O_4$:	C 66.2	H 5.36	N 8.59	O 19.6
	found	66.2	5.54	8.46	20.0

Example 13

Preparation of 1,1-Ethandiol bis-(trans-4-aminomethylcyclohexanecarboxylate) dihydrochloride (Method F)

- 45 1,1-Ethandiol bis-(trans-4-cyanocyclohexanecarboxylate) (6 g) was dissolved in a mixture of anhydrous ethanol and chloroform. Platinum oxide (1 g; was added and the mixture was hydrogenated at 3.1 MPa at 22°C for 15 h. The catalyst was filtered off and the solvent evaporated. The product was crystallized from a mixture of 2-propanol and methanol. Yield 5.5 g, m.p. 260°C.

Calculated for

50	$C_{18}H_{34}N_2O_4Cl_2$:	C 52.3	H 8.29	N 6.78	O 15.5	Cl 17.2
	found	51.6	8.33	6.97	15.6	17.4

The starting material used in Example 13 was prepared as follows.

55 1,1-Ethandiol bis-(trans-4-cyanocyclohexanecarboxylate)

- Trans-4-cyanocyclohexanecarboxylic acid (11.5 g; 0.075 mol) and tetrabutylammonium hydrogen sulfate (25.5 g; 0.075 mol) was dissolved in 2M sodium hydroxide and extracted with ethanolfree chloroform. The chloroform solution was dried and the solvent evaporated. The residue was dissolved in trichloroethylene (600 ml) and 1-(trans-4-cyanocyclohexanoyloxy)ethyl chloride (10.8 g; 0.05 mol) was added. The solution was refluxed for 8 h. It was then washed, dried and evaporated. Yield 17.1 g, m.p. 75–76°C.

Example 14

1,1-Propandiol bis-(trans-4-aminomethylcyclohexanecarboxylate) dihydrochloride (Method F)

- 65 The title compound, m.p. 270°C, was obtained from 1,1-propandiol bis-(trans-4-cyanocyclohexane-

carboxylate) in analogy with Example 13. M.p. 270°C. The NMR spectrum was in accordance with the expected structure.

5	Calculated for $C_{19}H_{36}Cl_2N_2O_4$:	C 53.4	H 8.49	N 6.56	O 15.3	Cl 16.6
	found	52.5	8.51	6.46	14.8	16.0

The starting material used in Example 14, 1,1-propandiol bis-(trans-4-cyanocyclohexanecarboxylate) was an oil which was obtained from 1-(trans-4-cyanocyclohexanoyloxy)propyl chloride as for 1,1-ethandiol bis-(trans-4-cyanocyclohexanecarboxylate).

1-(trans-4-cyanocyclohexanoyloxy)propyl chloride was an oil which was obtained in the same manner as 1-(trans-4-cyanocyclohexanoyloxy)ethyl chloride (Example 12a).

Example 15

15 Preparation of methandiol bis-(trans-4-aminomethylcyclohexanecarboxylate) dihydrochloride (Method G)
 Diiodomethane (53.6 g; 0.2 mol), trans-4-(tert.-butoxycarbonylaminomethyl)cyclohexanecarboxylic acid (51.4 g; 0.2 mol) and triethylamine (44 g; 0.44 mol) was dissolved in dimethylformamide (400 ml) and stirred at 45°C for 144 h. Additional triethylamine (44 g; 0.44 mol) was added and the stirring was continued at 70°C for another 96 h. The solvent was evaporated on vacuum. Yield 163 g. 5.4 g of this crude material was dissolved in ethyl acetate (100 ml) and hydrochloric acid in ethyl acetate was added (150 ml). After addition of ether (2.5 L) a precipitate was obtained (3.7 g). This was dissolved in methanol and precipitated with acetone. Yield 2.7 g, m.p. 270°C.

25	Calculated for $C_{17}H_{32}N_2Cl_2O_4$:	C 51.1	H 8.08	N 7.02	O 16.0	Cl 17.8
	found	51.1	7.99	6.89	15.9	17.1

Example 16

30 Preparation of 2,2-dihydroxy-N,N-dimethylacetamide bis-(trans-4-aminomethylcyclohexanecarboxylate) (Method G)

a) 2,2-Dihydroxy-N,N-dimethylacetamide bis-[trans-4-(tert.-butoxycarbonylaminomethyl)cyclohexanecarboxylate]

35 Sodium bromide (10.2 g; 0.1 mol) and 1,1-dichloro-N,N-dimethylacetamide (7.8 g; 0.05 mol) was added to dry dimethylformamide (100 ml) and the mixture was stirred for 4 h. Triethylamine (20.7 g; 0.2 mol) and trans-4-(tert.-butoxycarbonylaminomethyl)cyclohexanecarboxylic acid (25.7 g; 0.1 mol) dissolved in dimethylformamide was added. The mixture was stirred for 84 h at 50°C. The solvent was evaporated and the residue was taken up into diethylether and washed, dried and evaporated. The oily residue was stirred with pentane. Yield 7 g, m.p. 110°C.

40	Calculated for $C_{30}H_{51}N_3O_9$:	C 60.3	H 8.60	N 7.03	O 24.0
	found	59.8	8.49	7.06	23.8

45 b) 2,2-Dihydroxy-N,N-dimethylacetamide bis-(trans-4-aminomethylcyclohexanecarboxylate)

2,2-Dihydroxy-N,N-dimethylacetamide bis-[trans-4-(tert.-butoxycarbonylaminomethyl)cyclohexanecarboxylate] (3 g) was dissolved in ethyl acetate (50 ml) and ethyl acetate containing hydrochloric acid (50 ml) was added. After 2 h the solvent was evaporated and the residue dissolved in methanol and ether was added. The precipitate formed (0.9 g) had a m.p. of 220°C.

50	Calculated for $C_{20}H_{37}Cl_2N_3O_5$:	C 51.1	H 7.93	N 8.93	O 17.0	Cl 15.1
	found	50.0	7.93	8.61	17.0	15.1

Example 17

55 2,2-Dihydroxy-N,N-dimethylacetamide bis-(trans-4-aminomethylcyclohexanecarboxylate) (Method G)

The title compound was obtained from 1,1-dibromo-N,N-diethylacetamide and trans-4-(tert.-butoxycarbonylaminomethyl)cyclohexanecarboxylic acid in analogy with Example 16. M.p. 220°C.

60	Calculated for $C_{22}H_{41}Cl_2N_3O_5$:	C 53.0	H 8.29	N 8.43	O 16.1	Cl 14.2
	found	52.9	8.36	8.19	16.3	14.2

65

Example 18

Preparation of ethyl bis-(trans-4-aminomethylcyclohexanecarboxyloxyacetate (Method G)

The title compound m.p. 150°C was obtained from ethyl bis-[trans-4-(tert.butyloxycarbonylamino-methyl)cyclohexanecarboxyloxy] acetate, m.p. 126°C, in the same way as described in Example 16.

Calculated for

$C_{20}H_{36}N_2O_6Cl_2$:	C 51.0	H 7.10	N 5.94	O 20.4	Cl 15.0
found	50.0	7.65	6.09	19.9	15.1

Example 19

Preparation of bis-(pivaloyloxymethyl trans-4-aminomethylcyclohexanecarboxylate) fumarate

To a solution of pivaloyloxymethyl trans-4-aminomethylcyclohexanecarboxylate (1 g; 4 mmol) in ethyl acetate (200 ml) a solution of fumaric acid (0.35 g; 3 mmol) in methanol (10 ml) was added. The solvent were evaporated and the residue was treated with diisopropyl ether. A crystalline product, m.p. 158°C was obtained.

Calculated for

$C_{32}H_{54}N_2O_{12}$:	C 58.3	H 8.26	N 4.25	O 29.1
found	57.9	8.18	4.33	28.9

Example 20

Preparation of methandiol bis-(4-aminomethylcyclohexanecarboxylate) dihydrochloride (Method F)

Methandiol bis-4-cyanobenzoate (2 g; 0.014 mol) was dissolved in a mixture of absolute ethanol and chloroform and hydrogenated for 5 h at 40°C and 3.5 MPa in the presence of platinum oxide (0.3 g). The catalyst was filtered off and the solvent evaporated. The residue was taken up in isopropanol and filtered. Diisopropyl ether was added and the precipitate was collected. Yield 1.3 g, m.p. 250°C.

Calculated for

$C_{17}H_{32}N_2O_4Cl_2$:	C 51.2	H 8.08	N 7.02	Cl 17.8
found	50.3	7.92	7.01	17.8

The starting material used in Example 20 was prepared as follows:

Methandiol bis-4 cyanobenzoate

4-cyanobenzoic acid (29.4 g; 0.2 mol) was dissolved in 400 ml 1M sodium hydroxide and extracted with dichloromethane. The dichloromethane solution was refluxed for 96 h. The solution was washed with diluted sulphuric acid, water and sodium bicarbonate solution and dried. On evaporation of the solvent 20.1 g, m.p. 208°C, was obtained.

Calculated for

$C_{17}H_{10}N_2O_4$:	C 66.7	H 3.29	N 9.15	O 20.9
found	66.5	3.31	8.95	21.2

Example 21

Preparation of methandiol trans-4-aminomethylcyclohexanecarboxylate 4-aminomethylbenzoate dihydrochloride (Method H)

Tetrabutylammonium trans-4-(benzyloxycarbonylaminomethyl)cyclohexanecarboxylate (42.5 g; 0.08 mol) and tetrabutylammonium 4-(tert.-butoxycarbonylaminomethyl)benzoate (39.4 g; 0.08 mol) was refluxed in dichloromethane (800 ml) for 120 h. After washing and drying and evaporation of solvent 31 g of an oil was obtained. This oil was dissolved in glacial acetic acid and hydrochloric acid dissolved in acetic acid was added. After 3 h a precipitate (11.7 g) was collected, m.p. >270°C. This precipitate was discarded.

To the mother liquor 11.7 g diethyl ether was added and a precipitate was collected, 7.0 g. This product was recrystallized from 2-propanol several times to yield 2.3 g of methandiol trans-4-(benzyloxycarbonylaminomethyl)cyclohexanecarboxylate 4-aminomethylbenzoate hydrochloride, m.p. 162°C. 0.7 g of this product was dissolved in 50 ml acetic acid and hydrogenated at atmospheric pressure using 10% palladium on carbon as a catalyst. After 20 h the catalyst was filtered off and hydrochloric acid dissolved in ethyl acetate was added. The solvent was evaporated. The product was crystallized from isopropyl alcohol-diisopropyl ether mixtures. Yield 0.3 g, m.p. 240°C.

Calculated for

$C_{17}H_{26}N_2O_4Cl_2$:	C 51.9	H 6.66	N 7.12	Cl 18.0
found	50.1	6.87	7.19	17.5

The following examples illustrate how the compounds of the invention can be incorporated in pharmaceutical compositions:

5	Each tablet contains:		Example 22 Tablets	
10	Active substance, in the form of its hydrochloride	500.0 mg		
	Cellulose	100.0 mg		
	Polyvinylpyrrolidon	20.0 mg		
15	Talc	15.0 mg		
	Magnesium stearate	15.0 mg		
		650.0 mg		

25	Each suppository contains:		Example 23 Suppositories	
	Active substance, in the form of its hydrochloride	300.0 mg		
30	Ascorbyl palmitate	1.0 mg		
	Suppository base (Imhausen H)	ad 2.00 0.0 mg		

35	Example 24 Gel			
	Active compound in form of its hydrochloride	50 mg		
40	Liquid paraffin	190 mg		
	White soft paraffin	760 mg		

45	Example 25 Syrup	
	Active compound in form of its hydrochloride	100 mg
50	Sorbitol	180 mg
	Sorbic acid	1 mg
55	Sodiumpyrosulfite	0.1 mg
	Aroma	
	purified water	ad 1 ml

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Example 26
Solution

5	Active compound in form of its hydrochloride	100 mg
	Distilled water	ad 1 ml

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Example 27
Ointment

15	Active compound in form of its hydrochloride	50 mg
	Cotton seed oil	28.5 mg
	Cholesterol	28.5 mg
20	White soft paraffin	893 mg

Biological tests

25 In the biological tests described in sections A, B and C below, the test compounds were used in *trans* form and in the form of hydrochloride salt. The test results given in Tables 1 and 2 are average values.

A. In vivo test — absorption of compounds of the invention in rats after oral administration

Rats were chosen to study the absorption after oral administration of compounds of the invention which are esters of tranexamic acid. Absorption of tranexamic acid itself is very poor in rats.

30 The determination of absorption in the rats was performed in the following way: Male rats in groups of three or four were given the test compound by gavage (1 mmol/kg — 0.01 mmol/kg, 2 ml/kg). The urine was collected at the intervals 0—6, 6—24, 24—48 and 48—72 hours. At the end of each interval the cages were rinsed with 20 ml of distilled water, which also was collected and analyzed. The urine samples were then analysed for their content of tranexamic acid by a gaschromatographic method according to
35 Wessman J., Strömberg S., Anal. Chem. 49 (1977) 369. The results are shown in table 1, where the total absorption is given as the molar amount of tranexamic acid which was recovered in the urine samples compared to the amount of administered test compound, also calculated as tranexamic acid.

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TABLE 1

Absorption of compound of the invention after oral administration

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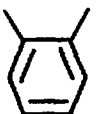
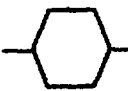
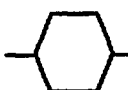
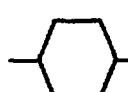
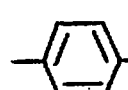
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Test compound			Absorption Mole % (average values of four tests)
$\text{H}_2\text{NCH}_2-\text{C}_6\text{H}_{10}-\text{COOCH}(\text{R}^2)-\text{OCO}-\text{R}^1$			
R ¹	R ²		
Tranexamic acid (reference)			11 ± 1.4
CH ₃	CH ₃		59 ± 6
CH(CH ₃) ₂	H		53 ± 3
CH(CH ₃) ₂	CH ₃		69 ± 3
C(CH ₃) ₃	H		60 ± 10
C(CH ₃) ₃	CH ₃		76 ± 4
OCH ₂ CH ₃	CH ₃		67 ± 11
OCH(CH ₃) ₂	CH ₃		87 ± 14
 (R ¹ and R ² together)			56 ± 11
 CH ₂ NH ₂	H		66 ± 11
 CH ₂ NH ₂	COOCH ₂ CH ₃		63 ± 8
 CH ₂ NH ₂	CON(CH ₃) ₂		55 ± 18
 CH ₂ NH ₂	H		34 ± 9

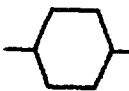
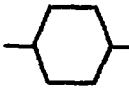
It is seen in Table 1 that all of the tested compounds were absorbed to a much higher degree than tranexamic acid. In particular, the compound where R¹ is OCH(CH₃)₂ and R² is CH₃ was absorbed to a very high degree, or 87%. Tranexamic acid was absorbed to 11%.

B. In vitro test — hydrolysis of compounds of the invention in phosphate buffer and in human plasma

The compounds of the present invention, which are esters of tranexamic acid, are converted to tranexamic acid in vivo either during the absorption through the gastro-intestinal wall or by enzymes present in the blood. In order to test the stability of compounds of the invention the half life in human plasma of a number of compounds of the invention was compared to the half life of the same ester in a phosphate buffer of the same pH. The half life, that is, the time within which the amount of unhydrolysed test compound is reduced by 50%, was calculated from the decrease of intact test compound with time. This decrease of intact test compound was monitored by UV-detection at 210 nm using high performance liquid chromatography (HPLC) in the reversed phase mode with mixtures of methanol and phosphate buffer as eluents. The stability in plasma was studied by addition of 50—100 ml of a stock solution of the test compound to 500—1000 ml of plasma thermostated to 37°C. The concentration of the test compound in plasma amounted to $2.3 \cdot 10^{-3}$ M. The plasma samples were injected directly into the column after filtration. The half life in buffer solution were determined in the same way except that no filtration was needed. The results are given in Table 2.

