Exhibit 9 – Part 7 of 7

A. (2S,3S)-2,3-O-Isopropylidene-1,4-bis-(3-((t-butyl)amino)carbonyl-1,2,3,4-tetrahydroisoquinolin-2-yl)-butan-2,3-diol.

Using the procedure of Examaple 201A but replacing L-valine methyl ester hydrochloride with the resultant compound of Example 330C and replacing benzyl bromoacetate with 2,3-isopropylidenethreitol 1,4-ditosylate provided the desired compound.

Example 333

A. (2S,3S)-2,3-O-Isopropylidene-1,4-bis-(3-((t-butyl)amino)carbonyl-decahydroisoquinolin-2-yl)-butan-2,3-diol.

Using the procedure of Example 211 with the resultant compound of Example 332 provided the desired compound.

Fluorogenic Assay for Screening Inhibitors of HIV Protease

The inhibitory potency of the compounds of the invention can be determined by the following method.

A compound of the invention is dissolved in DMSO and a small aliquot further diluted with DMSO to 100 times the final concentration desired for testing. The reaction is carried out in a 6 X 50 mm tube in a total volume of 300 microliters. The final concentrations of the components in the reaction buffer are: 125 mM sodium acetate, 1 M sodium chloride, 5 mM dithiothreitol, 0.5 mg/ml bovine serum albumin, 1.3 uM fluorogenic substrate, 2% (v/v) dimethylsulfoxide, pH 4.5. After addition of inhibitor, the reaction mixture is placed in the fluorometer cell holder and incubated at 30 ° C for several minutes. The reaction is initiated by the addition of a small aliquot of cold HIV protease. The fluorescence intensity (excitation 340 nM, emmision 490 nM) is recorded as a function of time. The reaction rate is determined for the first six to eight minutes. The observed rate is directly proportional to the moles of substrate cleaved per unit time. The percent inhibition is 100 X (1 - (rate in presence of inhibitor)/(rate in absence of inhibitor)).

Fluorogenic substrate: Dabcyl-Ser-Gln-Asp-Tyr-Pro-Ile-Val-Gln-EDANS wherein DABCYL = 4-(4-dimethylaminophenyl)azobenzoic acid and EDANS = 5-((2-aminoethyl)amino)naphthalene-1-sulfonic acid.

Compounds of the invention inhibit HIV-1 protease at concentrations between 0.01 nM and 500,000 nM. Table 3 shows the inhibitory potencies of specific compounds of the invention against HIV-1 protease.

TABLE 3

Compound of Example	Percent Inhibition	Inhibitor Concentration (micromolar)
12	75	50
34C	95	270
35	68	50
43C	94	270
55	37	0.01
59	50	0.01
62	100	270
65	79	0.1
66	95	0.1
68	51	0.91
70	75	0.01
160D	47	0.005
161C	59	0.005
162C	63	0.005

163C	59	0.0025
165C	40	0.005
166C	31	0.005
170B	40	0.01
172B	74	0.001
178	58	0.005
182	59	0.0025
183	70	0.001
202	82	0.1
203	62	0.01
206	44	0.01
209	56	0.001
210	65	0.001
211	67	0.1
213	86	0.005
214	73	0.005
215	81	0.001
216	84	0.001
217	78	0.001
218	45	0.001
219	68	0.001
220	62	0.001
221	53	0.05
222	78	0.1
223	38	0.001
224	62	0.005
225	74	0.005
228	44	0.002
229	78	0.001
230	69	0.001
231	67	0.005

233	68	0.01
235	45	0.01
237	69	0.001
238	35	0.1
239	53	0.1
240	52	0.01
241	63	0.01
242	31	0.01
243	53	0.005
244	33	0.001
245	82	0.1
246	81	0.1
247	74	0.001
248	33	0.01
249	40	0.001
251	60	0.1
252	56	0.05
254	79	0.05
255	49	0.05
258	46	0.01
259	78	0.005
264	45	0.005
265	62	0.001
267	92	0.005
267	53	0.001
268	71	0.001
269	47	0.1
270	48	0.01
276	51	0.005
280	41	0.01
281	30	0.01

283	70	0.1
284	87	0.1
291	52	0.005
292	36	0.01

Antiviral Activity

The anti-HIV activity of the compounds of the invention can be determined by the following method.

