AUSTRALIA 672867

PATENTS ACT 1990

PATENT REQUEST : STANDARD PATENT

I/We being the person(s) identified below as the Applicant(s), request the grant of a patent to the person(s) identified below as the Nominated Person(s), for an invention described in the accompanying standard complete specification.

Full application details follow:

[71/70] Applicant(s)/Nominated Person(s):

Sandoz Ltd.

of

Lichtstrasse 35, CH-4002 Basle, Switzerland

[54] Invention Title: 4-amino-3-hydroxycarboxylic acid and their use as antivirals

~~Improvements in or relating to organic compounds~~

[72] Name(s) of actual inventor(s):

Andreas BILLICH
Brigitte CHARPIOT
Peter ETTMAYER
Hubert GSTACH
Philipp LEHR
Dieter SCHOLZ

[74] Address for service in Australia:

DAVIES COLLISON CAVE, Patent Attorneys, 1 Little Collins Street, Melbourne, Victoria, Australia. Attorney Code: DM

Basic Convention Application(s) Details:

[31] Application Number	[33] Country	Code	[32] Date of Application
9305144.9	United Kingdom	GB	12 March 1993
9319667.3	United Kingdom	GB	23 September 1993

DATED this TENTH day of MARCH 1994

AUSTRALIAN PATENT OFFICE

054073 100394

Keith L Davies

.....

a member of the firm of DAVIES COLLISON CAVE for and on behalf of the applicant(s)

AUSTRALIA

PATENTS ACT 1990

NOTICE OF ENTITLEMENT

We, **Sandoz Ltd.**, the applicant/Nominated Person named in the accompanying Patent Request state the following:-

The Nominated Person is entitled to the grant of the patent because the Nominated Person derives title to the invention from the inventors by assignment.

The Nominated Person is entitled to claim priority from the basic applications listed on the patent request because the Nominated Person made the basic applications, and because those applications were the first applications made in a Convention country in respect of the invention.

DATED this TENTH day of MARCH 1994

.....

a member of the firm of
DAVIES COLLISON
CAVE for and on behalf
of the applicant(s)

(DCC ref: 1654748)

AU9457737

(12) PATENT ABRIDGMENT (11) Document No. AU-B-57737/94
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 672867

(54) Title
4-AMINO-3-HYDROXYCARBOXYLIC ACID AND THEIR USE AS ANTIVIRALS

International Patent Classification(s)

(51)[5]	C07C 271/22	C07C 237/20	C07C 275/34	C07D 213/40
	C07D 235/14	C07D 249/12	C07D 277/74	C07D 487/04
	C07K 005/02	A61K 031/165	C07D 285/125	

(21) Application No. : **57737/94** (22) Application Date : **10.03.94**

(30) Priority Data

(31) Number	(32) Date	(33) Country
9305144	12.03.93	GB UNITED KINGDOM
9319667	23.09.93	GB UNITED KINGDOM

(43) Publication Date : **15.09.94**

(44) Publication Date of Accepted Application : **17.10.96**

(71) Applicant(s)
SANDOZ LTD.

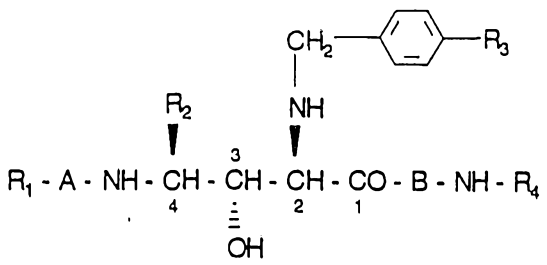
(72) Inventor(s)
ANDREAS BILLICH; BRIGITTE CHARPIOT; PETER ETTMAYER; HUBERT GSTACH; PHILIPP LEHR; DIETER SCHOLZ

(74) Attorney or Agent
DAVIES COLLISON CAVE , 1 Little Collins Street, MELBOURNE VIC 3000

(56) Prior Art Documents
AU 21944/92 C07C A61K
WO 93/01166

(57) Claim

1. A compound of formula I



I

wherein

A and B independently represent a bond or an optionally substituted amino acyl moiety;

R_1 represents hydrogen; an amino protecting group; or a group of formula R_5Y- wherein

R_5 represents hydrogen or an optionally substituted alkyl, alkenyl, alkinyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl group; and

Y represents -CO-; -NHCO-; -NHCS-; $-SO_2-$; -O-CO-; or -O-CS-;

.../2

R_2 represents the side chain of a natural amino acid; an alkyl, arylalkyl, heteroarylalkyl or cycloalkylalkyl group; or trimethylsilylmethyl, 2-thienylmethyl or styrylmethyl;

R_3 represents halogen, alkyl, alkoxy or hydroxyalkoxy; and

R_4 represents 2(R)-hydroxyindan-1(S)-yl; (S)-2-hydroxy-1-phenylethyl; or 2-hydroxy-benzyl optionally substituted in 4 position by methoxy

in free form or salt form.

7. A pharmaceutical composition comprising a compound of formula I as defined in claim 1 in free form or pharmaceutically acceptable salt form, together with at least one pharmaceutically acceptable carrier or diluent.

8. A method of treating retroviral diseases, especially diseases caused by HIV, which comprises administering to a subject in need of such treatment an effective amount of a compound of formula I as defined in claim 1 in free form or in pharmaceutically acceptable salt form.

AUSTRALIA

PATENTS ACT 1990

COMPLETE SPECIFICATION

NAME OF APPLICANT(S):

Sandoz Ltd.

ADDRESS FOR SERVICE:

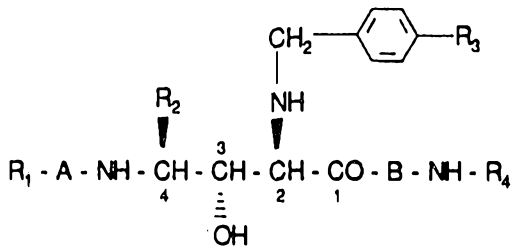
DAVIES COLLISON CAVE
Patent Attorneys
1 Little Collins Street, Melbourne, 3000.

INVENTION TITLE:

~~Improvements in or relating to organic compounds~~ 4-amino-3-hydroxycarboxylic acid derivatives and their use as antivirals.

The following statement is a full description of this invention, including the best method of performing it known to me/us:-

The invention relates to 4-amino-3-hydroxycarboxylic acid derivatives. It concerns the compounds of formula I



I

wherein

A and B independently represent a bond or an optionally substituted amino acyl moiety;

R_1 represents hydrogen; an amino protecting group; or a group of formula R_5Y- wherein

R_5 represents hydrogen or an optionally substituted alkyl, alkenyl, alkinyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl group; and

Y represents -CO-; -NHCO-; -NHCS-; $-SO_2-$; -O-CO-; or -O-CS-;

R_2 represents the side chain of a natural amino acid; an alkyl, arylalkyl, heteroarylalkyl or cycloalkylalkyl group; or trimethylsilylmethyl, 2-thienylmethyl or styrylmethyl;

R_3 represents halogen, alkyl, alkoxy or hydroxyalkoxy; and

R_4 represents 2(R)-hydroxyindan-1(S)-yl; (S)-2-hydroxy-1-phenylethyl; or 2-hydroxy-benzyl optionally substituted in 4 position by methoxy;

in free form or salt form;

hereinafter briefly named "the compounds of the invention".