TABLE 2

Half life of esters of tranexamic acid in phosphate buffer of pH 7.5 and in human plasma

Test compound		Half life in	
$\text{H}_2\text{NCH}_2 - \text{C}_6\text{H}_{10} - \text{C}(=\text{O}) - \text{O} - \underset{\text{R}^2}{\text{CH}} - \text{O} - \text{C}(=\text{O}) - \text{R}^1$		phosphate buffer pH 7.5 (minutes)	human plasma (minutes)
R ¹	R ²		
CH ₃	CH ₃	$4.08 \cdot 10^3$	9
CH(CH ₃) ₂	H	$2.16 \cdot 10^3$	0.5
C(CH ₃) ₃	H	$8.82 \cdot 10^3$	5
OCH ₂ CH ₃	CH ₃	$5.40 \cdot 10^3$	1.5
	H	$1.56 \cdot 10^3$	1.5
	CH ₃	$4.20 \cdot 10^3$	11

It is seen in Table 2 that the tested compounds of the invention were hydrolyzed very rapidly in human plasma compared to the rate of hydrolysis in phosphate buffer.

C. Antifibrinolytic activity compared to tranexamic acid

The antifibrinolytic properties of tranexamic acid and a number of compounds of the invention were tested in an artificial circulating blood system, the Chandler loop (Chandler A.B., In vitro thrombolytic coagulation of blood. A method for producing a thrombus. Lab. Invest. 7, 110, 1958). Human blood was mixed with ¹²⁵I-labelled fibrinogen, divided into 1.5 ml portions and filled into plastic tubings. After recalcification the loops were rotated for 24 hours during which ¹²⁵I-labelled clots were formed. Fibrinolysis as measured with release of ¹²⁵I-labelled fibrin degradation products from the clot, was initiated by adding 20 PU/ml of porcine tissue activator to the loops. Clot lysis was followed during six hours and the

cumulative release of ^{125}I FDL was plotted v.s. time of lysis. When tranexamic acid was added to the system before addition of tissue activator, clot lysis was inhibited in a dose dependent manner. The effect on the clot lysis of compounds of the invention was tested in this system and compared to the inhibitory effect of tranexamic acid. The mean inhibitory effect of the test compounds at a concentration of 1 micromole/litre is listed in Table 3. No significant difference ($p > 0.05$) between the antifibrinolytic effect of tranexamic acid and the tested compounds of the invention was found in this test system.

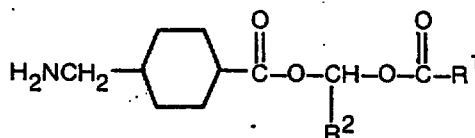
TABLE 3

Antifibrinolytic effect of compounds of the invention compared to the antifibrinolytic effect of tranexamic acid.

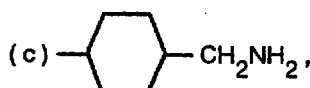
Test compound		Percent inhibition of fibrinolytic activity induced by porcine tissue activator
$\text{H}_2\text{NCH}_2 - \text{C}_6\text{H}_{10} - \text{COOCH}(\text{R}^2) - \text{OCO} - \text{R}^1$		
R^1	R^2	
Tranexamic acid (reference)		25.6 ± 3.9
CH_3	CH_3	19.5 ± 4.7
$\text{CH}(\text{CH}_3)_2$	H	32.4 ± 5.3
$\text{CH}(\text{CH}_3)_2$	CH_3	23.8 ± 5.7
$\text{C}(\text{CH}_3)_3$	H	19.3 ± 4.3
OCH_2CH_3	CH_3	23.4 ± 5.1
$\text{OCH}(\text{CH}_3)_2$	CH_3	25.8 ± 5.5
	$\text{CON}(\text{CH}_3)_2$	32.2 ± 4.7

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

1. A compound of the formula



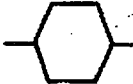
and therapeutically acceptable salt thereof, wherein R¹ is selected from the group consisting of
 (a) alkyl groups containing 1—4 carbon atoms,
 (b) alkoxy groups containing 1—4 carbon atoms,



cumulative release of ^{125}I FDL was plotted v.s. time of lysis. When tranexamic acid was added to the system before addition of tissue activator, clot lysis was inhibited in a dose dependent manner. The effect of the clot lysis of compounds of the invention was tested in this system and compared to the inhibitory effect of tranexamic acid. The mean inhibitory effect of the test compounds at a concentration of 1 micromole/litre is listed in Table 3. No significant difference ($p > 0.05$) between the antifibrinolytic effect of tranexamic acid and the tested compounds of the invention was found in this test system.

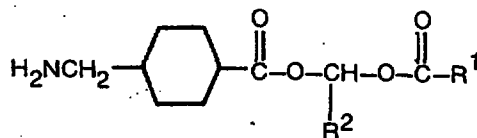
TABLE 3

Antifibrinolytic effect of compounds of the invention compared to the antifibrinolytic effect of tranexamic acid.

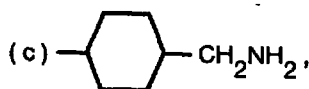
Test compound		Percent inhibition of fibrinolytic activity induced by porcine tissue activator
$\text{H}_2\text{NCH}_2 - \text{C}_6\text{H}_{10} - \text{COOCH}(\text{R}^2) - \text{OCO-R}^1$		
R^1	R^2	
Tranexamic acid (reference)		25.6 ± 3.9
CH_3	CH_3	19.5 ± 4.7
$\text{CH}(\text{CH}_3)_2$	H	32.4 ± 5.3
$\text{CH}(\text{CH}_3)_2$	CH_3	23.8 ± 5.7
$\text{C}(\text{CH}_3)_3$	H	19.3 ± 4.3
OCH_2CH_3	CH_3	23.4 ± 5.1
$\text{OCH}(\text{CH}_3)_2$	CH_3	25.8 ± 5.5
 CH_2NH_2 ;	$\text{CON}(\text{CH}_3)_2$	32.2 ± 4.7

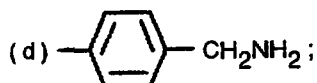
Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. A compound of the formula



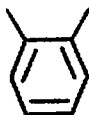
and therapeutically acceptable salt thereof, wherein R¹ is selected from the group consisting of
 (a) alkyl groups containing 1—4 carbon atoms,
 (b) alkoxy groups containing 1—4 carbon atoms,





R^2 is selected from the group consisting of

- (a) H,
 - (b) alkyl groups containing 1—4 carbon atoms,
 - (c) $-\text{COOR}^3$, wherein R^3 is an alkyl group containing 1—4 carbon atoms,
 - (d) $-\text{CONR}^4\text{R}^5$, wherein R^4 and R^5 are the same or different alkyl groups containing 1—3 carbon atoms;
- or wherein R^1 and R^2 represent together the radical

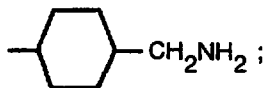


2. A compound according to claim 1 and therapeutically acceptable salts thereof, wherein R^2 is H or CH_3 .

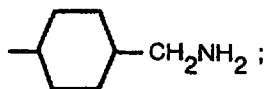
3. A compound according to claim 1 and therapeutically acceptable salts thereof wherein R^1 is an alkyl group containing 1—4 carbon atoms.

4. A compound according to claim 1, and therapeutically acceptable salts thereof, wherein R^1 is an alkoxy group containing 1—4 carbon atoms.

5. A compound according to claim 1, and therapeutically acceptable salts thereof, wherein



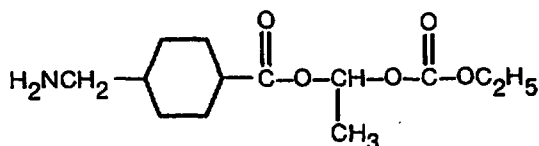
6. A compound according to claim 1, and therapeutically acceptable salt thereof wherein R^1 is an alkyl group containing 1—4 carbon atoms, an alkoxy group containing 1—4 carbon atoms, or the radical



and wherein R^2 is H or CH_3 .

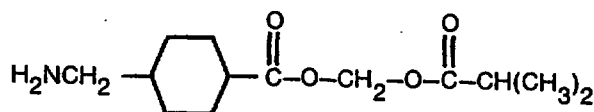
7. A compound according to claim 1, and therapeutically acceptable salts thereof, wherein R^1 is an alkoxy group containing 1—4 carbon atoms and R^2 is H or CH_3 .

8. A compound of the formula



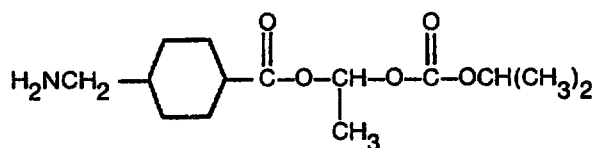
or a therapeutically acceptable salt thereof.

9. A compound of the formula



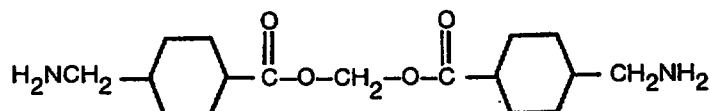
or a therapeutically acceptable salt thereof.

10. A compound of the formula



or a therapeutically acceptable salt thereof.

11. A compound of the formula



or a therapeutically acceptable salt thereof.

12. A compound according to any of claims 1—11 in the form of its *trans* isomer.

13. A compound according to any of claims 1—12 in the form of its hydrochloride.

14. A pharmaceutical preparation, containing as active ingredient a compound as defined in any of claims 1—13, optionally in combination with a pharmaceutically acceptable carrier.

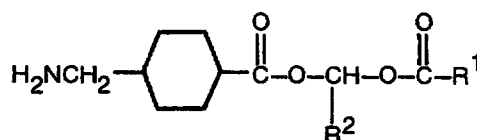
15. A pharmaceutical preparation according to claim 14 in dosage unit form.

16. A compound as defined in any of claims 1—13 for use in the treatment of ailments in mamma's and man, which are due to increased fibrinolysis.

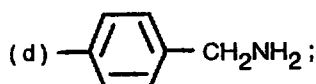
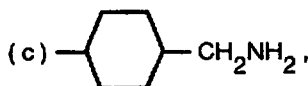
17. A compound as defined in any of claims 1—13 for use in the treatment of peptic ulcer in man.

18. A compound as defined in any of claims 1—13 for use in the treatment of hereditary angio-neurotic edema in man.

19. A process for the preparation of a compound of the formula



and therapeutically acceptable salts thereof, wherein R^1 is selected from the group consisting of
(a) alkyl groups containing 1—4 carbon atoms,
(b) alkoxy groups containing 1—4 carbon atoms,



R^2 is selected from the group consisting of

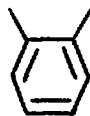
(a) H,

(b) alkyl groups containing 1—4 carbon atoms,

(c) $-\text{COOR}^3$, wherein R^3 is an alkyl group containing 1—4 carbon atoms,

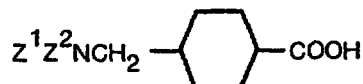


(d) $-\text{CONR}^4\text{R}^5$, wherein R^4 and R^5 are the same or different alkyl groups containing 1—3 carbon atoms; or wherein R^1 and R^2 represent together the radical



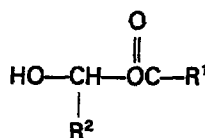
by

A. reacting a compound of the formula



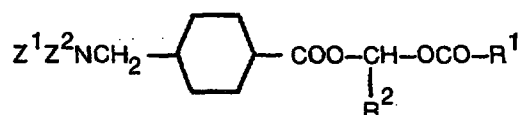
II

wherein Z^1 and Z^2 are H or a protecting group, or a functionally equivalent derivative thereof, with a compound of the formula



III

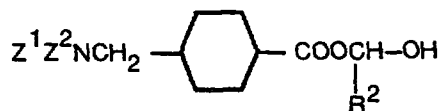
or a functionally equivalent derivative thereof, wherein R^1 and R^2 are as defined previously, whereby the possible amine substituent in R^1 also may be protected by protecting groups Z^1 and Z^2 , to the formation of a compound of the formula



IV

whereafter if necessary protecting groups Z^1 and Z^2 are removed to the formation of a compound of the formula I;

B. reacting a compound of the formula



V

wherein Z^1 and Z^2 are H or a protecting group, or a functionally equivalent derivative thereof, with a compound of the formula



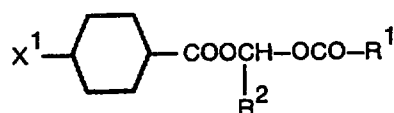
VI

wherein R^1 is as defined above, or a functionally equivalent derivative thereof, whereby the possible amine substituent in R^1 also may be protected by protecting groups Z^1 and Z^2 , to the formation of a compound of formula IV whereafter, if necessary, protecting groups Z^1 and Z^2 are removed to the formation of a compound of formula I;



C. reduction of a compound of the formula

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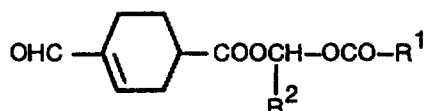
VII

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wherein R^1 and R^2 are as defined above and X^1 is $-\text{CN}$, $-\text{CH}_2\text{NO}_2$, $-\text{CH}_2\text{N}_3$, $-\text{CONH}_2$ or $-\text{CH}=\text{N}-\text{OH}$ to the formation of a compound of the formula I;

D. reduction of a compound of the formula

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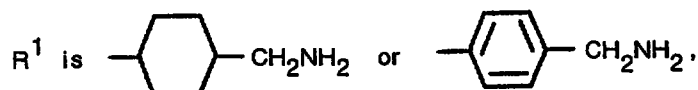
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VIII

wherein R^1 and R^2 are as defined above, in the presence of NH_3 to the formation of a compound of the formula I;

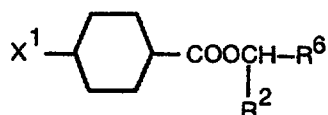
E. for the preparation of compounds of the formula I wherein

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35 reduction of a compound of the formula

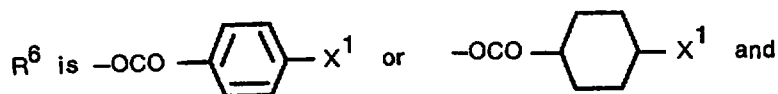
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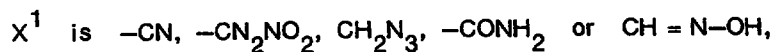
IX

45 wherein R^2 is as defined above,

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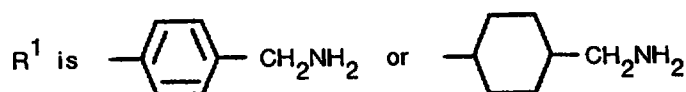
55



to the formation of a compound of the formula I wherein

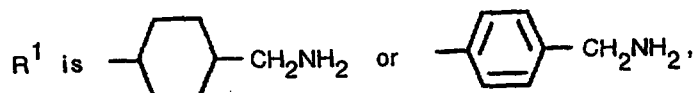
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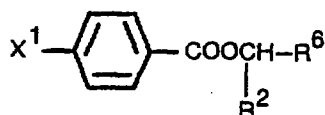
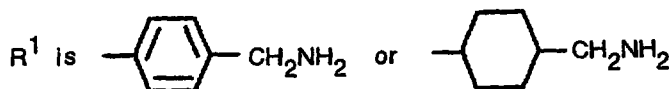


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F. for the preparation of compounds of the formula I wherein



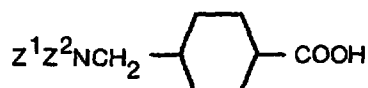
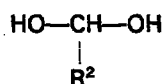
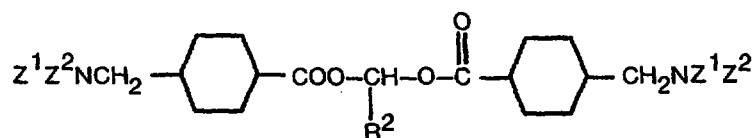
10 reduction of a compound of the formula

20 wherein R^2 , R^6 and X^1 are as defined above, to the formation of a compound of the formula I wherein

30 G. for the preparation of compounds of the formula I wherein



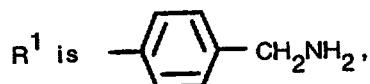
40 reacting a compound of the formula

50 wherein Z^1 and Z^2 are H or a protecting group as defined above, or a functionally equivalent derivative thereof, with a compound of the formula60 wherein R^2 is as defined above, or a functionally equivalent derivative thereof, to give a compound of the formula

whereafter if necessary protecting groups Z^1 and Z^2 are removed.