A mixture of 0.1 ml (2 X 10^5 cells/ml) of H9 cells and 0.1 ml (100 infectious units) of HIV-1_{3B} was incubated on a shaker for 2 h at 37° C. The resulting culture was washed three times and resuspended into 2 ml of medium containing 10 ul of a compound of the invention in dimethylsulfoxide. The control culture was treated in an identical manner except no compound was added to the medium. Aliquots of culture supernatants were removed at 3 time points, usually 4, 7 and 10 days, and monitored for HIV-1 antigen EIA (HIVAG-1) (Paul, et al., J. Med. Virol., 22 357 (1987)). Cell viability was determined by trypan blue dye exclusion, and cells were refed with media containing compound (except for control wells which were refed with media only) at these time points. Per cent inhibition of HIV by the compound was determined by comparing HIV antigen levels in the supernatants of infected cells incubated with compound to supernatants from the control culture without compound. The IC_{50} is the concentration of compound that gives 50% inhibition of HIV activity. The LD_{50} is the concentration of compound at which 50% of the cells remain viable.

Table 4 shows the inhibitory potencies of compounds of the invention against HIV-1 in H9 cells:

TABLE 4

Compound of Example	IC_{50} (micromolar)	LD_{50} (micromolar)
55	0.17-0.24	20
70	0.3-0.8	120
160	0.3-0.8	15
161	0.6-1.1	20
162	0.6-1.0	25
163	0.6-1.1	>100
165	0.5-1.0	>100
166	6.1-9.4	21
169	6.2-11.2	54
172	0.12	11
174	1.1-2.7	>100
175	0.75-1.1	>100
206	2.3-4.5	25
209	0.015-0.027	60
210	0.05-0.07	>100
213	0.54	30
215	0.10	>100
216	0.04-0.1	>100
218	0.42	>100
219	0.05-0.1	>100
220	0.09-0.18	>100
225	0.27	>100
237	0.4-1.6	>100

241	2.4-5.0	75
242	4.50	>100
244	0.5-1.0	>100
247	0.25	180
248	1.2-7.5	>100
249	0.3-0.9	45
268	0.11-0.22	25
269	3-6	130
270	4-15	35
286	2-6	20

Additionally a decrease in infectivity of HIV as a measure of anti-HIV activity of the compounds of the invention can be assessed as follows:

After incubation of the culture containing a compound of the invention as descrived above for approximately 6 days (range: 4-10 days), an aliquot (0.1 ml) of the supernatant was withdrawn, 5-fold dilutions were made in media, and these dilutions were then incubated with fresh H9 cells (4×10^5 cells/ml) on a shaker for 2 hr at 37° C. The resulting cultures were washed three times, resuspended in 2 ml of medium with and without compound, and incubated and maintained as above. Production of virus in the culture supernatant was monitered at various time points using the Abbott HIV-1 antigen EIA. Loss of infectivity was determined by comparing HIV antigen end point dilutions of cultures with and without compound. In this manner, the compound of Example 70 reduced the HIV infectivity 25-fold.

The compounds of the present invention can be used in the form of salts derived from inorganic or organic acids. These salts include but are not limited to the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, mesylate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as loweralkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid. Other salts include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic bases.