To date, there is a definite need for finding compounds which effectively inhibit retroviruses in a human infected by such a virus, and thus treat or prevent diseases caused thereby, such as acquired immunodeficiency syndrome (AIDS).

One approach for effecting retroviral inhibition is the use of an inhibitor of a viral proteinase essential for processing viral polypeptide precursors by proteolytic maturation, e.g. the HIV proteinase.

The compounds of the present invention are antivirally active. They inhibit the HIV proteinase. They have particularly beneficial pharmacological properties, especially oral bioavailability, making them better suited for that use than structurally similar compounds.

R_1 preferably is hydrogen, 2-pyridylmethoxycarbonyl, benzyl-CH(OH)-carbonyl, phenoxymethylcarbonyl or an amino protecting group such as tert-butoxycarbonyl or benzyloxycarbonyl; it especially is tert-butoxycarbonyl or benzyloxycarbonyl, even more preferably benzyloxycarbonyl.

When A is an optionally substituted aminoacyl moiety, it preferably is an optionally substituted α-aminoacyl moiety such as alanine, leucine, isoleucine, asparagine, valine, tert-butylglycine, tert-leucine or histidine. It preferably is the optionally protected moiety of a natural α-amino acid, preferably of an amino acid which is a normal constitutive part of proteins, or tert-leucine. A especially is L-valine, L-tert-leucine or a bond, even more preferably L-tert-leucine.

R_2 preferably is the side chain of a natural amino acid, preferably of an α-amino acid, preferably of an amino acid which is a normal constitutive part of proteins. It is e.g. isopropyl, aminocarbonylmethyl, methyl, 1-methylpropyl, benzyl, 4-hydroxybenzyl or isobutyl, preferably benzyl.

When B is an optionally substituted aminoacyl moiety, it preferably is an optionally substituted α-aminoacyl moiety, such as phenylalanine, valine, leucine, isoleucine, alanine or asparagine. It preferably is the optionally substituted moiety of a natural α-amino acid, preferably of an amino acid which is a normal constitutive part of proteins. B especially is L-valine or a bond, even more preferably a bond.

R_3 preferably is halogen, methyl or methoxy, especially methoxy.

R_4 preferably is 2(R)-hydroxyindan-1(S)-yl or 2-hydroxybenzyl optionally substituted as defined above, especially 2(R)-hydroxyindan-1(S)-yl.

Y preferably is -CO- or -O-CO-, especially -O-CO-.

R_5 preferably is an optionally substituted alkyl, arylalkyl or heteroarylalkyl group, especially alkyl; when it is optionally substituted heteroarylalkyl it preferably is

pyridylalkyl, especially 2-pyridylmethyl; when it is optionally substituted arylalkyl it preferably is benzyl-CH(OH)-; when it is substituted alkyl it preferably is phenoxymethyl.

An optionally substituted aminoacyl moiety preferably is unsubstituted. When it is substituted it e.g. is substituted by alkyl of 1 to 4 carbon atoms, such as in O-tert-butyl-L-aspartyl, or substituted at the nitrogen atom by e.g. (2-pyridylmethyl)N(methyl)CO-, (5-methyl-1,3,4-thiadiazol-2-yl)SCH_2CO-, (benzthiazol-2-yl)SCH_2CO-, (1-methyl-1,3,4-triazol-2-yl)SCH_2CO- or (benzimidazol-2-yl-methyl)N(methyl)CO-. It preferably has the S configuration. It preferably is an α-aminoacyl moiety, such as valine or tert-leucine.

Optionally substituted alkyl preferably is alkyl of 1 to 5 carbon atoms, preferably of 1 to 4 carbon atoms, e.g. methyl, ethyl, isopropyl or tert-butyl; it is especially of 1 or 4 carbon atoms. The substituent is e.g. phenoxy, hydroxy or optionally protected amino.

Optionally substituted arylalkyl is e.g. phenylalkyl of altogether 7 to 10 carbon atoms, such as benzyl or 2-phenylethyl; it is optionally substituted by e.g. hydroxy, such as in benzyl-CH(OH)- or phenyl-$CH(CH_2OH)$-, or is e.g. naphthylalkyl of 1 to 4 carbon atoms in the alkylene part.

An amino protecting group preferably is benzyloxycarbonyl or tert-butoxycarbonyl.

Optionally substituted heteroarylalkyl preferably is pyridylalkyl, especially 2-pyridylmethyl.

Aryl, heteroaryl and the aryl parts of arylalkyl and heteroarylalkyl may be mono- or polycyclic, such as e.g. pyridyl, naphthyl, 9-fluorenylmethoxycarbonyl (FMOC) or benzimidazolyl. The alkylene part of arylalkyl or heteroarylalkyl may be substituted by e.g. hydroxy.

A heterocyclyl group, and the heterocyclyl part of a heterocyclylalkyl group, is a saturated heterocyclic group having one or more heteroatoms selected from nitrogen, oxygen and sulfur. It preferably has 5 or 6 ring constitutent atoms, and preferably up to 3 heteroatoms.

Cycloalkylalkyl preferably is cyclohexylalkyl; it preferably is of 1 to 4 carbon atoms in the alkylene part.

Halogen is fluorine, chlorine, bromine or iodine, preferably chlorine or bromine.

Alkyl and alkoxy preferably are of 1 to 4 carbon atoms, especially of 1 or 2 carbon atoms, more especially methyl or methoxy.

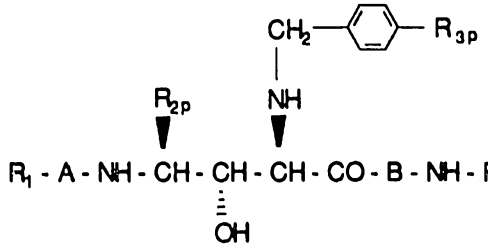
Hydroxyalkoxy preferably is ω-hydroxyalkoxy of 2 to 4 carbon atoms, especially 2-hydroxyethoxy.

A salt is e.g. an acid addition salt such as a hydrochloride.

The compounds of formula I have several chiral centers and can therefore exist in a variety of stereoisomers. The invention provides all stereoisomers as well as racemic mixtures unless specified otherwise. The isomers may be resolved or separated by conventional techniques, e.g. chromatographically. As appears from formula I the configuration at the carbon atom in the 2 position is R, in the 3 and 4 positions it is S.

A preferred subgroup of compounds of the invention is the compounds of formula I as defined above wherein R_4 is 2(R)-hydroxyindan-1(S)-yl, in free form or salt form; in another subgroup R_4 is (S)-2-hydroxy-1-phenylethyl; in another subgroup R_4 is 2-hydroxybenzyl or, preferably, 2-hydroxy-4-methoxybenzyl.

A further subgroup of compounds of the invention is the compounds of formula Ip_1



Ip_1

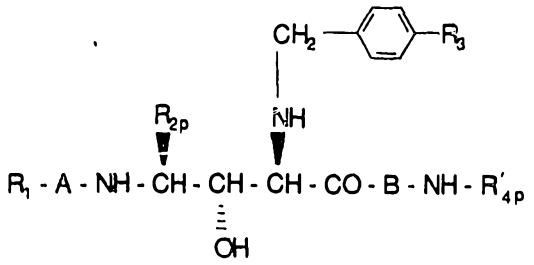
wherein

R_{2p} has the significance indicated above for R_2 with the proviso that cycloalkylalkyl represents cyclohexylalkyl,

R_{3p} represents alkoxy or hydroxyalkoxy,

R_{4p} represents 2(R)-hydroxyindan-1(S)-yl or (S)-2-hydroxy-1-phenylethyl; and
the remaining substituents are as defined above,
in free form or salt form.