H. for the preparation of compounds of the formula I wherein

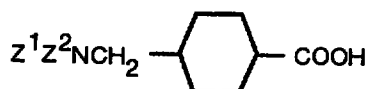
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10

reacting a compound of the formula

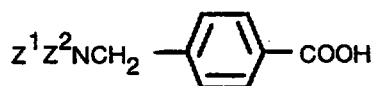
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XI

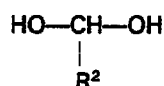
20 and a compound of the formula

25



XIV

30 in which formulas Z^1 and Z^2 are H or a protecting group as defined above, or a functionally equivalent derivative thereof, with a compound of the formula

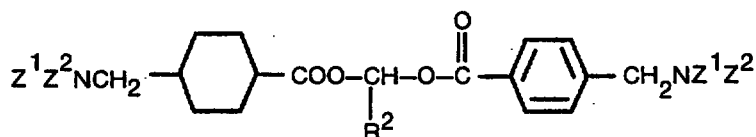


XV

35

wherein R^2 is as defined above, or a functionally equivalent derivative thereof, to give a compound of the formula

40



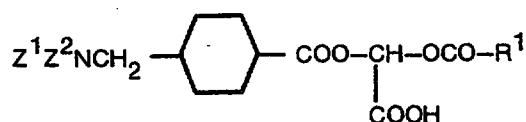
XVI

45

whereafter if necessary protecting groups Z^1 and Z^2 are removed.

50 I. for the preparation of a compound of the formula I wherein R^2 is COOR^3 , reacting a compound of the formula

55



XVII

60 wherein Z^1 and Z^2 are H or a protecting group as defined above and R^1 is as defined above, whereby the possible amine substituent in R^1 also may be protected by protecting groups Z^1 and Z^2 , or a functionally equivalent derivative thereof, with a compound of the formula



XVIII

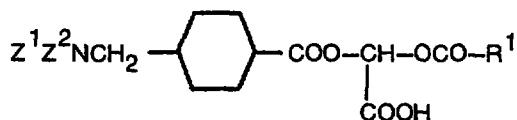
65 wherein R^3 is as defined above, or a functionally equivalent derivative thereof, whereafter if necessary,



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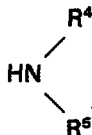
protecting groups Z^1 and Z^2 are removed, to the formation of a compound of the formula I wherein R^2 is COOR^3 .

J. for the preparation of a compound of the formula I wherein R^2 is CONR^4R^5 , reacting a compound of the formula



XVIII

wherein R^1 , Z^1 and Z^2 are as defined above, or a functionally equivalent derivative thereof, with a compound of the formula



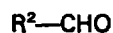
XIX

wherein R^4 and R^5 are as defined above, or a functionally equivalent derivative thereof, whereafter, if necessary, protecting groups Z^1 and Z^2 are removed, to the formation of a compound of the formula I wherein R^2 is CONR^4R^5 .

K. for the preparation of compounds wherein

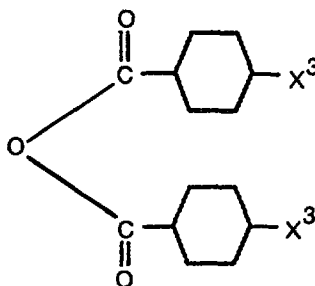


reacting a compound of the formula



XX

wherein R^2 is as defined above, with a compound of the formula



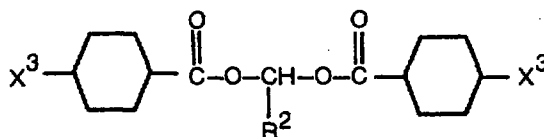
XXI

wherein X^3 is

(a) $\text{CH}_2\text{NZ}^1\text{Z}^2$

wherein Z^1 and Z^2 are protecting groups as defined in method A, or

(b) CN , CH_2NO_2 , CH_2N_3 , CONH_2 or $\text{CH}=\text{N}-\text{OH}$,
to the formation of a compound of the formula



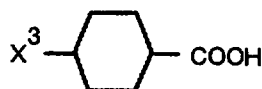
XXII



whereafter each of the groups X^3 are converted to CH_2NH_2 by removal of the protecting groups Z^1 and Z^2 or by reduction of the groups CN , CH_2NO_2 , CH_2N_3 , $CONH_2$, $CH=N-OH$ to the formation of a compound of the formula I wherein

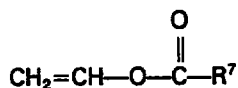


L. for the preparation of compounds of the formula I wherein R^1 is an alkyl group containing 1—4 carbon atoms, and R^2 is CH_3 , reacting a compound of the formula



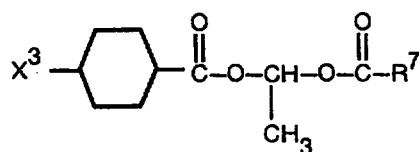
XXIII

20 wherein X^3 is as defined in Method K, with a compound of the formula



XXIV

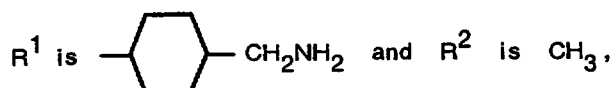
wherein R^7 is an alkyl group containing 1—4 carbon atoms, to the formation of a compound of the formula



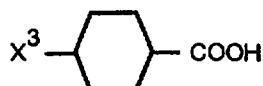
XXV

40 wherein X^3 and X^7 are as described above, whereafter X^3 is converted to CH_2NH_2 as described in Method K to the formation of a compound of the formula I wherein R^1 is an alkyl group containing 1—4 carbon atoms and wherein R^2 is CH_3 .

M. for the preparation of compounds of the formula I wherein



50 reacting a compound of the formula



XXIII

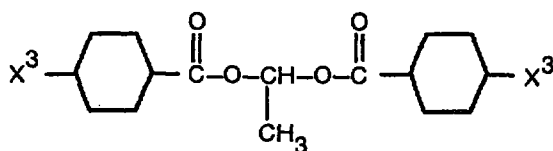
60 wherein X^3 is as defined in Method K, with a compound of the formula



XXVI

65 to the formation of a compound of the formula



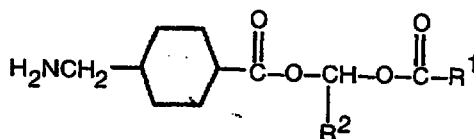


XXVII

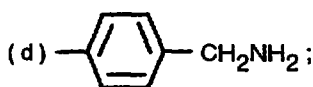
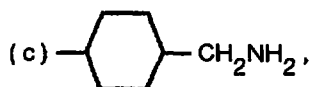
wherein X^3 is as defined above, whereafter X^3 is converted to CH_2NH_2 as described in Method K to the formation of a compound of the formula I, whereafter the compound of the formula I thus obtained if necessary is isolated in trans-form and/or is converted to a therapeutically acceptable salt.

Claims for the Contracting State: AT

1. A process for the preparation of a compound of the formula

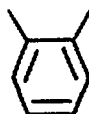


and therapeutically acceptable salts thereof, wherein R^1 is selected from the group consisting of
 (a) alkyl groups containing 1—4 carbon atoms,
 (b) alkoxy groups containing 1—4 carbon atoms,

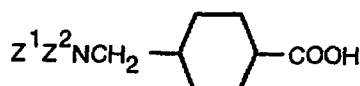


R^2 is selected from the group consisting of

- (a) H,
 - (b) alkyl groups containing 1—4 carbon atoms,
 - (c) $-\text{COOR}^3$, wherein R^3 is an alkyl group containing 1—4 carbon atoms,
 - (d) $-\text{CONR}^4\text{R}^5$, wherein R^4 and R^5 are the same or different alkyl groups containing 1—3 carbon atoms;
- or wherein R^1 and R^2 represent together the radical



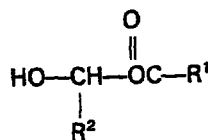
A. reacting a compound of the formula



wherein Z^1 and Z^2 are H or a protecting group, or a functionally equivalent derivative thereof, with a compound of the formula

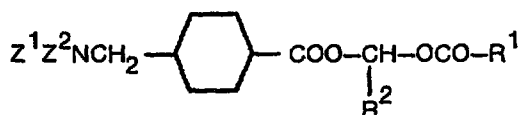


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III

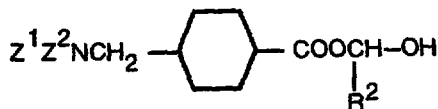
or a functionally equivalent derivative thereof, wherein R^1 and R^2 are as defined previously, whereby the possible amine substituent in R^1 also may be protected by protecting groups Z^1 and Z^2 , to the formation of a compound of the formula



IV

whereafter if necessary protecting groups Z^1 and Z^2 are removed to the formation of a compound of the formula I;

B. reacting a compound of the formula



V

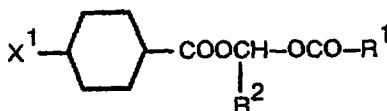
wherein Z^1 and Z^2 are H or a protecting group, or a functionally equivalent derivative thereof, with a compound of the formula



VI

wherein R^1 is as defined above, or a functionally equivalent derivative thereof, whereby the possible amine substituent in R^1 also may be protected by protecting groups Z^1 and Z^2 , to the formation of a compound of formula IV whereafter, if necessary, protecting groups Z^1 and Z^2 are removed to the formation of a compound of formula I;

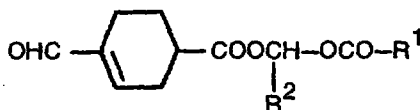
C. reduction of a compound of the formula



VII

wherein R^1 and R^2 are as defined above and X^1 is $-\text{CN}$, $-\text{CH}_2\text{NO}_2$, $-\text{CH}_2\text{N}_3$, $-\text{CONH}_2$ or $-\text{CH}=\text{N}-\text{OH}$ to the formation of a compound of the formula I;

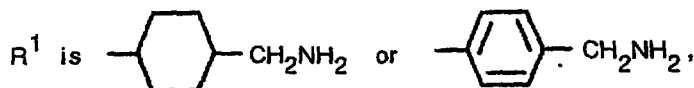
D. reduction of a compound of the formula



VIII

wherein R^1 and R^2 are as defined above, in the presence of NH_3 to the formation of a compound of the formula I;

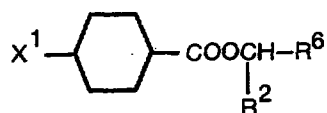
E. for the preparation of compounds of the formula I wherein



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reduction of a compound of the formula

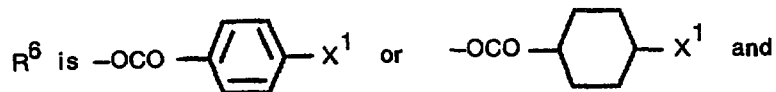
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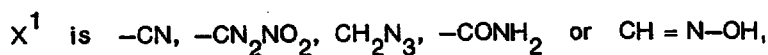
IX

10 wherein R^2 is as defined above,

15

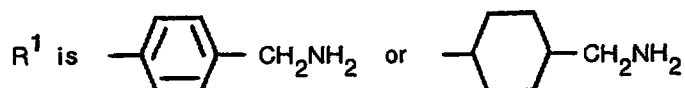


20



to the formation of a compound of the formula I wherein

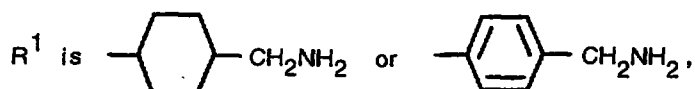
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30

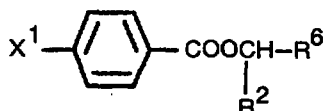
F. for the preparation of compounds of the formula I wherein

35



40 reduction of a compound of the formula

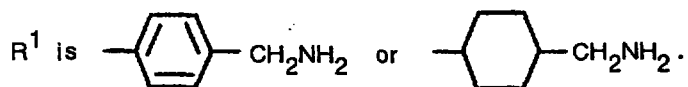
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X

50 wherein R^2 , R^6 and X^1 are as defined above, to the formation of a compound of the formula I wherein

55



60

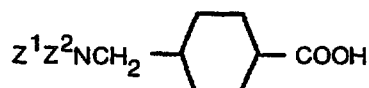
G. for the preparation of compounds of the formula I wherein

65



65 reacting a compound of the formula



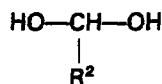


XI

5

wherein Z^1 and Z^2 are H or a protecting group as defined above, or a functionally equivalent derivative thereof, with a compound of the formula

10

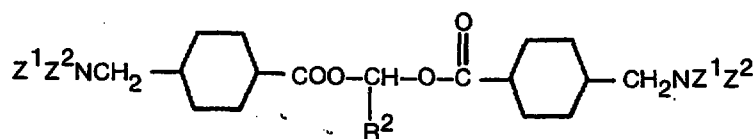


XII

wherein R^2 is as defined above, or a functionally equivalent derivative thereof, to give a compound of the formula

15

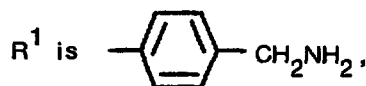
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XIII

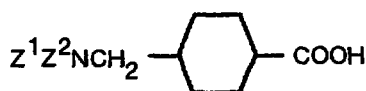
whereafter if necessary protecting groups Z^1 and Z^2 are removed.
H. for the preparation of compounds of the formula I wherein

30



35 reacting a compound of the formula

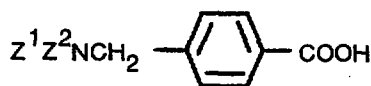
40



XI

and a compound of the formula

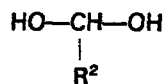
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XIV

50 in which formulas Z^1 and Z^2 are H or a protecting group as defined above, or a functionally equivalent derivative thereof, with a compound of the formula

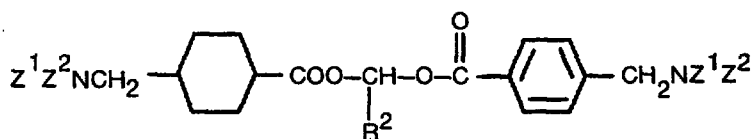
55



XII

wherein R^2 is as defined above, or a functionally equivalent derivative thereof, to give a compound of the formula

60



XV

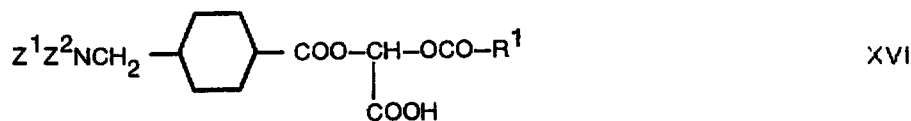
65



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whereafter if necessary protecting groups Z^1 and Z^2 are removed.

I. for the preparation of a compound of the formula I wherein R^2 is COOR^3 , reacting a compound of the formula

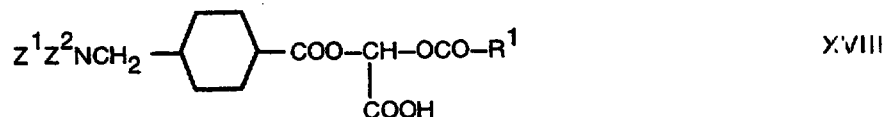


wherein Z^1 and Z^2 are H or a protecting group as defined above and R^1 is as defined above, whereby the possible amine substituent in R^1 also may be protected by protecting groups Z^1 and Z^2 , or a functionally equivalent derivative thereof, with a compound of the formula



wherein R^3 is as defined above, or a functionally equivalent derivative thereof, whereafter if necessary, protecting groups Z^1 and Z^2 are removed, to the formation of a compound of the formula I wherein R^2 is COOR^3 .

J. for the preparation of a compound of the formula I wherein R^2 is CONR^4R^5 , reacting a compound of the formula

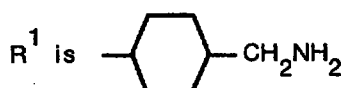


wherein R^1 , Z^1 and Z^2 are as defined above, or a functionally equivalent derivative thereof, with a compound of the formula



wherein R^4 and R^5 are as defined above, or a functionally equivalent derivative thereof, whereafter, if necessary, protecting groups Z^1 and Z^2 are removed, to the formation of a compound of the formula I wherein R^2 is CONR^4R^5 .