The compounds of the present invention can also be used in the form of esters. Examples of such esters include a hydroxyl-substituted compound of formula I which has been acylated with a blocked or unblocked amino acid residue, a phosphate function, a hemisuccinate residue or a benzoyl group which is substituted on the phenyl ring with $-NR_{800}R_{801}$ wherein R_{800} and R_{801} are independently selected from hydrogen and loweralkyl or the group $-NR_{800}R_{801}$ forms a nitrogen containing heterocyclic ring. The amino acid esters of particular interest are glycine and lysine; however, other amino acid residues can also be used, including those wherein the amino acyl group is $-C(O)CH_2NR_{800}R_{801}$ wherein R_{800} and R_{801} are independently selected from hydrogen and loweralkyl or the group $-NR_{800}R_{801}$ forms a nitrogen containing heterocyclic ring. These esters serve as pro-drugs of the compounds of the present invention and serve to increase the solubility of these substances in the gastrointestinal tract. These esters also serve to increase solubility for intravenous administration of the compounds. These pro-drugs are metabolized in vivo to provide the hydroxyl-substituted compound of formula I. The preparation of the pro-drug esters is carried out by reacting a hydroxyl-substituted compound of formula I with an activated amino acyl, phosphoryl, hemisuccinyl or substituted benzoyl derivative as defined above. The resulting product is then deprotected to provide the desired pro-drug ester.

The compounds of the present invention are useful for the treatment or prophylaxis of diseases caused

by retroviruses in mammals (especially humans) and are particularly useful for the treatment or prophylaxis of acquired immune deficiency syndrome or an HIV infection.

Total daily dose administered to a host in single or divided doses may be in amounts, for example, from 0.001 to 10 mg/kg body weight daily and more usually 0.01 to 1 mg. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy.

The compounds of the present invention may be administered orally, parenterally, by inhalation spray, by aerosols, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of sublingual dosage forms, transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

Injectable preparations, for example, sterile injectable aqueous or oleagenous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

The present agents can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic.

Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N. Y. (1976), p. 33 et seq.

While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more immunomodulators, antiviral agents, other antiinfective agents or vaccines. Other antiviral agents to be administered in combination with a compound of the present invention include AL-721, beta interferon, polymannoacetate, ganciclovir, dideoxycytidine, trisodium phosphonoformate, HPA-23, eflornithine, Peptide T, Reticulose (nucleophosphoprotein), zidovudine (AZT), ansamycin LM 427, trimetrexate, UA001, ribavirin, alpha interferon and acyclovir. Immunomodulators that can be administered in combination with a compound of the present invention include bropirimine, Ampligen, anti-human alpha interferon antibody, colony stimulating factor, CL246,738, Imreg-1, Imreg-2, diethyldithiocarbamate, interleukin-2, alpha-interferon, inosine pranobex, methionine enkephalin, muramyl-tripeptide, TP-5, erythropoietin, naltrexone and tumor necrosis factor. Other antiinfective agents that can be administered in combination with a compound of the present invention include

pentamidine isethionate. Any of a variety of HIV or AIDS vaccines can be used in combination with a compound of the present invention.

It will be understood that agents which can be combined with the compounds of the present invention for the treatment or prophylaxis of AIDS or an HIV infection are not limited to those listed above, but include in principle any agents useful for the treatment or prophylaxis of AIDS or an HIV infection.

When administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or different times, or the therapeutic agents can be given as a single composition.