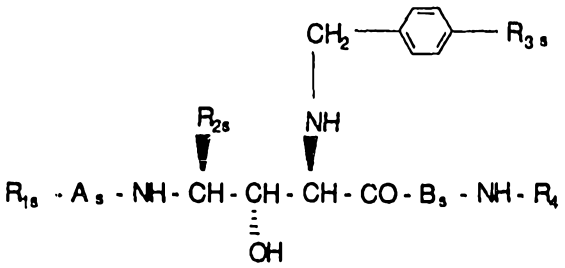
A further subgroup of compounds of the invention is the compounds of formula Ip_2



Ip_2

wherein R'_{4p} represents 2(R)-hydroxyindan-1(S)-yl; (S)-2-hydroxy-1-phenylethyl; or 2-hydroxy-4-methoxybenzyl; and
the remaining substituents are as defined above,
in free form or salt form.

A further subgroup of compounds of the invention is the compounds of formula Is



Is

wherein

A_s represents a bond; L-tert-leucinoyl optionally substituted at the nitrogen atom by (5-methyl-1,3,4-thiadiazol-2-yl)-SCH_2CO-), (benzthiazol-2-yl)SCH_2CO- or (1-methyl-1,3,4-triazol-2-yl)SCH_2CO-; L-valinoyl optionally substituted at the nitrogen atom by (2-pyridylmethyl)N(methyl)-CO- or (benzimidazol-2-ylmethyl)N(methyl)-CO-; L-isoleucinoyl; L-aspartyl optionally substituted at the free carboxyl moiety by alkyl of 1 to 4 carbon atoms; L-asparaginoyl; or a cis-1-aminocyclopent-2-ylcarbonyl or

cis-1-aminocyclohex-2-ylcarbonyl moiety optionally substituted at the nitrogen atom by (5-methyl-1,3,4-thiadiazol-2-yl)SCH_2CO-;

B_s represents a bond or L-valinoyl;

R_{1s} represents hydrogen; tert-butoxycarbonyl or benzyloxycarbonyl; or a group of formula $R_{5s}Y_s$- wherein

R_{5s} represents isobutyl, 2-hydroxy-4-methoxyphenyl, imidazo[1,2-a]pyrimidin-2-yl, imidazo[1,2-a]tetrahydropyrimidin-2-yl, imidazo[1,2-a]pyrimidin-2-ylmethyl, or 2-(benzimidazol-2-yl)ethyl;

Y_s represents -CO-; -NHCO-; or -O-CO-;

R_{2s} represents benzyl;

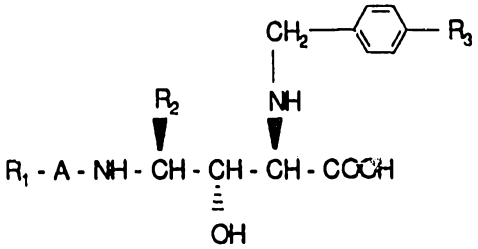
R_{3s} represents chlorine, bromine, methyl, methoxy, ethoxy or 2-hydroxyethoxy; and

R_4 is as defined above,

in free form or salt form.

The compounds of the invention may be prepared by a process which comprises

a) reacting a compound of formula



II

wherein the substituents are as defined above,

with a compound of formula H-B-NH-R_4 wherein B and R_4 are as defined above, or

b) for the preparation of the compounds of formula I

wherein R_1 is other than hydrogen or HY-,

appropriately substituting a corresponding compound of formula I

wherein R_1 is hydrogen or HY-,

and where indicated

deprotecting a resultant compound of formula I in protected form, or

appropriately protecting a resultant compound of formula I in unprotected form,

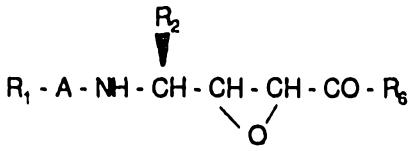
and recovering the resultant compounds of formula I in free form or salt form.

The process variants of the invention can be effected in conventional manner for coupling amino acids. For process variant a), the compound of formula H-B-NH-R_4 can be in optionally protected and/or substituted form, or ester or amide forms of the reagents can be used. For process variant b), the reaction is appropriately effected with a corresponding N-terminally protected and/or substituted amino acid, or with a compound of formula R_1-A-Z wherein Z represents a leaving group such as a nitrophenol or N-hydroxysuccinimide and R_1 is as defined above.

The process variants of the invention may be effected for example in a solvent inert under the reaction conditions, such as an amide, e.g. dimethylformamide, or an ether, e.g. tetrahydrofuran, at reaction temperatures of between about room temperature (which is preferred) and the boiling point of the reaction mixture.

End products can be isolated and purified according to known methods, e.g. chromatographically.

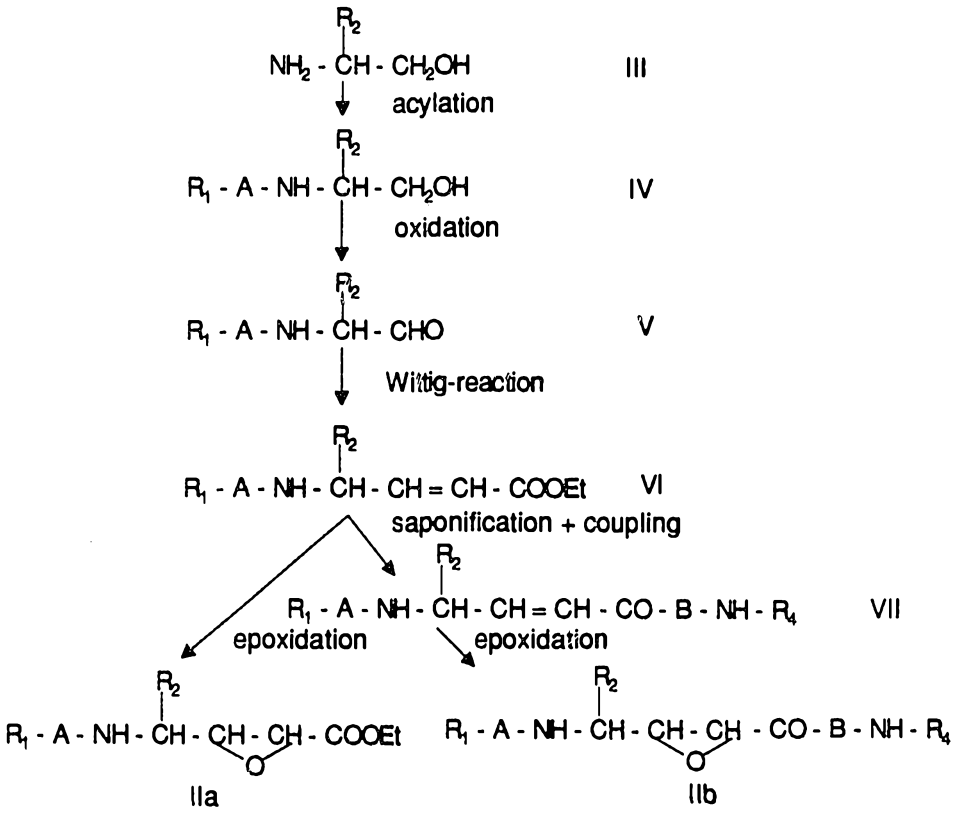
The starting compounds can be prepared in conventional manner. The compounds of formula II can be prepared e.g. by opening the epoxy ring of compounds of formula IIc



IIc

wherein R_6 represents optionally protected hydroxy or a group -B-NH-R_4 and the remaining substituents are as defined above, in the presence of an appropriate benzyl amine. This may be carried out in conventional manner, e.g. in a solvent inert under the reaction conditions, such as an ether, e.g. tetrahydrofuran, or in an alcohol, e.g. ethanol, at reaction temperatures of between about -50°C and the boiling temperature of the reaction mixture, preferably between about -20°C and about 80°C.