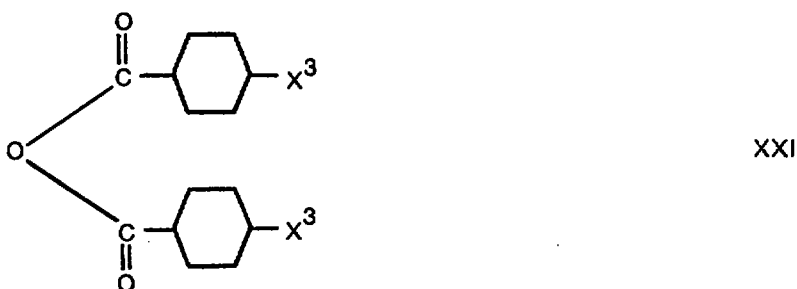
K. for the preparation of compounds wherein



reacting a compound of the formula



wherein R^2 is as defined above, with a compound of the formula



wherein X^3 is

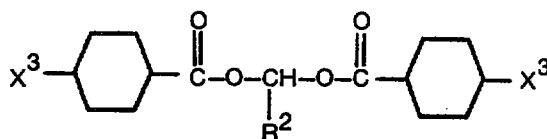
(a) $CH_2NZ^1Z^2$

wherein Z^1 and Z^2 are protecting groups as defined in method A, or

(b) CN , CH_2NO_2 , CH_2N_3 , $CONH_2$ or $CH=N-OH$,

5 to the formation of a compound of the formula

10



XXII

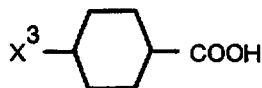
15 whereafter each of the groups X^3 are converted to CH_2NH_2 by removal of the protecting groups Z^1 and Z^2 or by reduction of the groups CN , CH_2NO_2 , CH_2N_3 , $CONH_2$, $CH=N-OH$ to the formation of a compound of the formula I wherein

20



25 L. for the preparation of compounds of the formula I wherein R^1 is an alkyl group containing 1—4 carbon atoms, and R^2 is CH_3 , reacting a compound of the formula

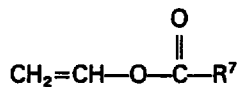
30



XXIII

wherein X^3 is as defined in Method K, with a compound of the formula

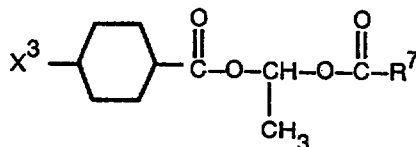
35



XXIV

40 wherein R^7 is an alkyl group containing 1—4 carbon atoms, to the formation of a compound of the formula

45

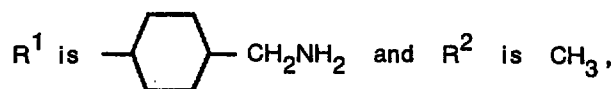


XXV

50 wherein X^3 and R^7 are as defined above, whereafter X^3 is converted to CH_2NH_2 as defined in Method K to the formation of a compound of the formula I wherein R^1 is an alkyl group containing 1—4 carbon atoms and wherein R^2 is CH_3 .

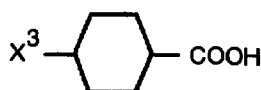
M. for the preparation of compounds of the formula I wherein

55



60 reacting a compound of the formula

65



XXIII



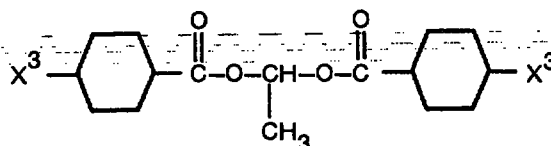
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wherein X^3 is as defined in Method K, with a compound of the formula



XXVI

to the formation of a compound of the formula



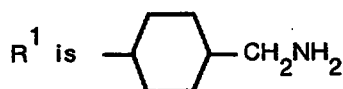
XXVII

wherein X^3 is as defined above, whereafter X^3 is converted to CH_2NH_2 as described in Method K to the formation of a compound of the formula I, whereafter the compound of the formula I thus obtained if necessary is isolated in trans-form and/or is converted to a therapeutically acceptable salt.

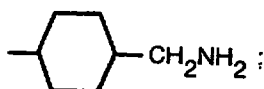
2. A process according to claim 1 for the preparation of a compound of the formula I and therapeutically acceptable salts thereof, wherein R^2 is H or CH_3 .

3. A process according to claim 1 for the preparation of a compound of the formula I and therapeutically acceptable salts thereof wherein R^1 is an alkyl group containing 1—4 carbon atoms or an alkoxy group containing 1—4 carbon atoms.

4. A process according to claim 1 for the preparation of a compound of the formula I and therapeutically acceptable salts thereof, wherein R^1 is



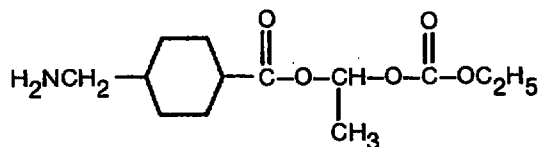
5. A process according to claim 1 for the preparation of a compound of the formula I and therapeutically acceptable salts thereof, wherein R^1 is an alkyl group containing 1—4 carbon atoms, an alkoxy group containing 1—4 carbon atoms, or the radical



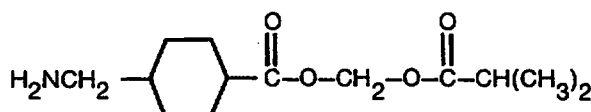
and wherein R^2 is H or CH_3 .

6. A process according to claim 1 for the preparation of a compound of the formula I and therapeutically acceptable salts thereof, wherein R^1 is an alkoxy group containing 1—4 carbon atoms and R^2 is H or CH_3 .

7. A process according to claim 1 for the preparation of a compound of the formula

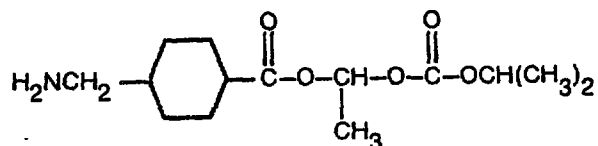


or a therapeutically acceptable salt thereof,

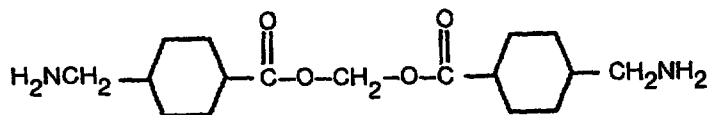


or a therapeutically acceptable salt thereof,





or a therapeutically acceptable salt thereof, or



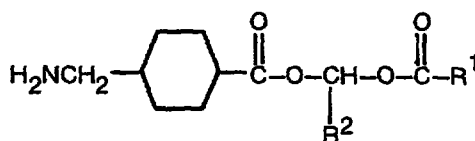
or a therapeutically acceptable salt thereof.

8. A process according to claim 1 for the preparation of a compound as defined in claims 1—7 in the form of its *trans* isomer.

9. A process according to claim 1 for the preparation of a compound as defined in claims 1—7, in the form of its hydrochloride.

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

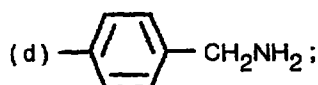
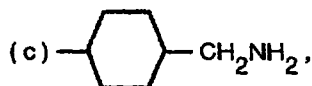
1. Verbindung der Formel



und deren therapeutisch annehmbare Salze, worin

R¹ (a) eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen,

(b) eine Alkoxygruppe mit 1 bis 4 Kohlenstoffatomen,

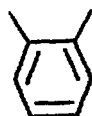


R² (a) Wasserstoff,

(b) eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen,

(c) $-\text{COOR}^3$, worin R³ eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen ist,

(d) $-\text{CONR}^4\text{R}^5$, worin R⁴ und R⁵ gleich oder verschieden sind und Alkylgruppen mit 1 bis 3 Kohlenstoffatomen sind; bedeutet oder R¹ und R² zusammen die Gruppe



darstellen.

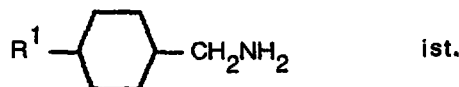


2. Verbindung nach Anspruch 1 und deren therapeutisch annehmbare Salze, worin R^2 Wasserstoff oder CH_3 ist.

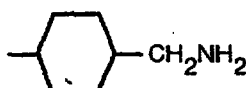
3. Verbindung nach Anspruch 1 und deren therapeutisch annehmbare Salze, worin R^1 eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen ist.

4. Verbindung nach Anspruch 1 und deren therapeutisch annehmbare Salze, worin R^1 eine Alkoxygruppe mit 1 bis 4 Kohlenstoffatomen ist.

5. Verbindung nach Anspruch 1 und deren therapeutisch annehmbare Salze, worin



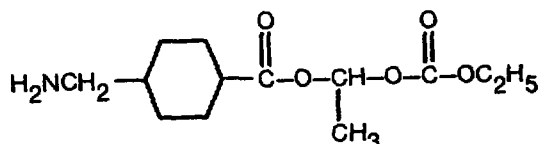
6. Verbindung nach Anspruch 1 und deren therapeutisch annehmbare Salze, worin R^1 eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen, eine Alkoxygruppe mit 1 bis 4 Kohlenstoffatomen oder den rest



bedeutet und R^2 Wasserstoff oder CH_3 ist.

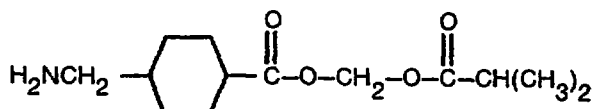
7. Verbindung nach Anspruch 1 und deren therapeutisch annehmbare Salze, worin R^1 eine Alkoxygruppe mit 1 bis 4 Kohlenstoffatomen und R^2 Wasserstoff oder CH_3 ist.

8. Verbindung der Formel



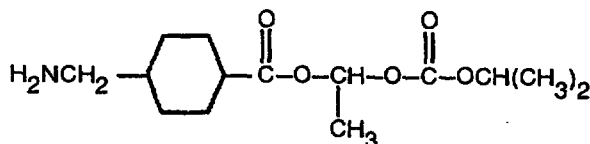
oder ein therapeutisch annehmbares Salz davon.

9. Verbindung der Formel



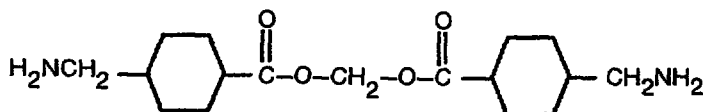
oder ein therapeutisch annehmbares Salz davon.

10. Verbindung der Formel



oder ein therapeutisch annehmbares Salz davon.

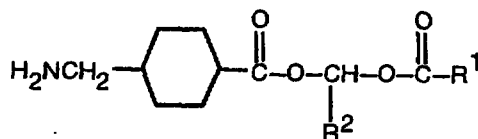
11. Verbindung der Formel



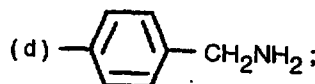
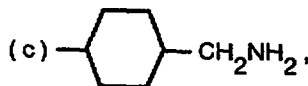
oder ein therapeutisch annehmbares Salz davon.



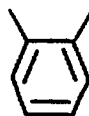
12. Verbindung, wie in den Ansprüchen 1 bis 11 definiert, in Form ihres trans-Isomeren.
 13. Verbindung, wie in den Ansprüchen 1 bis 11 definiert, in Form ihres Hydrochlorids.
 14. Pharmazeutisches Präparat, das als aktiven Bestandteil eine Verbindung nach einem der Ansprüche 1 bis 13, gegebenenfalls in Kombination mit einem pharmazeutisch unbedenklichen Träger enthält.
 15. Pharmazeutisches Präparat nach Anspruch 14 in der Darreichungsform von Dosiereinheiten.
 16. Verbindung nach einem der Ansprüche 1 bis 13 zur Verwendung in der Behandlung von Erkrankungen bei Säugetieren und Menschen, verursacht durch erhöhte Fibrinolyse.
 17. Verbindung nach einem der Ansprüche 1 bis 13 zur Verwendung in der Behandlung von Ulcus pepticum beim Menschen.
 18. Verbindung nach einem der Ansprüche 1 bis 13 zur Verwendung in der Behandlung hereditärer angioneurotischer Ödeme beim Menschen.
 19. Verfahren zur Herstellung einer Verbindung der Formel



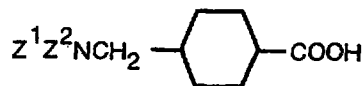
und therapeutisch annehmbarer Salze derselben, worin
 R¹ (a) eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen,
 (b) eine Alkoxygruppe mit 1 bis 4 Kohlenstoffatomen,



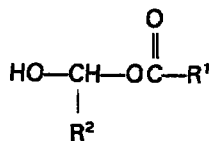
R² (a) Wasserstoff,
 (b) eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen,
 (c) $-\text{COOR}^3$, worin R³ eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen ist,
 (d) $-\text{CONR}^4\text{R}^5$, worin R⁴ und R⁵ gleich oder verschieden sind und Alkylgruppen mit 1 bis 3 Kohlenstoffatomen sind; bedeutet oder R¹ und R² zusammen die Gruppe



darstellen, indem
 A. eine Verbindung der Formel

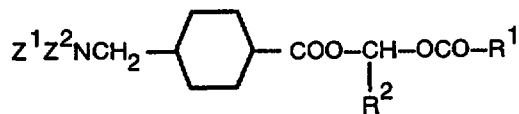


worin Z¹ und Z² Wasserstoff oder eine Schutzgruppe bedeuten, oder ein funktionell äquivalentes Derivat davon mit einer Verbindung der Formel



oder einem funktionell äquivalenten Derivat davon, worin R^1 und R^2 wie oben definiert sind, wobei der mögliche Amin-Substituent in R^1 auch durch Schutzgruppen Z^1 und Z^2 geschützt sein kann, umgesetzt wird unter Bildung einer Verbindung der Formel

5



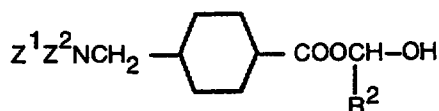
IV

10

wonach nötigenfalls die Schutzgruppen Z^1 und Z^2 unter Bildung einer Verbindung der Formel I entfernt werden;

B. eine Verbindung der Formel

15



V

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worin Z^1 und Z^2 Wasserstoff oder eine Schutzgruppe sind, oder ein funktionell äquivalentes Derivat davon mit einer Verbindung der Formel

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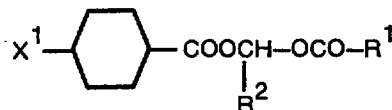


VI

30 worin R^1 wie oben definiert ist, oder einem funktionell äquivalenten Derivat davon umgesetzt wird, wobei der mögliche Amins substituent in R^1 auch durch Schutzgruppen Z^1 und Z^2 geschützt sein kann, unter Bildung einer Verbindung der Formel IV, wonach nötigenfalls die Schutzgruppen Z^1 und Z^2 unter Bildung einer Verbindung der Formel I entfernt werden;

C. eine Verbindung der Formel

35



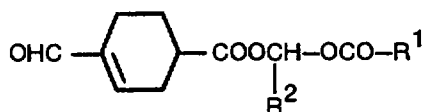
VII

40

worin R^1 und R^2 wie oben definiert sind und X^1 $-\text{CN}$, $-\text{CH}_2\text{NO}_2$, $-\text{CH}_2\text{N}_3$, $-\text{CONH}_2$ oder $-\text{CH}=\text{N}-\text{OH}$ bedeutet, unter Bildung einer Verbindung der Formel I reduziert wird;

45

D. eine Verbindung der Formel



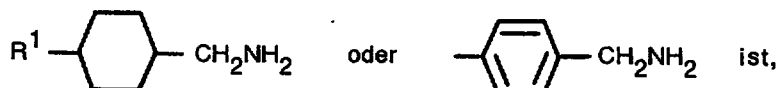
VIII

50

55 worin R^1 und R^2 wie oben definiert sind, in Gegenwart von NH_3 unter Bildung einer Verbindung der Formel I reduziert wird;

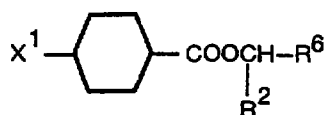
E. für die Herstellung einer Verbindung der Formel I, worin