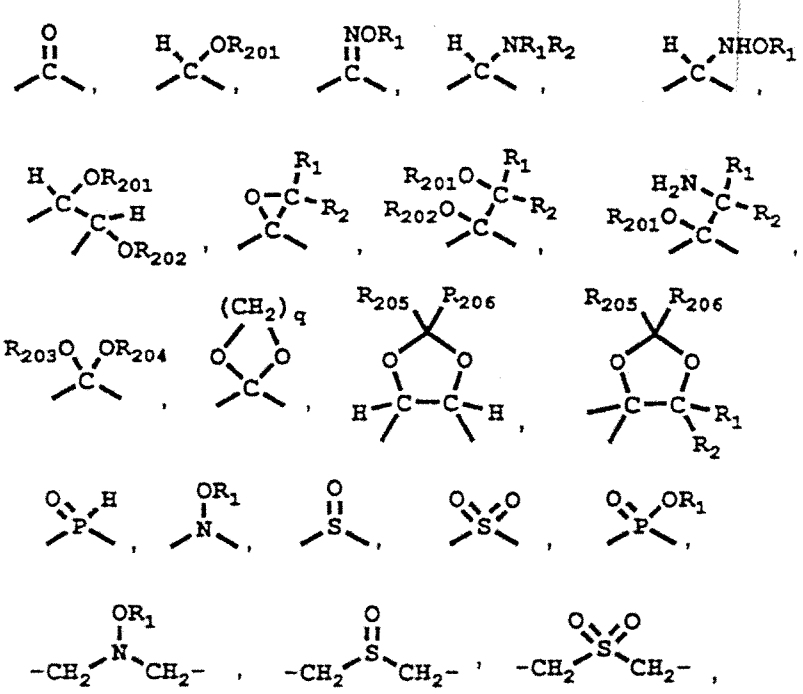
The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

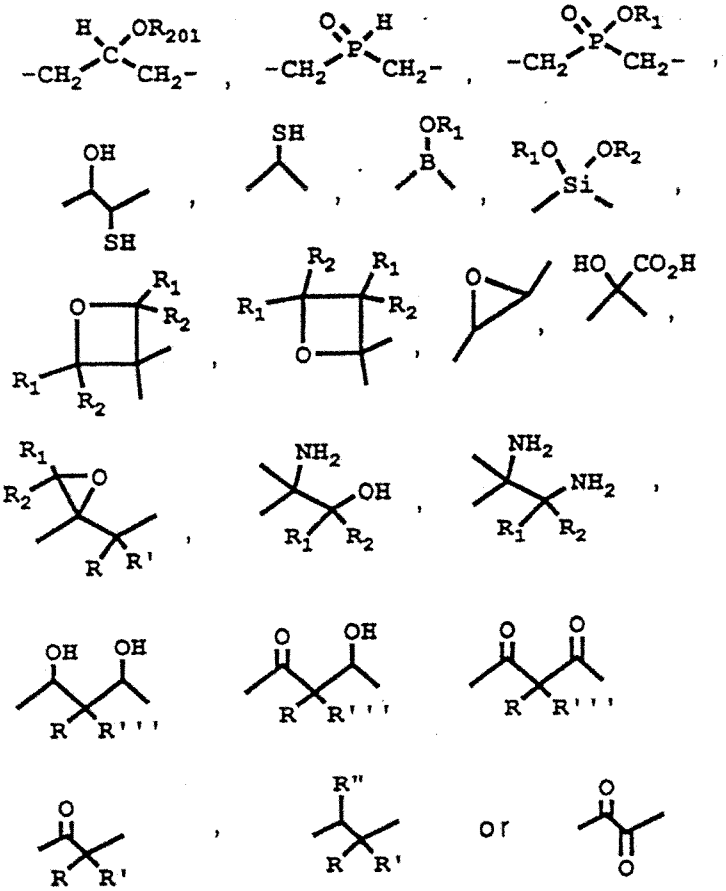
Claims

1. A compound of the formula:

A - X - B

wherein X is





wherein R_1 and R_2 are independently selected from
(1) hydrogen,
(2) loweralkyl,
(3) hydroxyalkyl and
(4) alkoxyalkyl; and
R_{201} and R_{202} are independently selected from
(1) hydrogen,
(2) alkoxyalkyl,
(3) thioalkoxyalkyl and
(4) alkoxyalkoxyalkyl;
R_{203} is loweralkyl;
R_{204} is loweralkyl;
R_{205} and R_{206} are independently selected from
(1) hydrogen
(2) loweralkyl
(3) alkoxyalkyl;
R is hydrogen or halogen;
R' is hydrogen, halogen, loweralkyl, $-NH_2$, -NH(loweralkyl) or $-OR_{206}$ wherein R_{206} is defined as above;
R" is $-NH_2$, -NH(loweralkyl) or $-OR_{206}$ wherein R_{206} is independently defined as above;
R"' is halogen; and
q is 2 or 3;
A is
(1) substituted amino,
(2) substituted carbonyl,
(3) functionalized imino,