The starting compounds of formula IIc can be prepared e.g. according to the following reaction scheme:



In this reaction scheme the substituents are as defined above. The single reaction steps of this reaction scheme may be carried out according to reaction conditions conventionally employed in such reactions, whereby the various intermediates can, where appropriate, be reacted further without isolation.

The remaining starting materials and intermediate compounds are either known or can be prepared according to known methods or analogously to known methods or analogously as described in the examples. 1(S)-amino-2(R)-hydroxyindan can be prepared e.g. as described in the literature (J. Am. Chem. Soc. 73 [1951] 1639; J. Med. Chem. 35 [1992] 1685) or via fractional crystallization of diastereoisomeric salts of racemic trans-1-amino-2-hydroxyindan, e.g. the (+)-0,0'-dibenzoyltartaric acid salts.

The following Examples illustrate the invention but are not limitative. All temperatures are in degrees centigrade. The abbreviations for amino acids follow the international (IUPAC) rules. The following further abbreviations are used:

b	=	in free base form
BOC	=	tert-butoxycarbonyl
Bz	=	benzyl
ch	=	in hydrochloride salt form
dch	=	in dihydrochloride salt form
depr.	=	deprotection
Et	=	ethyl
Ex.	=	Example
iBu	=	2-methylpropyl
Me	=	methyl
m.p.	=	melting point
OMe	=	methoxy
Phe	=	phenyl
prot.	=	protection
tLeu	=	tert-leucinoyl = -NHCH[-C$(CH_3)_3$]CO-
Z	=	benzyloxycarbonyl

Example 1: 4(S)-tert-Butoxycarbonylamino-3(S)-hydroxy-2(R)-(4-methoxybenzyl-amino)-5-phenyl-pentanoic acid 1(S)-amino-2(R)-hydroxyindan-amide (process variant a)

[A, B = bond; R_1 = BOC; R_2 = Bz; R_3 = OMe; R_4 = 2(R)-hydroxyindan-1(S)-yl]

390 mg of 4(S)-tert-butoxycarbonylamino-3(S)-hydroxy-2(R)-(4-methoxybenzyl-amino)-5-phenyl-pentanoic acid (compound of formula II) are dissolved in 50 ml of dimethylformamide. 130 mg of 1(S)-amino-2(R)-hydroxyindan, 120 mg of hydroxybenzotriazole and 170 mg of N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide hydrochloride are added and the mixture is stirred for 3 days at room temperature. The solvent is evaporated, ethyl acetate is added, the solution is washed with 1 N HCl, saturated $NaHCO_3$ solution and brine, dried, and the solvent is evaporated. The title compound is obtained (m.p. 183-185° - from cyclohexane/ethyl acetate 1/2).

The starting material may be prepared in the following manner:

a) 4(S)-tert-Butoxycarbonylamino-5-phenyl-pent-2(E)-enoic acid ethylester (formula VI)

3.12 ml of oxalylchloride are dissolved in 40 ml of dry dichloromethane and cooled to -55°. Then 2.81 ml of dimethylsulfoxide are added dropwise carefully and thereafter 6.98 g of BOC-L-phenylalaninol dissolved in 40 ml of dichloromethane and 3.125 ml of dimethylsulfoxide are added at -50°. The reaction mixture is stirred at -60° for one hour, reacted with triethylamine and stirred until it reaches room temperature. After dilution with 200 ml of dichloromethane the mixture is washed with 1 N HCl, dried and the solvent evaporated. The residue is dissolved in toluene, 6.32 g of ethoxycarbonylmethylene-triphenylphosphorane are added and the reaction mixture is heated to 80° for 1 hour. After evaporation of the solvent, the residue is chromatographed on silicagel (solvent: toluene/ethyl acetate 4/1) (m.p. 47°).

b) 4(S)-tert-Butoxycarbonylamino-2(S),3(R)-epoxy-5-phenyl-pentanoic acid ethylester (formula IIc)

3 g of 4(S)-tert-Butoxycarbonylamino-5-phenyl-pent-2(E)-enoic acid ethylester are dissolved in 30 ml of dichloromethane. 1.37 g of m-chloroperbenzoic acid are added and the reaction mixture is stirred for 5 days. After evaporation of the solvent, the residue is chromatographed on silicagel (solvent: toluene/ethyl acetate 4/1) (m.p. 55-61°).

c) 4(S)-tert-Butoxycarbonylamino-3(S)-hydroxy-2(R)-(4-methoxybenzylamino)-5-phenyl-pentanoic acid ethylester

12.8 g of 4(S)-tert-butoxycarbonyl-2(S),3(R)-epoxy-5-phenyl-pentanoic acid ethylester are dissolved in 100 ml of ethanol. 10 g of 4-methoxybenzylamine are added and the solution is stirred at 70° for 12 hours. The solvent is evaporated and the residue is chromatographed on silicagel (solvent: cyclohexane/ethyl acetate 3/1) (oil).

d) 4(S)-tert-Butoxycarbonylamino-3(S)-hydroxy-2(R)-(4-methoxybenzylamino)-5-phenyl-pentanoic acid (formula II)

9 g of 4(S)-tert-butoxycarbonylamino-3(S)-hydroxy-2(R)-(4-methoxybenzylamino)-5-phenyl-pentanoic acid ethylester are dissolved in 300 ml of tetrahydrofuran and 22 ml of 1 N aqueous sodium hydroxide solution are added. The reaction mixture is stirred for 16 hours at room temperature and diluted with 300 ml of water. Tetrahydrofuran is evaporated and the aqueous solution is washed with ethyl acetate. Acidification with 1 N HCl leads to a white precipitate which is filtered off and dried (m.p.: 203-206°).