60



65 eine Verbindung der Formel





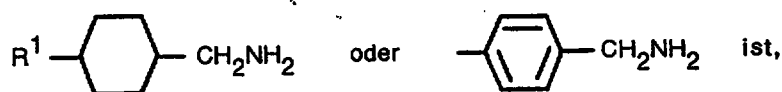
IX

5 worin R^2 wie oben definiert ist,



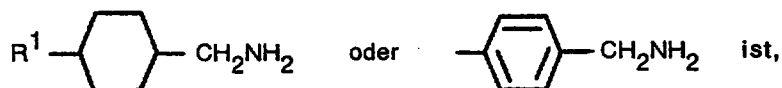
10 ist und X^1 $-\text{CN}$, $-\text{CH}_2\text{NO}_2$, $-\text{CH}_2\text{N}_3$, $-\text{CONH}_2$ oder $-\text{CH}=\text{N}-\text{OH}$ bedeutet,

15 unter Bildung einer Verbindung der Formel I, worin

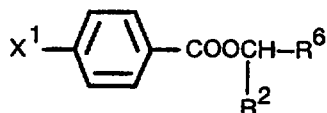


20 reduziert wird;

F. für die Herstellung einer Verbindung der Formel I, worin



25 eine Verbindung der Formel



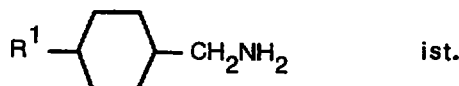
X

30 worin R^2 , R^6 und X^1 wie oben definiert sind, unter Bildung einer Verbindung der Formel I, worin



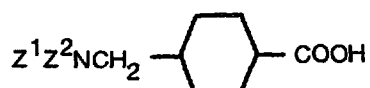
35 reduziert wird;

G. für die Herstellung einer Verbindung der Formel I, worin



40 eine Verbindung der Formel



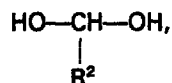


XI

5

worin Z^1 und Z^2 Wasserstoff oder eine Schutzgruppe wie oben definiert sind, oder ein funktionell äquivalentes Derivat davon mit einer Verbindung der Formel

10

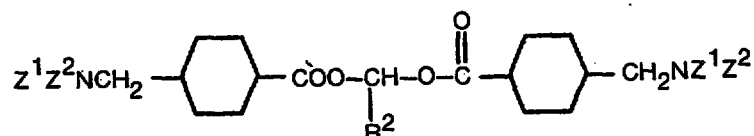


XII

15

worin R^2 wie oben definiert ist, oder einem funktionell äquivalenten Derivat davon unter Bildung einer Verbindung der Formel

20

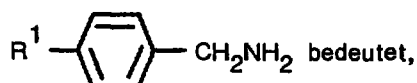


XIII

25

umgesetzt wird, wonach nötigenfalls die Schutzgruppen Z^1 und Z^2 entfernt werden;
H. für die Herstellung einer Verbindung der Formel I, worin

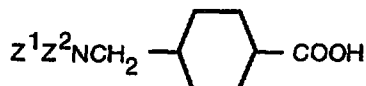
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35

eine Verbindung der Formel

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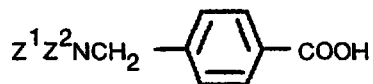


XI

45

und eine Verbindung der Formel

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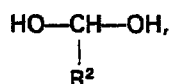


XIV

55

worin Z^1 und Z^2 Wasserstoff oder eine Schutzgruppe wie oben definiert sind, oder ein funktionell äquivalentes Derivat davon mit einer Verbindung der Formel

60

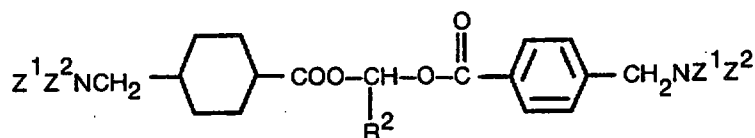


XII

65

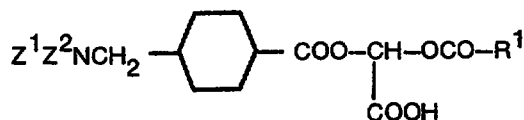
worin R^2 wie oben definiert ist, oder einem funktionell äquivalenten Derivat davon zu einer Verbindung der Formel





XV

umgesetzt wird, wonach nötigenfalls die Schutzgruppen Z^1 und Z^2 entfernt werden;
I. für die Herstellung einer Verbindung, worin R^2 $COOR^3$ ist, eine Verbindung der Formel



XVI

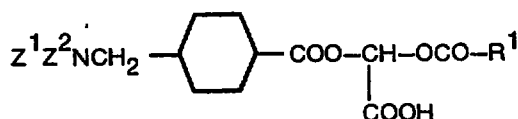
worin Z^1 und Z^2 Wasserstoff oder eine Schutzgruppe wie oben definiert sind und R^1 wie oben definiert ist,
wobei der mögliche Aminsубstituent in R^1 auch durch Schutzgruppen R^1 und R^2 geschützt sein kann, oder
ein funktionell äquivalentes Derivat davon mit einer Verbindung der Formel



XVII

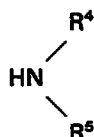
worin R^3 wie oben definiert ist, oder einem funktionell äquivalenten Derivat davon umgesetzt wird, wonach
nötigenfalls die Schutzgruppen Z^1 und Z^2 unter Bildung einer Verbindung der Formel I, worin R^2 $COOR^3$ ist,
entfernt werden;

J. für die Herstellung einer Verbindung der Formel I, worin R^2 $CONR^4 R^5$ ist, eine Verbindung der Formel



XVIII

worin R^1 , Z^1 , und Z^2 wie oben definiert sind, mit einer Verbindung der Formel



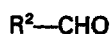
XIX

worin R^4 und R^5 wie oben definiert sind, oder einem funktionell äquivalenten Derivat davon umgesetzt
wird, wonach nötigenfalls die Schutzgruppen Z^1 und Z^2 unter Bildung einer Verbindung der Formel I, worin
 R^2 $CONR^4 R^5$ bedeutet, entfernt werden;

K. für die Herstellung von Verbindungen, worin



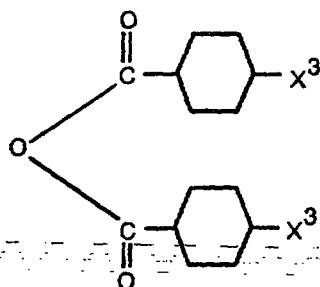
eine Verbindung der Formel



XX

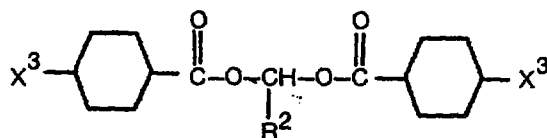
worin R^2 wie oben definiert ist, mit einer Verbindung der Formel





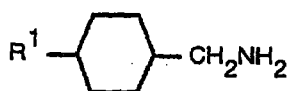
XXI

15 worin X^3 (a) $CH_2NZ^1Z^2$ ist, wobei Z^1 und Z^2 Schutzgruppen bedeuten, wie in Verfahren A definiert, oder (b) CN , CH_2NO_2 , CH_2N_3 , $CONH_2$ oder $CH=N-OH$ ist, umgesetzt wird unter Bildung einer Verbindung der Formel



XXII

25 wonach jede der Gruppen X^3 durch Entfernung der Schutzgruppen Z^1 und Z^2 oder durch Reduzieren der Gruppen CN , CH_2NO_2 , CH_2N_3 , $CONH_2$, $CH=N-OH$ in die CH_2NH_2 -Gruppe überführt wird, unter Bildung einer Verbindung der Formel I, worin



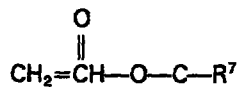
ist.

35 L. für die Herstellung von Verbindungen der Formel I, worin R^1 eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen und R^2 CH_3 ist, eine Verbindung der Formel



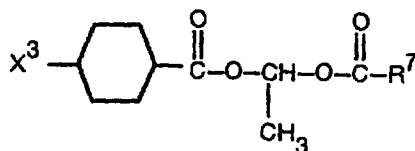
XXIII

45 worin X^3 wie in Verfahren K definiert ist, mit einer Verbindung der Formel



XXIV

50 worin R^7 eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen ist, umgesetzt wird unter Bildung einer Verbindung der Formel



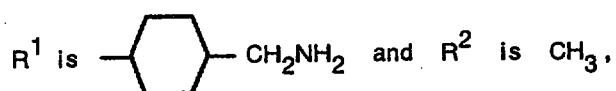
XXV

65 worin X^3 und R^7 wie oben definiert sind, wonach X^3 zu CH_2NH_2 wie in Verfahren K beschrieben umgesetzt wird, unter Bildung einer Verbindung der Formel I, worin R^1 eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen und R^2 CH_3 ist;



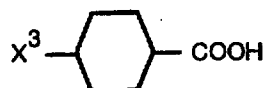
M. für die Herstellung von Verbindungen der Formel I, worin

5



10 eine Verbindung der Formel

15



XXIII

worin X^3 wie in Verfahren K definiert ist, mit einer Verbindung der Formel

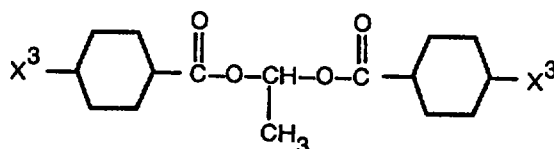
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XXVI

unter Bildung einer Verbindung der Formel

25



XXVII

30

worin X^3 wie oben definiert ist, umgesetzt wird, wonach X^3 zu CH_2NH_2 umgesetzt wird, wie in Verfahren K beschrieben, unter Bildung einer Verbindung der Formel I; wonach die so erhaltene Verbindung der Formel I nötigenfalls in der trans-Form isoliert wird und/oder in ein therapeutisch annehmbares Salz überführt wird.

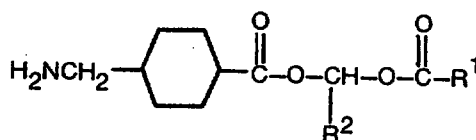
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Patentansprüche für den Vertragsstaat: AT

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1. Verfahren zur Herstellung einer Verbindung der Formel

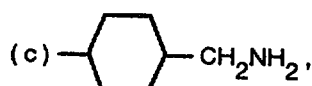
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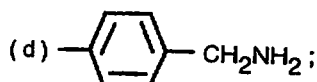
50

und therapeutisch annehmbarer Salze derselben, worin
 R^1 (a) eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen,
 (b) eine Alkoxygruppe mit 1 bis 4 Kohlenstoffatomen,

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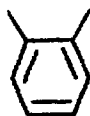


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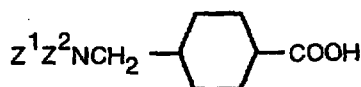
R^2 (a) Wasserstoff,
 (b) eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen,



- (c) $-\text{COOR}^3$, worin R^3 eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen ist,
 (d) $-\text{CONR}^4\text{R}^5$, worin R^4 und R^5 gleich oder verschieden sind und Alkylgruppen mit 1 bis 3 Kohlenstoffatomen sind; bedeutet oder R^1 und R^2 zusammen die Gruppe

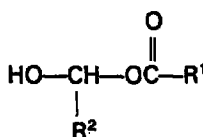


darstellen, indem
 A. eine Verbindung der Formel



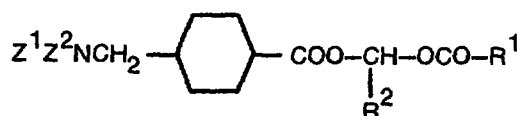
II

worin Z^1 und Z^2 Wasserstoff oder eine Schutzgruppe bedeuten, oder ein funktionell äquivalentes Derivat davon mit einer Verbindung der Formel



III

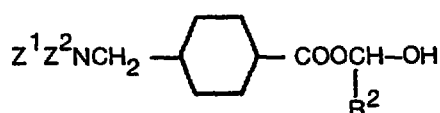
oder einem funktionell äquivalenten Derivat davon, worin R^1 und R^2 wie oben definiert sind, wobei der mögliche Amin-Substituent in R^1 auch durch Schutzgruppen Z^1 und Z^2 geschützt sein kann, umgesetzt wird unter Bildung einer Verbindung der Formel



IV

wonach nötigenfalls die Schutzgruppen Z^1 und Z^2 unter Bildung einer Verbindung der Formel I entfernt werden;

B. eine Verbindung der Formel



V

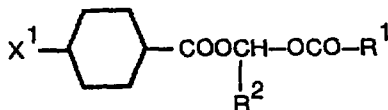
worin Z^1 und Z^2 Wasserstoff oder eine Schutzgruppe sind, oder ein funktionell äquivalentes Derivat davon mit einer Verbindung der Formel



VI

worin R^1 wie oben definiert ist, oder einem funktionell äquivalenten Derivat davon umgesetzt wird, wobei der mögliche Amins substituent in R^1 auch durch Schutzgruppen Z^1 und Z^2 geschützt sein kann, unter Bildung einer Verbindung der Formel IV, wonach nötigenfalls die Schutzgruppen Z^1 und Z^2 unter Bildung einer Verbindung der Formel I entfernt werden;

C. eine Verbindung der Formel

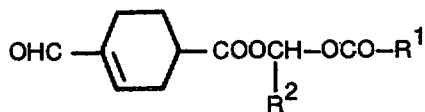


VII



worin R^1 und R^2 wie oben definiert sind und X^1 $-\text{CN}$, $-\text{CH}_2\text{NO}_2$, $-\text{CH}_2\text{N}_3$, $-\text{CONH}_2$ oder $-\text{CH}=\text{N}-\text{OH}$ bedeutet, unter Bildung einer Verbindung der Formel I reduziert wird;

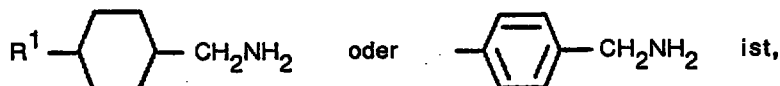
D. eine Verbindung der Formel



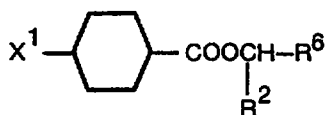
VIII

worin R^1 und R^2 wie oben definiert sind, in Gegenwart von NH_3 unter Bildung einer Verbindung der Formel I reduziert wird;

E. für die Herstellung einer Verbindung der Formel I, worin



eine Verbindung der Formel



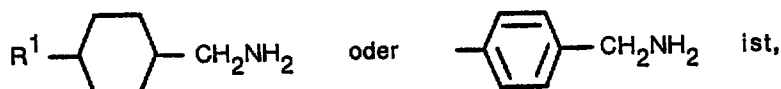
IX

worin R^2 wie oben definiert ist, R^6



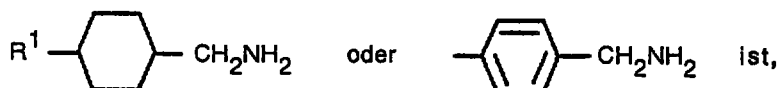
ist und X^1 $-\text{CN}$, $-\text{CH}_2\text{NO}_2$, $-\text{CH}_2\text{N}_3$, $-\text{CONH}_2$ oder $-\text{CH}=\text{N}-\text{OH}$ bedeutet,

unter Bildung einer Verbindung der Formel I, worin



reduziert wird;

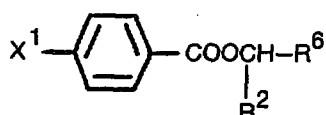
F. für die Herstellung einer Verbindung der Formel I, worin



eine Verbindung der Formel



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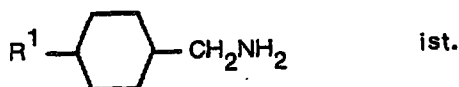
X

worin R^2 , R^6 und X^1 wie oben definiert sind, unter Bildung einer Verbindung der Formel I, worin

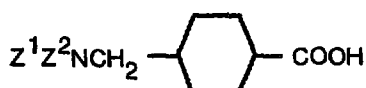


reduziert wird;