(4) functionalized alkyl,
(5) functionalized acyl,
(6) functionalized heterocyclic or
(7) functionalized (heterocyclic)alkyl; and
B is
(1) substituted carbonyl independently defined as herein,
(2) substituted amino independently defined as herein,
(3) functionalized imino independently defined as herein,
(4) functionalized alkyl independently defined as herein,
(5) functionalized acyl independently defined as herein,
(6) functionalized heterocyclic independently defined as herein or
(7) functionalized (heterocyclic)alkyl independently defined as herein;
or a pharmaceutically acceptable salt, ester or prodrug thereof.

2. The compound of Claim 1 wherein A is functionalized alkyl or functionalized acyl; B is functionalized alkyl or functionalized acyl; and X is -CH(OR_{201})-, -CH(OR_{201})CH(OR_{202})-, -C(O)-C(R)(R′)- or -CH(R″)-C(R)-(R′)- wherein R_{201} and R_{202} are independently selected from hydrogen, alkoxyalkyl, thioalkoxyalkyl and alkoxyalkoxyalkyl; R is hydrogen or halogen; R′ is hydrogen, halogen, loweralkyl, -NH_2, -NH(loweralkyl) or -OR_{206} wherein R_{206} is hydrogen, loweralkyl or alkoxyalkyl; and R″ is -NH_2, -NH(loweralkyl) or -OR_{206} wherein R_{206} is independently defined as above.

3. A compound of the formula:
A - X - B
wherein X is -CH(OR_{201})-, -CH(OR_{201})CH(OR_{202})-, -C(O)-C(R)(R′)- or -CH(R″)-C(R)(R′)- wherein R_{201} and R_{202} are independently selected from hydrogen, alkoxyalkyl, thioalkoxyalkyl and alkoxyalkoxyalkyl; R is hydrogen or halogen; R′ is hydrogen, halogen, loweralkyl, -NH_2, -NH(loweralkyl) or -OR_{206} wherein R_{206} is hydrogen, loweralkyl or alkoxyalkyl; and R″ is -NH_2, -NH(loweralkyl) or -OR_{206} wherein R_{206} is independently defined as above;
A is
(1) substituted amino,
(2) substituted carbonyl,
(3) functionalized imino,
(4) functionalized alkyl,
(5) functionalized acyl,
(6) functionalized heterocyclic or
(7) functionalized (heterocyclic)alkyl; and
B is
(1) substituted carbonyl independently defined as herein,
(2) substituted amino independently defined as herein,
(3) functionalized imino independently defined as herein,
(4) functionalized alkyl independently defined as herein,
(5) functionalized acyl independently defined as herein,
(6) functionalized heterocyclic independently defined as herein or
(7) functionalized (heterocyclic)alkyl independently defined as herein;
or a pharmaceutically acceptable salt, prodrug or ester thereof.

4. A compound of the formula:
A - X - B
wherein X is -CH(OR_{201})CH(OR_{202})- wherein R_{201} and R_{202} are independently selected from hydrogen, alkoxyalkyl, thioalkoxyalkyl and alkoxyalkoxyalkyl; and A and B are -CH(Z)(R_3) wherein R_3 is (aryl)alkyl or (heterocyclic)alkyl and Z is -N(R_9)(G) wherein R_9 is hydrogen or loweralkyl and G is R_{17}-R_{800}-C(T)-E-CH-(R_3′)-C(T)-wherein R_{17} is (aryl)alkyl or (heterocyclic)alkyl, R_{800} is O, S or -N(R_{17})- wherein R_{17} is hydrogen or loweralkyl, T is independently selected at each occurrence from O or S, E is O, S or -NH- or -N-(loweralkyl)- and R_3′ is loweralkyl;
or a pharmaceutically acceptable salt, prodrug or ester thereof,