Example 2: 4(S)-(Benzyloxycarbonyl-L-tert-leucinoyl)amino-3(S)-hydroxy-2(R)-(4-methoxybenzylamino)-5-phenyl-pentanoic acid 1(S)-amino-2(R)-hydroxyindan-amide (process variant b)

[A = L-tLeu; B = bond; R_1 = Z; R_2 = Bz; R_3 = OMe; R_4 = 2(R)-hydroxyindan-1(S)-yl]

360 mg of N-methylmorpholine are added to a solution of 850 mg of 4(S)-amino-3(S)-hydroxy-2(R)-(4-methoxybenzylamino)-5-phenyl-pentanoic acid 1(S)-amino-2(R)-hydroxyindan-amide dihydrochloride (compound of Example 3) in 20 ml of dimethylformamide. 480 mg of N-benzyloxycarbonyl-L-tert-leucine, 290 mg of 3,4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazine and 340 mg of N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide hydrochloride are added and the solution is stirred for 3 days at room temperature. The solvent is evaporated, ethyl acetate is added, the mixture is washed with 1 N HCl, saturated $NaHCO_3$ solution and brine. The organic layer is dried, the solvent is evaporated and the residue is chromatographed on silicagel (solvent: cyclohexane/ethyl acetate 1/2). The title compound is obtained [m.p.: 146-148° - from ether; $[\alpha]^{20}_D$ = -28.9° (c = 1, CH_3OH); m.p. of hydrochloride: 128 - 134° - from ether; $[\alpha]^{20}_D$ = -16.8° (c = 1, CH_3OH)].

Example 3: 4(S)-Amino-3(S)-hydroxy-2(R)-(4-methoxybenzylamino)-5-phenyl-pentanoic acid 1(S)-amino-2(R)-hydroxyindan-amide (deprotection)

[A, B = bond; R_1 = H; R_2 = Bz; R_3 = OMe; R_4 = 2(R)-hydroxyindan-1(S)-yl]

6 g of 4(S)-tert-butoxycarbonylamino-3(S)-hydroxy-2(R)-(4-methoxybenzyl-amino)-5-phenyl-pentanoic acid 1(S)-amino-2(R)-hydroxyindan-amide (compound of Example 1) are dissolved in a mixture of 20 ml of dichloromethane and 4 ml of methanol. 300 ml of a 3 N solution of HCl in diethylether are added and the mixture is stirred for 3 hours at room temperature. The white precipitate is filtered off, washed with diethylether and dried in vacuo. The title compound is obtained in dihydrochloride salt form (m.p.: 147-151°).

Example 4: N-[4(S)-[(N-Benzyloxycarbonyl-tert-leucinoyl)amino]-3-(S)-hydroxy-2(R)-(4-methoxybenzylamino)-5-phenyl]pentanoyl-L-valine-N-[(2-hydroxy-4-methoxy)benzyl]amide (protection)

[A = L-tLeu; B = L-Val; R_1 = Z; R_2 = Bz; R_3 = OMe; R_4 = 2-OH,4-OMe-Bz]

[illegible] mg of 4(S)-[(N-(L-tert-leucinoyl)amino]-3(S)-hydroxy-2(R)-(4-methoxybenzylamino)-5-phenyl]pentanoyl-L-valine-N-[(2-hydroxy-4-methoxy)benzyl]amide (compound of Example 30) are dissolved in 20 ml of dimethylformamide. 34 µl of triethylamine and 62.3 mg of N-(benzyloxycarbonyloxy)-succinimide are added and the mixture is stirred at room temperature for 3 days. The solvent is evaporated and the residue is chromatographed on silicagel (solvent: ethyl acetate/methanol 98/2). The title compound is obtained (m.p.: 82-89°).

The following further compounds of the invention are obtained in analogous manner:

Ex. No.	R_1	A	R_3	B	R_4	Process variant	m.p.
A)	**R_2 = Bz:**						
5	BOC	bond	OMe	bond	(S)-CH(Phe)CH_2OH	a)	b 65-68°
6	BOC	bond	O$(CH_2)_2$OH	bond	2(R)-hydroxyindan-1(S)-yl	a)	b 77-82°
7	BOC	bond	OEt	bond	2(R)-hydroxyindan-1(S)-yl	a)	b 65-69°
8	BOC	bond	Br	bond	2(R)-hydroxyindan-1(S)-yl	a)	b 186-189°
9	BOC	bond	Cl	bond	2(R)-hydroxyindan-1(S)-yl	a)	b 180-183°
10	BOC	L-tLeu	OMe	bond	2(R)-hydroxyindan-1(S)-yl	a)	b 180-195°
11	BOC	L-tLeu	OMe	L-Val	2-OH,4-OMe-Bz	a)	b 85-92°
12	BOC	L-tLeu	OMe	L-Val	2-OH-Bz	a)	b 83-92°
13	Z	L-tLeu	OMe	bond	(S)-CH(Phe)CH_2OH	b)	b 143-147°
14	Z	L-tLeu	O$(CH_2)_2$OH	bond	2(R)-hydroxyindan-1(S)-yl	b)	b 109-113°
15	Z	L-tLeu	OEt	bond	2(R)-hydroxyindan-1(S)-yl	b)	b 104-109°
16	Z	L-tLeu	Cl	bond	2(R)-hydroxyindan-1(S)-yl	b)	b 134-136°
17	Z	L-tLeu	Br	bond	2(R)-hydroxyindan-1(S)-yl	b)	b 148-151°
18	Z	L-Val[1)]	OMe	bond	2(R)-hydroxyindan-1(S)-yl	b)	b 81-91°
19	H	L-Val[2)]	OMe	bond	2(R)-hydroxyindan-1(S)-yl	b)	b 70-76°
20	H	L-tLeu[2)]	OMe	bond	2(R)-hydroxyindan-1(S)-yl	b)	b 88-95°
21	H	L-tLeu	OMe	L-Val	2-OH,4-OMe-Bz	b)	b 95-98°
22	Z	L-Val	OMe	L-Val	2-OH,4-OMe-Bz	b)	b 78-82°
23	H	bond	OMe	bond	(S)-CH(Phe)CH_2OH	depr.	dch 134-136°
24	H	bond	O$(CH_2)_2$OH	bond	2(R)-hydroxyindan-1(S)-yl	depr.	
25	H	bond	OEt	bond	2(R)-hydroxyindan-1(S)-yl	depr.	
26	H	L-Val	OMe	bond	2(R)-hydroxyindan-1(S)-yl	depr.	dch 185-190°
27	H	bond	Br	bond	2(R)-hydroxyindan-1(S)-yl	depr.	dch 151-156°
28	H	bond	Cl	bond	2(R)-hydroxyindan-1(S)-yl	depr.	dch 160-164°
29	H	L-tLeu	OMe	bond	2(R)-hydroxyindan-1(S)-yl	depr.	dch 185-190°
30	H	L-tLeu	OMe	L-Val	2-OH,4-OMe-Bz	depr.	dch 178-181°
31	H	L-tLeu	OMe	L-Val	2-OH-Bz	depr.	dch R_f=0.1[8)]
32	Z	L-tLeu	OMe	L-Val	2-OH-Bz	prot.	b 73-80°