G. für die Herstellung einer Verbindung der Formel I, worin

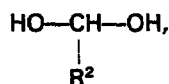


eine Verbindung der Formel



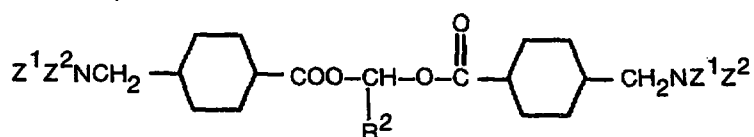
XI

worin Z^1 und Z^2 Wasserstoff oder eine Schutzgruppe wie oben definiert sind, oder ein funktionell äquivalentes Derivat davon mit einer Verbindung der Formel



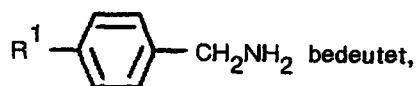
XII

worin R^2 wie oben definiert ist, oder einem funktionell äquivalenten Derivat davon unter Bildung einer Verbindung der Formel

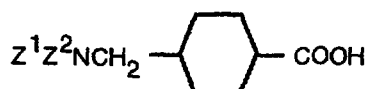


XIII

umgesetzt wird, wonach nötigenfalls die Schutzgruppen Z^1 und Z^2 entfernt werden;
H. für die Herstellung einer Verbindung der Formel I, worin



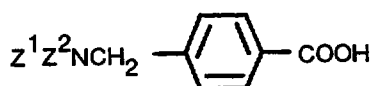
eine Verbindung der Formel



XI

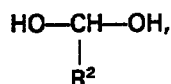


und eine Verbindung der Formel



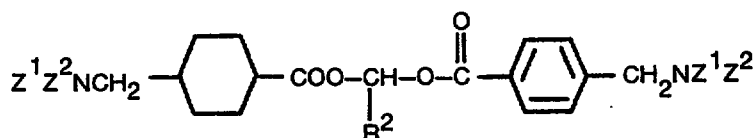
X'V

10 worin Z^1 und Z^2 Wasserstoff oder eine Schutzgruppe wie oben definiert sind, oder ein funktionell äquivalentes Derivat davon mit einer Verbindung der Formel



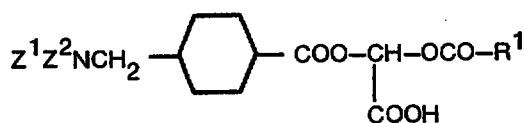
XII

20 worin R^2 wie oben definiert ist, oder einem funktionell äquivalenten Derivat davon zu einer Verbindung der Formel



XV

30 umgesetzt wird, wonach nötigenfalls die Schutzgruppen Z^1 und Z^2 entfernt werden;
I. für die Herstellung einer Verbindung, worin R^2 COOR^3 ist, eine Verbindung der Formel



XVI

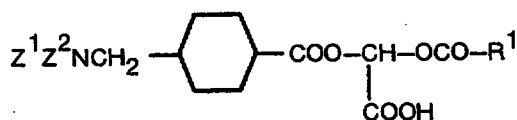
40 worin Z^1 und Z^2 Wasserstoff oder eine Schutzgruppe wie oben definiert sind und R^1 wie oben definiert ist, wobei der mögliche Amins substituent in R^1 auch durch Schutzgruppen R^1 und R^2 geschützt sein kann, oder ein funktionell äquivalentes Derivat davon mit einer Verbindung der Formel



XVII

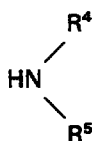
worin R^3 wie oben definiert ist, oder einem funktionell äquivalenten Derivat davon umgesetzt wird, wonach nötigenfalls die Schutzgruppen Z^1 und Z^2 unter Bildung einer Verbindung der Formel I, worin R^2 COOR^3 ist, entfernt werden;

50 J. für die Herstellung einer Verbindung der Formel I, worin R^2 CONR^4R^5 ist, eine Verbindung der Formel



XVIII

worin R^1 , Z^1 , und Z^2 wie oben definiert sind, mit einer Verbindung der Formel

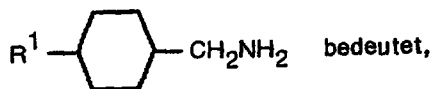


XIX

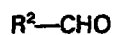


worin R^4 und R^5 wie oben definiert sind, oder einem funktionell äquivalenten Derivat davon umgesetzt wird, wonach nötigenfalls die Schutzgruppen Z^1 und Z^2 unter Bildung einer Verbindung der Formel I, worin R^2 CONR^4R^5 bedeutet, entfernt werden;

K. für die Herstellung von Verbindungen, worin R^1

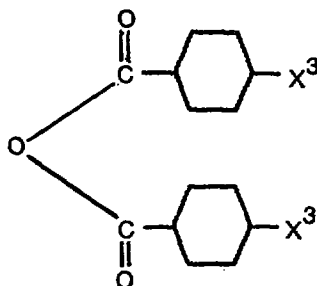


eine Verbindung der Formel



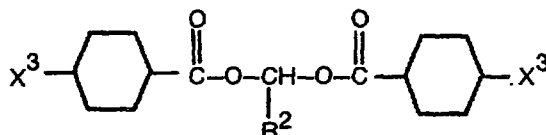
XX

worin R^2 wie oben definiert ist, mit einer Verbindung der Formel



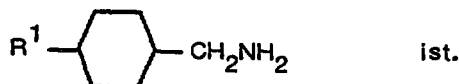
XXI

worin X^3 (a) $\text{CH}_2\text{NZ}^1\text{Z}^2$ ist, wobei Z^1 und Z^2 Schutzgruppen bedeuten, wie in Verfahren A definiert, oder (b) CN , CH_2NO_2 , CH_2N_3 , CONH_2 oder $\text{CH}=\text{N}-\text{OH}$ ist, umgesetzt wird unter Bildung einer Verbindung der Formel

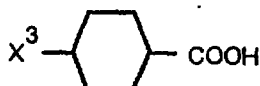


XXII

wonach jede der Gruppen X^3 durch Entfernung der Schutzgruppen Z^1 und Z^2 oder durch Reduzieren der Gruppen CN , CH_2NO_2 , CH_2N_3 , CONH_2 , $\text{CH}=\text{N}-\text{OH}$ in die CH_2NH_2 -Gruppe überführt wird, unter Bildung einer Verbindung der Formel I, worin



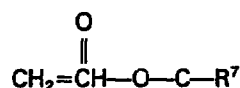
L. für die Herstellung von Verbindungen der Formel I, worin R^1 eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen und R^2 CH_3 ist, eine Verbindung der Formel



XXIII

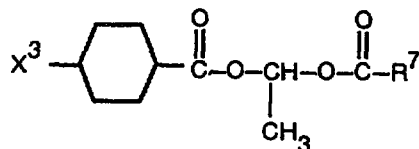
worin X^3 wie in Verfahren K definiert ist, mit einer Verbindung der Formel





XXIV

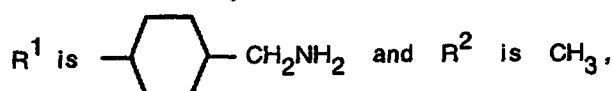
worin R^7 eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen ist, umgesetzt wird unter Bildung einer Verbindung der Formel



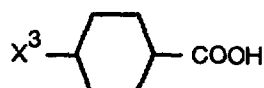
XXV

worin X^3 und R^7 wie oben definiert sind, wonach X^3 zu CH_2NH_2 wie in Verfahren K beschrieben umgesetzt wird, unter Bildung einer Verbindung der Formel I, worin R^1 eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen und R^2 CH_3 ist;

M. für die Herstellung von Verbindungen der Formel I, worin



eine Verbindung der Formel



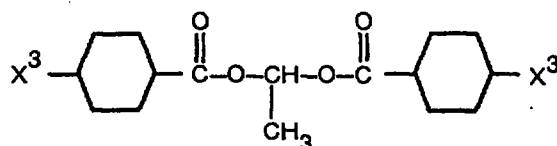
XXIII

worin X^3 wie in Verfahren K definiert ist, mit einer Verbindung der Formel



XXVI

unter Bildung einer Verbindung der Formel



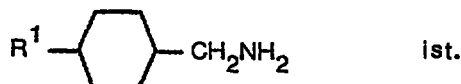
XXVII

worin X^3 wie oben definiert ist, umgesetzt wird, wonach X^3 zu CH_2NH_2 umgesetzt wird, wie in Verfahren K beschrieben, unter Bildung einer Verbindung der Formel I; wonach die so erhaltene Verbindung der Formel I nötigenfalls in der trans-Form isoliert wird und/oder in ein therapeutisch annehmbares Salz überführt wird.

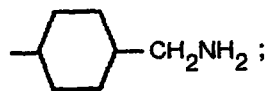
2. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung der Formel I und ihrer therapeutisch annehmbaren Salze, worin R^2 Wasserstoff oder CH_3 ist.

3. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung der Formel I und ihrer therapeutisch annehmbaren Salze, worin R^1 eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen oder eine Alkoxygruppe mit 1 bis 4 Kohlenstoffatomen ist.

4. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung der Formel I und deren therapeutisch annehmbaren Salze, worin



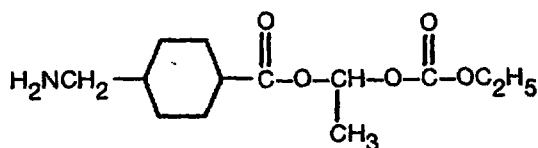
5. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung der Formel I und ihrer therapeutisch annehmbaren Salz, worin R¹ eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen, eine Alkoxygruppe mit 1 bis 4 Kohlenstoffatomen oder den Rest



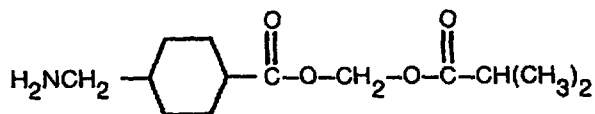
bedeutet und R² Wasserstoff oder CH₃ ist.

6. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung der Formel I und ihrer therapeutisch annehmbaren Salze, worin R¹ eine Alkoxygruppe mit 1 bis 4 Kohlenstoffatomen und R² Wasserstoff oder CH₃ ist.

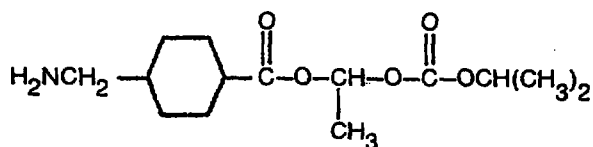
7. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung der Formel



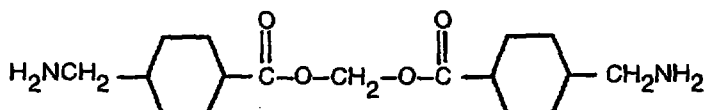
oder eines therapeutisch annehmbaren Salzes davon,



oder eines therapeutisch annehmbaren Salzes davon,



oder eines therapeutisch annehmbaren Salzes davon oder



oder eines therapeutisch annehmbaren Salzes davon.

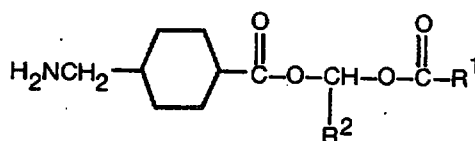
8. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung, wie in den Ansprüchen 1 bis 7 definiert, in Form ihres trans-isomeren.

9. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung, wie in den Ansprüchen 1 bis 7 definiert, in Form ihres Hydrochlorids.



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

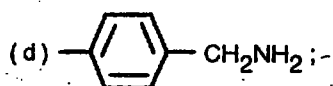
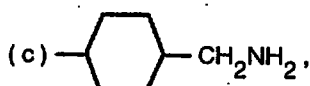
1. Composé de formule:



[dans laquelle

R¹ est choisi dans l'ensemble constitué par:

- (a) des groupes alkyles contenant 1 à 4 atomes de carbone,
- (b) des groupes alcoxy contenant 1 à 4 atomes de carbone,



R² est choisi dans l'ensemble constitué par:

- (a) H,
 - (b) des groupes alkyles contenant 1 à 4 atomes de carbone,
 - (c) $-\text{COOR}^3$, où R³ est un groupe alkyle contenant 1 à 4 atomes de carbone,
 - (d) $-\text{CONR}^4\text{R}^5$, où R⁴ et R⁵ sont des groupes alkyles, identiques ou différents, contenant 1 à 3 atomes de carbone;
- ou bien R¹ et R², pris ensemble, représentent le radical



et son sel thérapeutiquement acceptable.

2. Composé selon la revendication 1, dans lequel R² représente H ou CH₃, et ses sels thérapeutiquement acceptables.

3. Composé selon la revendication 1, (dans lequel R¹ est un groupe alkyle contenant 1 à 4 atomes de carbone) et ses sels thérapeutiquement acceptables.

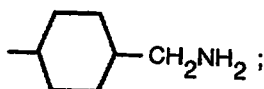
4. Composé selon la revendication 1, (dans lequel R¹ est un groupe alcoxy contenant 1 à 4 atomes de carbone) et ses sels thérapeutiquement acceptables.

5. Composé selon la revendication 1,



et ses sels thérapeutiquement acceptables.

6. Composé selon la revendication 1, dans lequel R¹ est un groupe alkyle contenant 1 à 4 atomes de carbone, un groupe alcoxy contenant 1 à 4 atomes de carbone ou le radical

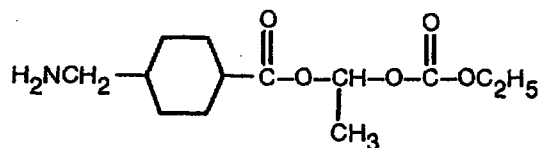


et R₂ représente H ou CH₃ et son sel thérapeutiquement acceptable.



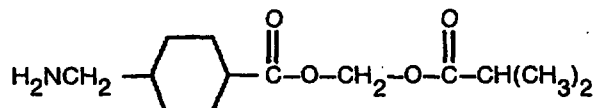
7. Composé selon la revendication 1 (dans lequel R¹ est un groupe alcoxy contenant 1 à 4 atomes de carbone, et R² représente H ou CH₃) et ses sels thérapeutiquement acceptables.

8. Composé de formule



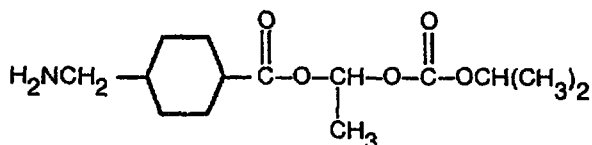
ou son sel thérapeutiquement acceptable.

9. Composé de formule



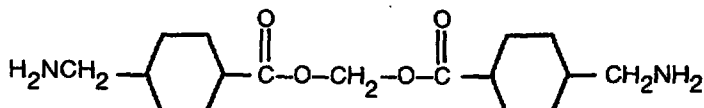
ou son sel thérapeutiquement acceptable.

10. Composé de formule



ou son sel thérapeutiquement acceptable.

11. Composé de formule



ou son sel thérapeutiquement acceptable.

12. Composé selon l'une quelconque des revendications 1 à 11, sous forme de son isomère trans.

13. Composé selon l'une quelconque des revendications 1 à 12, sous forme de son chlorhydrate.

14. Préparation pharmaceutique, contenant comme substance active un composé tel que défini dans l'une quelconque des revendications 1 à 13, éventuellement en combinaison avec un support ou véhicule pharmaceutiquement acceptable.

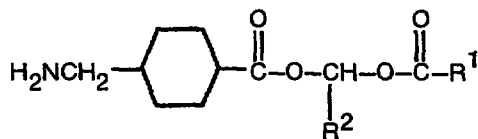
15. Préparation pharmaceutique selon la revendication 14, sous forme de dose unitaire.

16. Composé tel que défini dans l'une quelconque des revendications 1 à 13, destiné à servir au traitement de maladies des mammifères et de l'être humain, qui sont dues à une fibrinolyse accrue.

17. Composé tel que défini dans l'une quelconque des revendications 1 à 13, destiné à servir au traitement de l'ulcère peptique chez l'être humain.

18. Composé tel que défini dans l'une quelconque des revendications 1 à 13 destiné à servir au traitement de l'œdème angioneurotique héréditaire de l'être humain.