Ex. No.	R_1	A	R_3	Process variant	m.p.
B)	**R_2 = Bz; B = a bond; R_4 = 2(R)-hydroxyindan-1(S)-yl:**				
33	imidazo[1,2-a]pyrimidin-2-yl-CO-	L-tLeu	OMe	b)	b 104-110°
34	(2,4-di-OMe-Phe)-NHCO-	L-tLeu	OMe	b)	b 102-105°
35	2-(benzimidazol-2-yl)ethyl-CO-	L-tLeu	OMe	b)	b 130-134°
36	iBu-OCO-	bond	OMe	b)	b 123-125°
37	imidazo[1,2-a]tetrahydropyrimidin-2-yl-CO-	L-tLeu	OMe	b)	b 118-125°
38	imidazo[1,2-a]pyrimidin-2-ylmethyl-CO-	L-tLeu[3]	OMe	b)	b 110-120°
39	H	L-tLeu[4]	OMe	b)	b 90-95°
40	H	L-tLeu	OMe	b)	b 95-108°
41	Z	L-Val	OEt	b)	b 138-140°
42	Z	L-Val	$O(CH_2)_2OH$	b)	b 86-87°
43	Z	L-iLeu	OMe	b)	b 112-115°
44	Z	L-(O-tBu)Asp	OMe	b)	b 70-75°
45	Z	L-Asp	OMe	b);depr.	ch 111-114°
46[5]	Z	L-Asn	OMe	b)	b 158-162°
47[6]	BOC	cis-1-aminocyclopent-2-ylCO-	OMe	b)	b 79-82°
48[5]	BOC	cis-1-aminocyclopent-2-ylCO-	OMe	b)	b 70-78°
49[6]	BOC	cis-1-aminocyclohex-2-ylCO-	OMe	b)	b 78-86°
50[5]	BOC	cis-1-aminocyclohex-2-ylCO-	OMe	b)	b 82-93°
51[6]	H	cis-1-aminocyclohex-2-ylCO-	OMe	depr.	dch 103-107°
52[5]	H	cis-1-aminocyclohex-2-ylCO-	OMe	depr.	dch 128-138°
53[6]	H	cis-1-aminocyclopent-2-ylCO-	OMe	depr.	dch 98-102°
54[5]	H	cis-1-aminocyclopent-2-ylCO-[2]	OMe	depr.	dch 115-120°
55[6]	H	cis-1-aminocyclopent-2-ylCO-[2]	OMe	b)	b 75-83°
56	H	cis-1-aminocyclopent-2-ylCO-[2]	OMe	b)	b 83-90°
57	(2-OH,4-OMe-Phe)-NHCO-	L-Val	OMe	b)	b 95-105°
58	BOC	bond	Me	a)	b 71-73°
59	H	bond	Me	depr.	dch 145-151°
60	Z	L-tLeu	Me	b)	b 88-93°
61	H	L-Val[7]	OMe	b)	b 106-109°

Ex. No.	R_1	A	R_3	Process variant	m.p.

1) Substituted at N atom with (2-pyridylmethyl)N(CH_3)CO-
2) Substituted at N atom with (5-methyl-1,3,4-thiadiazol-2-yl)SCH_2CO-
3) Substituted at N atom with (benzthiazol-2-yl)SCH_2CO-
4) Substituted at N atom with (1-methyl-1,3,4-triazol-2-yl)SCH_2CO-
5) Isomer A with respect to configuration at cycloalkyl ring
6) Isomer B with respect to configuration at cycloalkyl ring
7) Substituted at N atom with (benzimidazol-2-ylmethyl)N(CH_3)CO-
8) In toluene/ethyl acetate 1/2

FURTHER INTERMEDIATES:

A) Compounds of formula II

Analogously as described above under Example 1 the following compounds of formula II are obtained wherein R_2 = Bz and R_1, A and R_3 respectively are:

- BOC, a bond and 2-hydroxyethoxy (m.p. 218-221°);
- BOC, a bond and ethoxy (m.p. 191-194°);
- BOC, L-tLeu and OMe (m.p. 124-125°);
- BOC, a bond and Br (m.p. 214-217°);
- BOC, a bond and Cl (m.p. 111-115°).

B) BOC-L-tert-leucinoyl-L-phenylalaninol

25 g of tert-butyloxycarbonyl-L-tert-leucine are dissolved in 250 ml of dry dimethylformamide, 16.36 g of phenylalaninol, 14.62 g of hydroxybenzotriazole and 24.9 g of N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride are added. The mixture is stirred for one day. The precipitate is filtered off, washed carefully with ethyl acetate and dried in vacuo (m.p. 198-201°).

C) L-Valine-[(2-hydroxy-4-methoxy)benzyl]amide

a) 2-Hydroxy-4-methoxy-benzaldehydoxime

10 g of 2-hydroxy-4-methoxy-benzaldehyde are dissolved in 200 ml of ethanol. 6.9 g of hydroxylamine hydrochloride and 13.7 ml of triethylamine are added and the mixture is stirred for 5 hours at room temperature. The solvent is evaporated, the residue is taken up in ethyl acetate and the organic layer is washed with $NaHCO_3$-solution and water. After drying over $MgSO_4$, the solvent is evaporated and the residue is used for the next step without further purification.

b) 2-Hydroxy-4-methoxy-benzylamine

11.1 g of 2-hydroxy-4-methoxy-benzaldehydoxime are dissolved in 400 ml of methanol containing 40 ml of formic acid. 1 g of palladium on charcoal is added and the solution is hydrogenated for 3 hours at room temperature. After filtration, the solvent is evaporated and the residue is chromatographed on silicagel (solvent: ethyl acetate/methanol 5/1 + 2 % NH_3-solution) to give an oil:

^{1}H-NMR (DMSO): 3.67 (s, 3H); 3.78 (bs, 2H); 4.70 (bs, 1H, exchangeable); 6.25 (d, J=9Hz, 1H); 6.30 (s, 1H); 6.95 (d, J=9Hz, 1H).

c) N-tert-Butyloxycarbonyl-L-valine-[(2-hydroxy-4-methoxy)benzyl]amide

306 mg of 2-hydroxy-4-methoxy-benzylamine are added to a solution of 676 mg of tert-butyloxycarbonyl-L-valine-p-nitrophenylester in 10 ml of dimethylformamide under argon. The reaction mixture is stirred for 2 days at room temperature. After evaporation of the solvent, the residue is dissolved in ethyl acetate and washed with 0.1 N NaOH, water and brine. The organic phase is dried over $MgSO_4$, the solvent is removed and the residue is chromatographed on silicagel (solvent: toluene/ethyl acetate 2/1). The product is obtained as a solid (m.p. 41-45°).

d) L-Valine-[(2-hydroxy-4-methoxy)benzyl]amide

A solution of 400 mg of N-tert-butyloxycarbonyl-L-valine-[(2-hydroxy-4-methoxy)benzyl]amide and 1.5 ml of trifluoroacetic acid in 10 ml of dichloromethane is stirred for 5 hours at room temperature. The dichloromethane is removed, the residue is taken up in ethyl acetate and washed several times with 5 % $NaHCO_3$-solution and then brine. The organic phase is dried over $MgSO_4$, the solvent is evaporated yielding the product as an oil:

^{1}H-NMR ($CDCl_3$): 0.80 (d, J=10Hz, 3H); 1.00 (d, J=10Hz, 3H); 2.25-2.40 (m, 1H); 3.23 (d, J=3.6Hz, 1H); 3.76 (s, 3H); 4.20-4.40 (m, 2H); 6.37 (dd, J=2.6Hz, J=8.3Hz, 1H); 6.50 (d, J=2.6Hz, 1H); 6.98 (d, J=8.3Hz, 1H); 8.24 (bs, 1H).

D) L-Valine-[(2-hydroxy)benzyl]amide

Is obtained as an oil analogously as described above under C):

^{1}H-NMR: d=0.79 (d, 3H); 1.00 (d, 3H); 2.37 (dsep, 1H); 3.30 (d, 1H); 4.20-4.41 (m, 2H); 6.81 (t, 1H), 6.93 (d, 1H); 7.08 (d, 1H); 7.20 (t, 1H); 8.22 (bs, 1H).

The compounds of formula I in free form or in pharmaceutically acceptable salt, e.g. acid addition salt form, hereinafter briefly named "the agents of the invention", possess interesting pharmaceutical properties. They are therefore indicated for use as pharmaceuticals. In particular, they exhibit antiviral activity, especially HIV-proteinase inhibiting activity, whereby they possess only low or inexistent inhibiting activity against human proteinases such as renin or pepsin. Further, they have particularly pronounced oral bioavailability over conventional peptidic anti-HIV proteinase agents. This activity can be shown in the following tests:

1. Assay of peptide cleavage by HIV-proteinase

Inhibition of HIV-proteinase is measured as described in the literature: A. Richards et al., J. Biol. Chem. 265, 7733-7736 (1990) and L.H. Philip et al., Biochem. Biophys. Res. Comun. 171, 439-444 (1990). Briefly the peptide H-Lys-Ala-Arg-Val-Leu-Nph-Glu-Ala-Nle-NH_2 (where Nph is p-nitrophenylalanine and Nle is norleucine) is used as substrate for recombinant HIV-1- and HIV-2-proteinase. Cleavage occurs between the Leu and Nph residues. The reaction is followed spectrophotometrically by the decrease in extinction at 300 nm which is observed upon cleavage.

In this test the agents of the invention exhibit K_i-values of from about 3 nM to about 1 µM for HIV-1-proteinase and of from about 8 nM to about 10 µM for HIV-2-proteinase.

2. Cellular assay

Inhibition of the HIV-1 (HTLV III_B)-induced cytopathic effect is measured in MT4-cells as described in the literature (R. Pauwels et al, J. Virol. Meth. 20 309-321 [1988]). Briefly, an HTLV-1 transformed T4 cell line, MT4, which has been shown previously to be highly permissive to HIV infection, serves as a target cell line. Inhibition of HIV-induced cytopathic effect is used as the end point. The viability of both HIV- and mock-infected cells is assessed spectrophotometrically via the in situ-reduction of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT). The comparison of the effects of various concentrations of the agent on HIV- versus mock-infected cells allows the determination of cytotoxic (TC_{50}) and virus-inhibitory (IC_{50}) concentrations.

In this test the agents of the invention exhibit IC_{50}-values of from about 10 nM to about 1 µM.

3. Assay of oral bioavailability in mice

As is known from the literature, peptide based drugs characteristically show poor oral bioavailability. Since with HIV patients long term medication with proteinase inhibitors is anticipated, it is important that a useful drug be orally bioavailable. This is one of the main obstacles in the development of effective drugs in this peptidic structural class. Surprisingly, the agents of the invention show excellent bioavailabilty after oral administration. This can be shown e.g. in the following test:

For peroral administration, a solution of the test substance (25 mg/ml) in a suitable solvent such as Cremophor RH40^{R} / Maisine^{R} / propylene glycol / ethanol (38/32/15/15) is prepared. Female Balb/c mice are fasted for 24 hours prior to the start, and throughout the experiment water is given ad libitum. At various times following drug administration, blood samples are obtained by sacrifycing animals under anaesthesia by cutting the vena jugularis, followed by cervical dislocation. Samples are collected in heparinized tubes (typically 0.4-0.6 ml). For sample analysis solid phase extraction and HPLC are used. Drug concentration in the samples is calculated by least-squares linear regression analysis of the peak area ratio (inhibitor/internal standard) of spiked blood standards versus concentration. From the concentration versus time data, the "Area Under the Curve" (AUC) value is calculated by the trapezoidal rule.

In this test the agents of the invention exhibit AUC-values of from about 25 µM.h to about 160 µM.h. at a dose of 125 mg/kg.

The agents of the invention are therefore indicated for use as pharmaceuticals, particularly as anti-HIV-proteinase agents, e.g. in the prophylaxy and treatment of retroviral infections. For this use, the effective dosage will, of course, vary depending on the particular agent employed, the mode of administration and the treatment desired. However, in general, satisfactory results are obtained when the agents are administered at a daily dosage of from about 0.02 mg/kg to about 50 mg/kg animal body weight, suitably given in divided doses two to four times daily. The total daily dosage is from about 1 mg to about 3500 mg, preferably from about 10 mg to about 2000 mg, especially from about 500 mg to about 1500 mg, especially about 600 mg given once or twice daily.

The agents may be administered in similar manner to known standards for use in such indications. It appears likely that metabolisation occurs according to known

patterns for structurally related compounds, e.g., for the agents of the invention wherein R_4 is 2(R)-hydroxyindan-1(S)-yl, starting with hydroxylation at the 3 or 4 position of the indanyl moiety.

The agent of Example 2, i.e. 4(S)-(benzyloxycarbonyl-L-tert-leucinoyl)amino-3(S)-hydroxy-2(R)-(4-methoxybenzylamino)-5-phenyl-pentanoic acid 1(S)-amino-2(R)-hydroxy-indan-amide in free form or in pharmaceutically acceptable salt form is the preferred agent of the invention as an anti-HIV-proteinase agent. It inhibits HIV-1 proteinase with K_i = 9.5 nM and HIV-2 proteinase with K_i = 50 nM, and further has excellent oral uptake. It is specific for the retroviral enzymes since it does not inhibit endogenous proteinases such as renin and cathepsin D. In the cellular assay it has an IC_{50} of 0.25 µM. It is indicated that for this anti-HIV indication this agent may be administered by similar modes of administration at similar or lower dosages than conventionally employed with known standards for such indications.

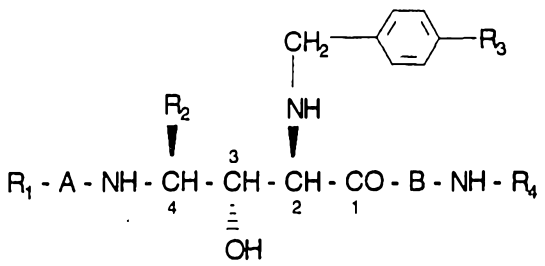
The invention also concerns a method of treating retroviral diseases, especially diseases caused by HIV, which comprises administering to a subject in need of such treatment an effective amount of an agent of the invention, as well as the agents of the invention for use as pharmaceuticals, particularly in the treatment of retroviral diseases, especially of diseases caused by HIV, especially as agents against HIV-proteinase.

The agents may be admixed with conventional chemotherapeutically acceptable diluents and carriers and administered e.g. parenterally or intravenously, preferably orally, in such forms as tablets or capsules. The concentrations of active substance will, of course, vary depending e.g. on the agent employed, the treatment desired and the nature of the form.