19. Procédé pour la préparation d'un composé de formule



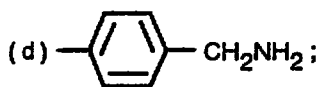
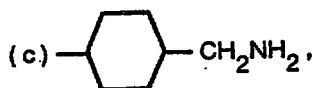
dans laquelle



0079 872

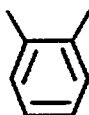
R¹ est choisi dans l'ensemble constitué par:

- (a) des groupes alkyles contenant 1 à 4 atomes de carbone,
 (b) des groupes alcoxy contenant 1 à 4 atomes de carbone,

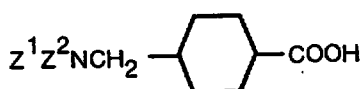


R² est choisi dans l'ensemble constitué par:

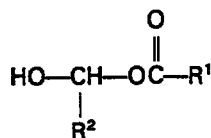
- (a) H,
 (b) des groupes alkyles contenant 1 à 4 atomes de carbone,
 (c) —COOR³, où R³ est un groupe alkyle contenant 1 à 4 atomes de carbone,
 (d) —CONR⁴R⁵, où R⁴ et R⁵ sont des groupes alkyles, identiques ou différents, contenant 1 à 3 atomes de carbone;
 ou bien R¹ et R², pris ensemble, représentent le radical



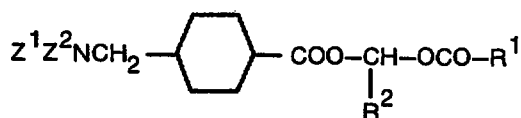
et de ses sels pharmaceutiquement acceptables, par:
 A) Réaction d'un composé de formule



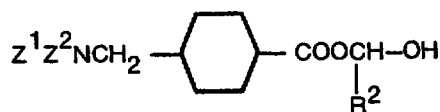
(dans laquelle Z¹ et Z² représentent H ou un groupe protecteur) ou d'un dérivé fonctionnellement équivalent de ce composé, avec un composé de formule:



(dans laquelle R¹ et R² sont comme définis ci-dessus, le substituant amine possible dans R¹ pouvant également être protégé par des groupes protecteurs Z¹ et Z²) ou son dérivé fonctionnellement équivalent, pour former un composé de formule:



puis, si nécessaire, enlèvement des groupes protecteurs Z¹ et Z² pour former un composé de formule I;
 B) Réaction d'un composé de formule:



(dans laquelle Z^1 et Z^2 représentent H ou un groupe protecteur) ou d'un dérivé fonctionnellement équivalent de ce composé, avec un composé de formule



VI

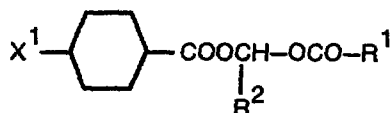
5

(dans laquelle R^1 est comme défini ci-dessus) ou un dérivé fonctionnellement équivalent de ce composé, le substituant amine possible dans R^1 pouvant également être protégé par des groupes protecteurs Z^1 et Z^2 , pour former un composé de formule IV puis, si nécessaire, enlèvement des groupes protecteurs Z^1 et Z^2 pour former un composé de formule I;

10

C) Réduction d'un composé de formule:

15



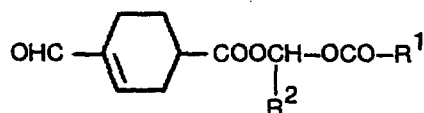
VII

(dans laquelle R^1 et R^2 sont comme définis ci-dessus, et X^1 représente $-\text{CN}$, $-\text{CH}_2\text{NO}_2$, $-\text{CH}_2\text{N}_3$, $-\text{CONH}_2$ ou $-\text{CH}=\text{N}-\text{OH}$) pour former un composé de formule I;

20

D) Réduction d'un composé de formule:

25



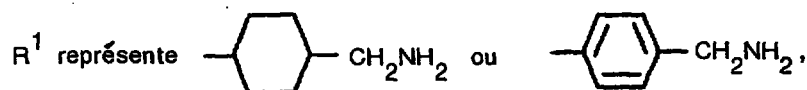
VIII

(dans laquelle R^1 et R^2 sont comme définis ci-dessus), en présence de NH_3 pour former un composé de formule I;

30

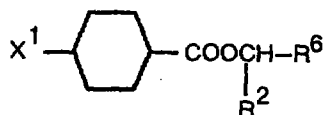
E) Pour préparer des composés de formule I, dans laquelle

35



40 réduction d'un composé de formule:

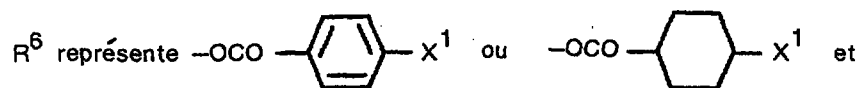
45



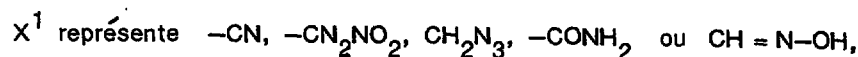
IX

(dans laquelle R^2 est comme défini ci-dessus;

50

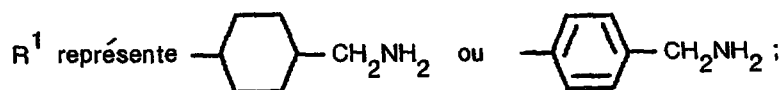


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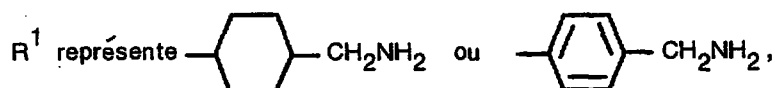


60 pour former un composé de formule I dans laquelle

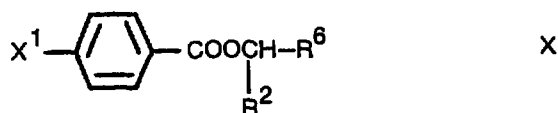
65



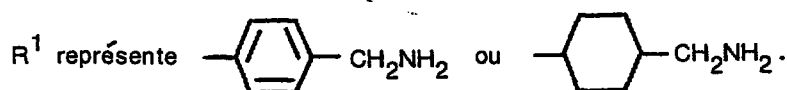
F) Pour préparer des composés de formule I, dans laquelle



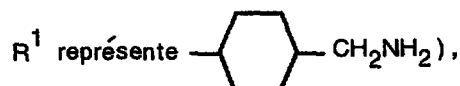
10 réduction d'un composé de formule:



(dans laquelle R^2 , R^6 et X^1 sont comme définis ci-dessus), pour former un composé de formule I dans laquelle



G) Pour préparer des composés de formule I (dans laquelle



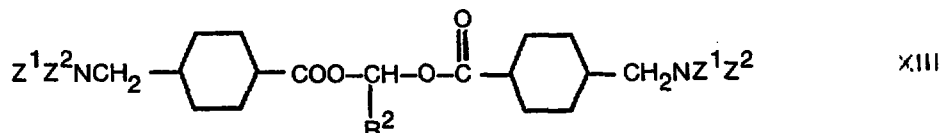
35 réaction d'un composé de formule:



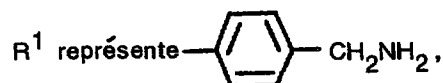
(dans laquelle Z^1 et Z^2 représentent H ou un groupe protecteur selon la définition ci-dessus), ou d'un dérivé fonctionnellement équivalent de ce composé, avec un composé de formule:



50 (dans laquelle R^2 est comme défini ci-dessus) ou un dérivé fonctionnellement équivalent de ce composé, pour obtenir un composé de formule:

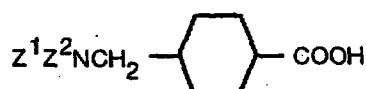


60 puis, si nécessaire, enlèvement des groupes protecteurs Z^1 et Z^2 ,
H) Pour préparer des composés de formule I dans laquelle



réaction d'un composé de formule:

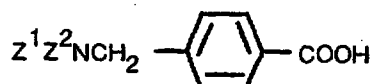
5



XI

et d'un composé de formule:

10

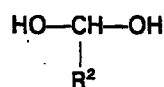


XIV

15

(formules dans lesquelles Z^1 et Z^2 représentent H ou un groupe protecteur selon la définition ci-dessus) ou d'un de leur dérivé fonctionnellement équivalent, avec un composé de formule:

20

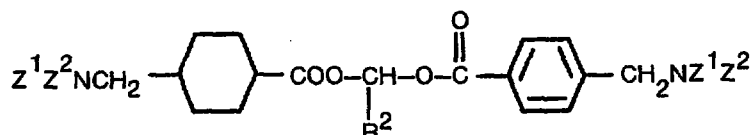


XII

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(dans laquelle R^2 est comme défini ci-dessus) ou un dérivé fonctionnellement équivalent de ce composé, pour obtenir un composé de formule:

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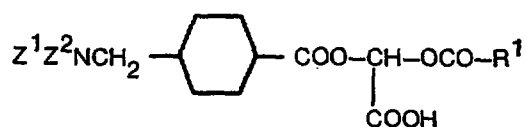
XV

35

puis, si nécessaire, enlèvement des groupes protecteurs Z^1 et Z^2 ;

I) Pour préparer un composé de formule I (dans laquelle R^2 représente COOR^3), réaction d'un composé de formule:

40



XVI

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(dans laquelle Z^1 et Z^2 représentent H ou un groupe protecteur selon la définition ci-dessus, et R^1 est comme défini ci-dessus; le substituant amine possible dans R^1 pouvant également être protégé par des groupes protecteurs Z^1 et Z^2), ou d'un dérivé fonctionnellement équivalent de ce composé, avec un composé de formule:

50



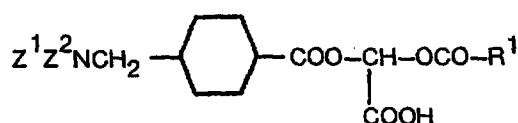
XVII

(dans laquelle R^3 est comme défini ci-dessus) ou un dérivé fonctionnellement équivalent de ce composé, puis, si nécessaire, enlèvement des groupes protecteurs Z^1 et Z^2 , pour former un composé de formule I dans laquelle R^2 représente COOR^3 ;

55

J) Pour préparer un composé de formule I (dans laquelle R^2 représente CONR^4R^5), réaction d'un composé de formule:

60

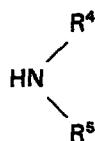


XVIII

65



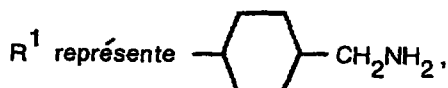
(dans laquelle R^1 , Z^1 et Z^2 sont comme définis ci-dessus) ou d'un dérivé fonctionnellement équivalent de ce composé, avec un composé de formule:



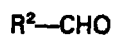
XIX

(dans laquelle R^4 et R^5 sont comme définis ci-dessus), ou un dérivé fonctionnellement équivalent de ce composé puis, si nécessaire, enlèvement des groupes protecteurs Z^1 et Z^2 , pour former un composé de formule I dans laquelle R^2 représente $CONR^4R^5$:

K) Pour préparer des composés dans lesquels

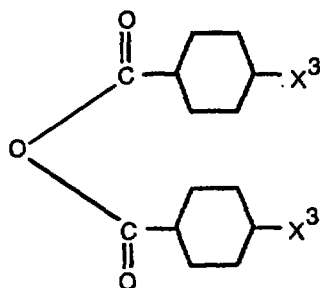


réaction d'un composé de formule:



XX

(dans laquelle R^2 est comme défini ci-dessus) avec un composé de formule:



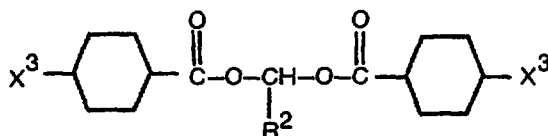
XXI

dans laquelle X^3 représente:

(a) $CH_2N^+Z^1Z^2$

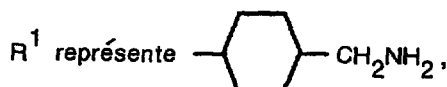
où Z^1 et Z^2 sont des groupes protecteurs tels que définis dans la méthode A, ou bien

(b) CN , CH_2NO_2 , CH_2N_3 , $CONH_2$ ou $CH=N-OH$, pour former un composé de formule



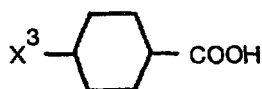
XXII

puis l'on transforme chacun des groupes X^3 en CH_2NH_2 par enlèvement des groupes protecteurs Z^1 et Z^2 ou par réduction des groupes CN , CH_2NO_2 , CH_2N_3 , $CONH_2$, $CH=N-OH$ pour former un composé de formule dans laquelle



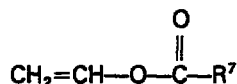
L) Pour préparer les composés de formule I (dans laquelle R^1 est un groupe alkyle contenant 1 à 4 atomes de carbone et R^2 représente CH_3), réaction d'un composé de formule:





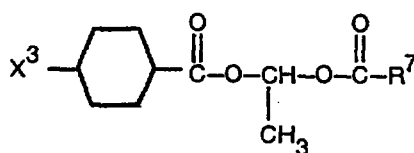
XXIII

(dans laquelle X^3 est comme défini à la méthode K) avec un composé de formule:



XXIV

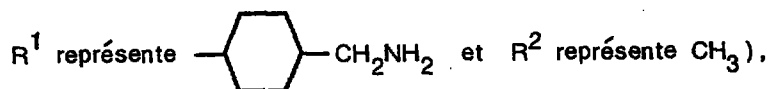
(dans laquelle R^7 est un groupe alkyle contenant 1 à 4 atomes de carbone), pour former un composé de formule:



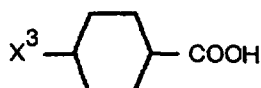
XXV

(dans laquelle X^3 et R^7 sont tels que définis ci-dessus), puis transformation de X^3 en CH_2NH_2 comme décrit à la méthode K pour former un composé de formule I, dans laquelle R^1 est un groupe alkyle contenant 1 à 4 atomes de carbone et R^2 représente CH_3);

M) Pour préparer des composés de formule I (dans laquelle



réaction d'un composé de formule:



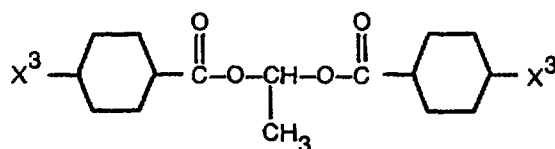
XXIII

(dans laquelle X^3 est comme défini dans la méthode K) avec un composé de formule:



XXVI

pour former un composé de formule



XXVII

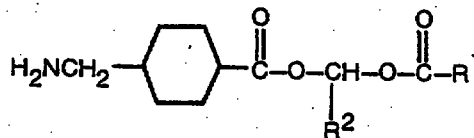
(dans laquelle X^3 est comme défini ci-dessus) puis transformation de X^3 en CH_2NH_2 comme décrit à la méthode K, pour former un composé de formule I, puis, si nécessaire, on isole sous forme trans le composé de formule I ainsi obtenu et/ou on le transforme en un sel thérapeutiquement acceptable.