Such compositions form part of the invention. The invention thus also includes pharmaceutical compositions comprising an agent of the invention together with at least one pharmaceutically acceptable carrier or diluent.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of formula I



I

wherein

A and B independently represent a bond or an optionally substituted amino acyl moiety;

R_1 represents hydrogen; an amino protecting group; or a group of formula R_5Y- wherein

R_5 represents hydrogen or an optionally substituted alkyl, alkenyl, alkinyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl group; and

Y represents -CO-; -NHCO-; -NHCS-; $-SO_2-$; -O-CO-; or -O-CS-;

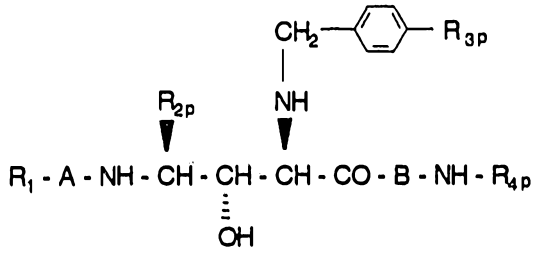
R_2 represents the side chain of a natural amino acid; an alkyl, arylalkyl, heteroarylalkyl or cycloalkylalkyl group; or trimethylsilylmethyl, 2-thienylmethyl or styrylmethyl;

R_3 represents halogen, alkyl, alkoxy or hydroxyalkoxy; and

R_4 represents 2(R)-hydroxyindan-1(S)-yl; (S)-2-hydroxy-1-phenylethyl; or 2-hydroxy-benzyl optionally substituted in 4 position by methoxy;

in free form or salt form.

2. A compound according to claim 1 of formula Ip_1



Ip_1

wherein

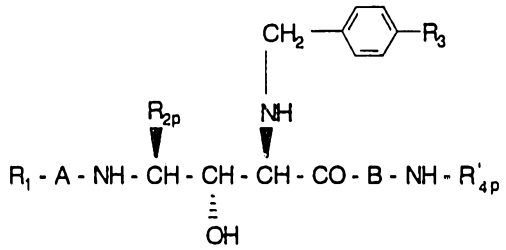
R_{2p} has the significance indicated in claim 1 for R_2 with the proviso that cycloalkyl-alkyl represents cyclohexylalkyl,

R_{3p} represents alkoxy or hydroxyalkoxy,

R_{4p} represents 2(R)-hydroxyindan-1(S)-yl or (S)-2-hydroxy-1-phenylethyl; and the remaining substituents are as defined in claim 1,

in free form or salt form.

3. A compound according to claim 1 of formula Ip_2



Ip_2

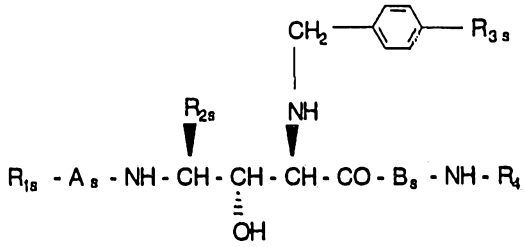
wherein

R_4' represents 2(R)-hydroxyindan-1(S)-yl; (S)-2-hydroxy-1-phenylethyl; or 2-hydroxy-4-methoxybenzyl; and

the remaining substituents are as defined in claim 1,

in free form or salt form.

4. A compound according to claim 1 of formula Is



Is

wherein

A_s represents a bond; L-tert-leucinoyl optionally substituted at the nitrogen atom by (5-methyl-1,3,4-thiadiazol-2-yl)-SCH_2CO-), (benzthiazol-2-yl)SCH_2CO- or (1-methyl-1,3,4-triazol-2-yl)SCH_2CO-; L-valinoyl optionally substituted at the nitrogen atom by (2-pyridylmethyl)N(methyl)-CO- or (benzimidazol-2-ylmethyl)N(methyl)-CO-; L-isoleucinoyl; L-aspartyl optionally substituted at the free carboxyl moiety by alkyl of 1 to 4 carbon atoms; L-asparaginoyl; or a cis-1-aminocyclopent-2-ylcarbonyl or cis-1-aminocyclohex-2-ylcarbonyl moiety optionally substituted at the nitrogen atom by (5-methyl-1,3,4-thiadiazol-2-yl)SCH_2CO-;

B_s represents a bond or L-valinoyl;

R_{1s} represents hydrogen; tert-butoxycarbonyl or benzyloxycarbonyl; or a group of formula $R_{5s}Y_s$- wherein

R_{5s} represents isobutyl, 2-hydroxy-4-methoxyphenyl, imidazo[1,2-a]pyrimidin-2-yl, imidazo[1,2-a]tetrahydropyrimidin-2-yl, imidazo[1,2-a]pyrimidin-2-ylmethyl, or 2-(benzimidazol-2-yl)ethyl;

Y_s represents -CO-; -NHCO-; or -O-CO-;

R_{2s} represents benzyl;

R_{3s} represents chlorine, bromine, methyl, methoxy, ethoxy or 2-hydroxyethoxy; and

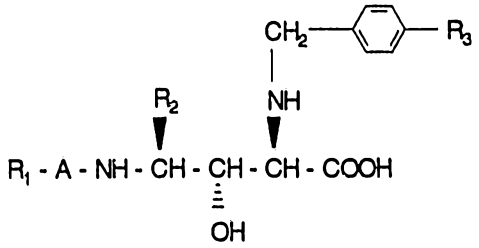
R_{4s} is as defined in claim 1,

in free form or salt form.

5. 4(S)-(Benzyloxycarbonyl-L-tert-leucinoyl)amino-3(S)-hydroxy-2(R)-(4-methoxybenzyl-amino)-5-phenyl-pentanoic acid 1(S)-amino-2(R)-hydroxyindan-amide,
in free form or salt form.

6. A process for the preparation of a compound according to claim 1 which comprises

a) reacting a compound of formula II



II

wherein the substituents are as defined in claim 1,

with a compound of formula H-B-NH-R_4 wherein B and R_4 are as defined in claim 1, or

b) for the preparation of the compounds according to claim 1

wherein R_1 is other than hydrogen or HY-,

appropriately substituting a corresponding compound of formula 1 wherein R_1 is hydrogen or HY-,

and where indicated

deprotecting a resultant compound of formula I in protected form, or

appropriately protecting a resultant compound of formula I in unprotected form,

and recovering the resultant compound of formula I in free form or salt form.

7. A pharmaceutical composition comprising a compound of formula I as defined in claim 1 in free form or pharmaceutically acceptable salt form, together with at least one pharmaceutically acceptable carrier or diluent.

8. A method of treating retroviral diseases, especially diseases caused by HIV, which comprises administering to a subject in need of such treatment an effective amount of a compound of formula I as defined in claim 1 in free form or in pharmaceutically acceptable salt form.

9. The compounds of formula I, methods for their preparation or pharmaceutical compositions or methods of treatment involving them substantially as hereinbefore described with reference to the Examples.

DATED this 26th day of August, 1996

Sandoz Ltd.

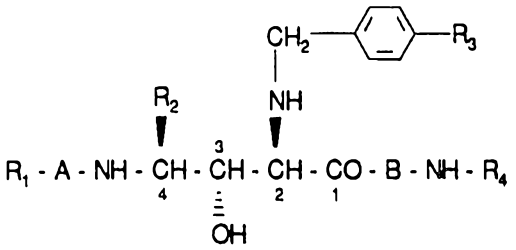
by DAVIES COLLISON CAVE

Patent Attorneys for the Applicant

Abstract:

2,4-DIAMINO-3-HYDROXYCARBOXYLIC ACID DERIVATIVES

The invention relates to compounds of formula I



I

wherein the substituents have various significances.

They can be prepared by conventional methods, e.g. coupling, substitution, deprotection or protection reactions.

They possess interesting pharmacological properties and are thus indicated for use in the treatment of retroviral infections, particularly as HIV proteinase inhibitors.