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Revendications pour l'État contractant: AT

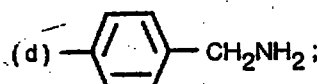
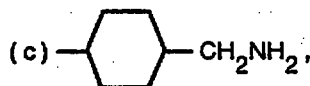
1. Procédé pour la préparation d'un composé de formule



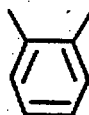
dans laquelle

R¹ est choisi dans l'ensemble constitué par:

- (a) des groupes alkyles contenant 1 à 4 atomes de carbone,
 (b) des groupes alcoxy contenant 1 à 4 atomes de carbone,

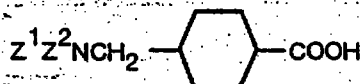
R² est choisi dans l'ensemble constitué par:

- (a) H,
 (b) des groupes alkyles contenant 1 à 4 atomes de carbone,
 (c) —COOR³, où R³ est un groupe alkyle contenant 1 à 4 atomes de carbone,
 (d) —CONR⁴R⁵, où R⁴ et R⁵ sont des groupes alkyles, identiques ou différents, contenant 1 à 3 atomes de carbone;
 ou bien R¹ et R², pris ensemble, représentent le radical

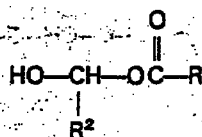


et de ses sels pharmaceutiquement acceptables, par:

A) Réaction d'un composé de formule

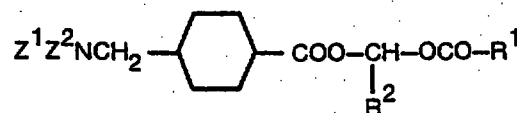


(dans laquelle Z¹ et Z² représentent H ou un groupe protecteur) ou d'un dérivé fonctionnellement équivalent de ce composé, avec un composé de formule:



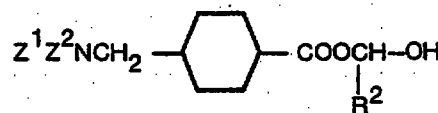
(dans laquelle R¹ et R² sont comme définis ci-dessus, le substituant amine possible dans R¹ pouvant également être protégé par des groupes protecteurs Z¹ et Z²) ou son dérivé fonctionnellement équivalent, pour former un composé de formule:





IV

puis, si nécessaire, enlèvement des groupes protecteurs Z^1 et Z^2 pour former un composé de formule I;
B) Réaction d'un composé de formule:



V

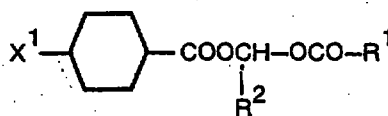
(dans laquelle Z^1 et Z^2 représentent H ou un groupe protecteur) ou d'un dérivé fonctionnellement équivalent de ce composé, avec un composé de formule



VI

(dans laquelle R^1 est comme défini ci-dessus) ou un dérivé fonctionnellement équivalent de ce composé, le substituant amine possible dans R^1 pouvant également être protégé par des groupes protecteurs Z^1 et Z^2 , pour former un composé de formule IV puis, si nécessaire, enlèvement des groupes protecteurs Z^1 et Z^2 pour former un composé de formule I;

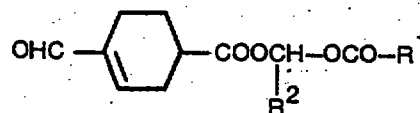
C) Réduction d'un composé de formule:



VII

(dans laquelle R^1 et R^2 sont comme définis ci-dessus, et X^1 représente $-\text{CN}$, $-\text{CH}_2\text{NO}_2$, $-\text{CH}_2\text{N}_3$, $-\text{CONH}_2$ ou $-\text{CH}=\text{N}-\text{OH}$) pour former un composé de formule I;

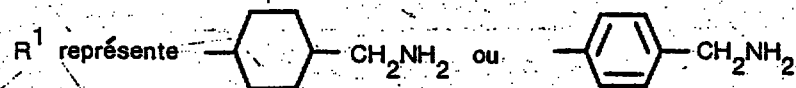
D) Réduction d'un composé de formule:



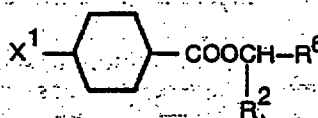
VIII

(dans laquelle R^1 et R^2 sont comme définis ci-dessus), en présence de NH_3 pour former un composé de formule I;

E) Pour préparer des composés de formule I, dans laquelle



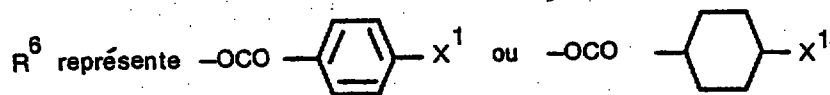
réduction d'un composé de formule:



IX

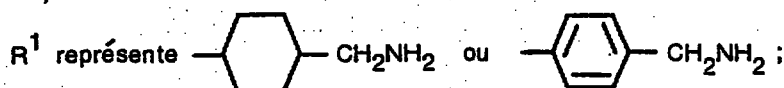
(dans laquelle R^2 est comme défini ci-dessus;



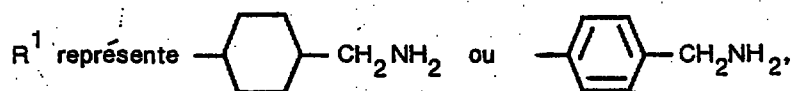


et X^1 représente $-\text{CN}$, $-\text{CH}_2\text{NO}_2$, $-\text{CH}_2\text{N}_3$, $-\text{CONH}_2$ ou $-\text{CH}=\text{N}-\text{OH}$,

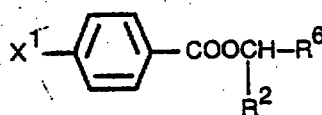
pour former un composé de formule I dans laquelle



F) Pour préparer des composés de formule I, dans laquelle

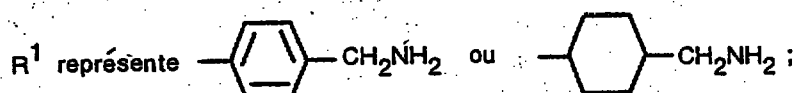


réduction d'un composé de formule:



X

(dans laquelle R^2 , R^6 et X^1 sont comme définis ci-dessus), pour former un composé de formule I dans laquelle



G) Pour préparer des composés de formule I (dans laquelle

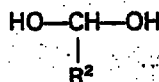


réaction d'un composé de formule:



XI

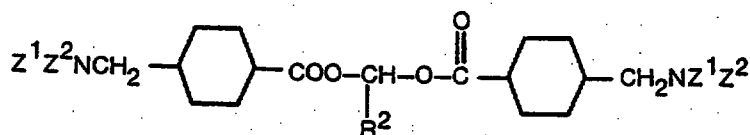
(dans laquelle Z^1 et Z^2 représentent H ou un groupe protecteur selon la définition ci-dessus), ou un dérivé fonctionnellement équivalent de ce composé, avec un composé de formule:



XII

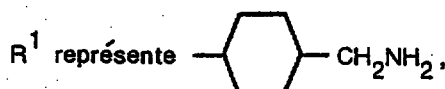


(dans laquelle R^2 est comme défini ci-dessus) ou un dérivé fonctionnellement équivalent de ce composé, pour obtenir un composé de formule:

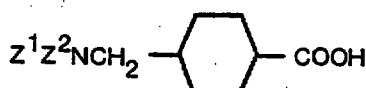


XIII

puis, si nécessaire, enlèvement des groupes protecteurs Z^1 et Z^2 ,
H) Pour préparer des composés de formule I dans laquelle

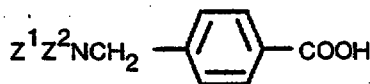


réaction d'un composé de formule:



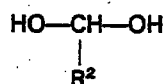
XI

et d'un composé de formule:



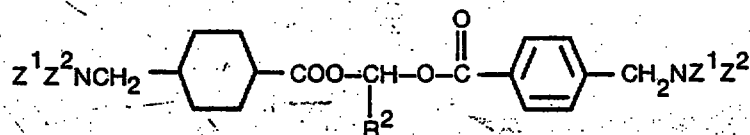
XIV

(formules dans lesquelles Z^1 et Z^2 représentent H ou un groupe protecteur selon la définition ci-dessus) ou d'un de leur dérivé fonctionnellement équivalent, avec un composé de formule:



XII

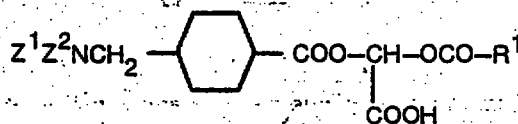
(dans laquelle R^2 est comme défini ci-dessus) ou un dérivé fonctionnellement équivalent de ce composé, pour obtenir un composé de formule:



XV

puis, si nécessaire, enlèvement des groupes protecteurs Z^1 et Z^2 ;

I) Pour préparer un composé de formule I (dans laquelle R^2 représente $COOR^3$), réaction d'un composé de formule:



XVI



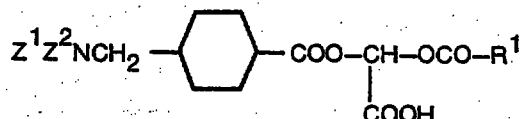
(dans laquelle Z^1 et Z^2 représentent H ou un groupe protecteur selon la définition ci-dessus, et R^1 est comme défini ci-dessus; le substituant amine possible dans R^1 pouvant également être protégé par des groupes protecteurs Z^1 et Z^2), ou d'un dérivé fonctionnellement équivalent de ce composé, avec un composé de formule:



XVII

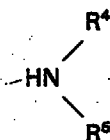
(dans laquelle R^3 est comme défini ci-dessus) ou un dérivé fonctionnellement équivalent de ce composé, puis, si nécessaire, enlèvement des groupes protecteurs Z^1 et Z^2 , pour former un composé de formule I dans laquelle R^2 représente $COOR^3$;

J) Pour préparer un composé de formule I' (dans laquelle R^2 représente $CONR^4R^5$), réaction d'un composé de formule:



XVIII

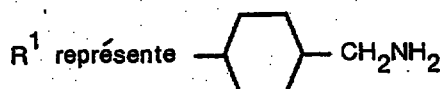
(dans laquelle R^1 , Z^1 et Z^2 sont comme définis ci-dessus) ou d'un dérivé fonctionnellement équivalent de ce composé, avec un composé de formule:



XIX

(dans laquelle R^4 et R^5 sont comme définis ci-dessus), ou un dérivé fonctionnellement équivalent de ce composé puis, si nécessaire, enlèvement des groupes protecteurs Z^1 et Z^2 , pour former un composé de formule I dans laquelle R^2 représente $CONR^4R^5$;

K) Pour préparer des composés dans lesquels

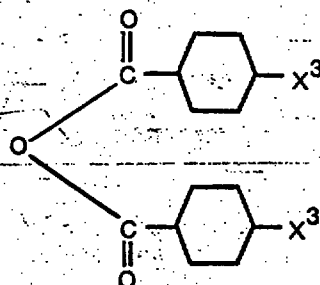


réaction d'un composé de formule:



XX

(dans laquelle R^2 est comme défini ci-dessus) avec un composé de formule:



XXI

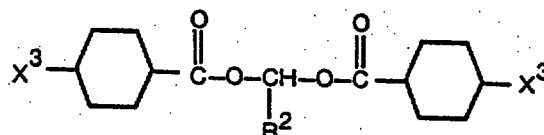
dans laquelle X^3 représente:

(a) $\text{CH}_2\text{NZ}^1\text{Z}^2$

où Z^1 et Z^2 sont des groupes protecteurs tels que définis dans la méthode A, ou bien

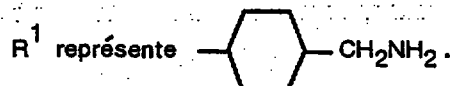
(b) CN , CH_2NO_2 , CH_2N_3 , CONH_2 ou $\text{CH}=\text{N}-\text{OH}$, pour former un composé de formule



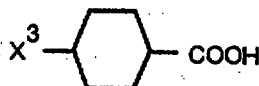


XXII

puis l'on transforme chacun des groupes X^3 en CH_2NH_2 par enlèvement des groupes protecteurs Z^1 et Z^2 ou par réduction des groupes CN , CH_2NO_2 , CH_2N_3 , CONH_2 , $\text{CH}=\text{N}-\text{OH}$ pour former un composé de formule I dans laquelle

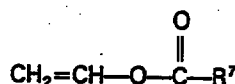


L) Pour préparer les composés de formule I (dans laquelle R^1 est un groupe alkyle contenant 1 à 4 atomes de carbone et R^2 représente CH_3), réaction d'un composé de formule:



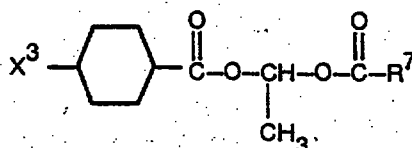
XXIII

(dans laquelle X^3 est comme défini à la méthode K) avec un composé de formule:



XXIV

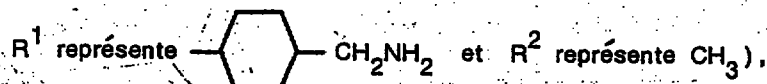
(dans laquelle R^7 est un groupe alkyle contenant 1 à 4 atomes de carbone), pour former un composé de formule:



XXV

(dans laquelle X^3 et R^7 sont tels que définis ci-dessus), puis transformation de X^3 en CH_2NH_2 comme décrit à la méthode K pour former un composé de formule I, dans laquelle R^1 est un groupe alkyle contenant 1 à 4 atomes de carbone et R^2 représente CH_3 ;

M) Pour préparer des composés de formule I (dans laquelle



réaction d'un composé de formule:



XXIII

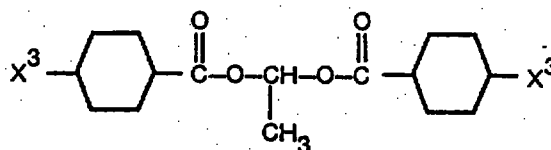
(dans laquelle X^3 est comme défini dans la méthode K) avec un composé de formule:



XXVI



pour former un composé de formule



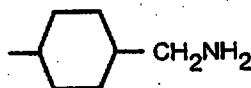
XXVII

(dans laquelle X^3 est comme défini ci-dessus) puis transformation de X^3 en CH_2NH_2 comme décrit à la méthode K, pour former un composé de formule I, puis, si nécessaire, on isole sous forme trans le composé de formule I ainsi obtenu et/ou on le transforme en un sel thérapeutiquement acceptable.

2. Procédé selon la revendication 1 pour préparer un composé de formule I (dans laquelle R^2 représente H ou CH_3) et ses sels thérapeutiquement acceptables.

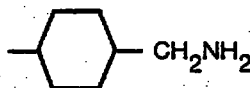
3. Procédé selon la revendication 1 pour préparer un composé de formule I (dans laquelle R^1 est un groupe alkyle contenant 1 à 4 atomes de carbone ou un groupe alcoxy contenant 1 à 4 atomes de carbone, et ses sels thérapeutiquement acceptables.

4. Procédé selon la revendication 1 pour préparer un composé de formule I (dans laquelle R^1 représente



et ses sels pharmaceutiquement acceptables.

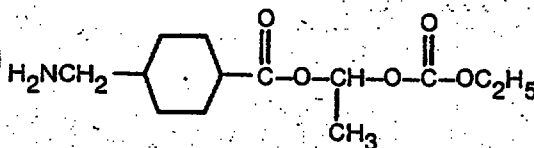
5. Procédé selon la revendication 1 pour préparer un composé de formule I (dans laquelle R^1 représente un groupe alkyle contenant 1 à 4 atomes de carbone, un groupe alcoxy contenant de 1 à 4 atomes de carbone, ou le radical



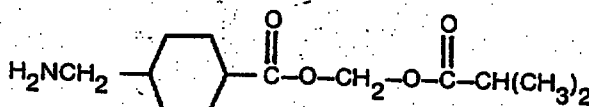
et R^2 représente H ou CH_3) et ses sels pharmaceutiquement acceptables.

6. Procédé selon la revendication 1 pour préparer un composé de formule I (dans laquelle R^1 est un groupe alcoxy contenant 1 à 4 atomes de carbone et R^2 représente H ou CH_3) et ses sels pharmaceutiquement acceptables.

7. Procédé selon la revendication 1 pour préparer un composé de formule:

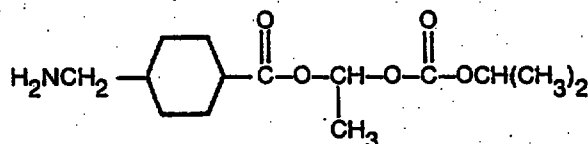


ou un sel pharmaceutiquement acceptable de ce composé,

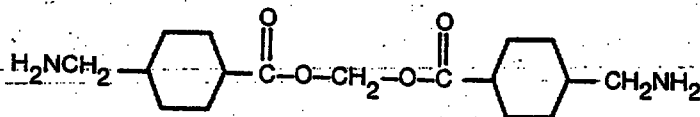


ou un sel pharmaceutiquement acceptable de ce composé,





ou un sel pharmaceutiquement acceptable de ce composé,



ou un sel pharmaceutiquement acceptable de ce composé.

8. Procédé selon la revendication 1 pour préparer, sous forme de son isomère trans, un composé tel que défini aux revendications 1 à 7.

9. Procédé selon la revendication 1 pour préparer, sous forme de son chlorhydrate, un composé tel que défini aux revendications 1 à 7.



* C L M S *