5. A compound of the formula:
A - X - B
wherein X is OCH(OR_{201})-, -C(O)-C(R)(R′)- or -CH(R″)-C(R)(R′)- wherein R_{201} and R_{202} are independently selected from hydrogen, alkoxyalkyl, thioalkoxyalkyl and alkoxyalkoxyalkyl; R is halogen; R′ halogen; and R″ is -NH_2, -NH(loweralkyl) or -OR_{206} wherein R_{206} is hydrogen, loweralkyl or alkoxyalkyl; and
A and B are -CH(Z)(R_3) wherein R_3 is (aryl)alkyl or (heterocyclic)alkyl and Z is -N(R_9)(G) wherein R_9 is

hydrogen or loweralkyl and G is R_{17}-R_{800}-C(T)-E-CH(R_3')-C(T)-wherein R_{17} is (aryl)alkyl or (heterocyclic)-alkyl, R_{800} is O, S or -N(R_{17})- wherein R_{17} is hydrogen or loweralkyl, T is independently selected at each occurrence from O or S, E is O, S or -NH- or -N(loweralkyl)- and R_3' is loweralkyl;
or a pharmaceutically acceptable salt, prodrug or ester thereof.

6. A compound selected from the group consisting of:
(2S,3R,4R,5S)-2,5-Di-(N-((N-Methyl-N-((2-pyridinyl)methyl)amino)carbonyl)-valinyl-amino)-3,4-dihydroxy-1,6-diphenylhexane;
(2S,3S,4S,5S)-2,5-Di-(N-((N-Methyl-N-((2-pyridinyl)methyl)amino)carbonyl)-valinyl-amino)-3,4-dihydroxy-1,6-diphenylhexane; and
(2S,3R,4S,5S)-2,5-Di-(N-((N-Methyl-N-((2-pyridinyl)methyl)amino)carbonyl)-valinyl-amino)-3,4-dihydroxy-1,6-diphenylhexane;
or a pharmaceutically acceptable salt, prodrug or ester thereof.

7. A compound selected from the group consisting of:
(2S,3R,4R,5S)-2,5-Di-(N-((2-pyridinyl)methoxycarbonyl)-valinyl-amino)-3,4-dihydroxy-1,6-diphenylhexane;
(2S,3S,4S,5S)-2,5-Di-(N-((2-pyridinyl)methoxycarbonyl)-valinyl-amino)-3,4-dihydroxy-1,6-diphenylhexane; and
(2S,3R,4S,5S)-2,5-Di-(N-((2-pyridinyl)methoxycarbonyl)-valinyl-amino)-3,4-dihydroxy-1,6-diphenylhexane;
or a pharmaceutically acceptable salt, prodrug or ester thereof.

8. A compound selected from the group consisting of:
(2S,3R,4S,5S)-2,5-Di-(N-((3-pyridinyl)methoxycarbonyl)-valinyl-amino)-3,4-dihydroxy-1,6-diphenylhexane; and
(2S,3S,4S,5S)-2,5-Di-(N-((3-pyridinyl)methoxycarbonyl)-valinyl-amino)-3,4-dihydroxy-1,6-diphenylhexane;
(2S,3R,4R,5S)-2,5-Di-(N-((3-pyridinyl)methoxycarbonyl)-valinyl-amino)-3,4-dihydroxy-1,6-diphenylhexane;
or a pharmaceutically acceptable salt, prodrug or ester thereof.

9. 2,4-Di-N-((2-pyridinyl)methoxycarbonyl)-valinyl-amino)-1,5-diphenyl-3-hydroxypentane;
or a pharmaceutically acceptable salt, prodrug or ester thereof.

10. 2,5-Bis-(2-pyridyl-methoxycarbonyl-valinyl-amino)-1,6-diphenyl-3,3-difluoro-4-hydroxyhexane; or a pharmaceutically acceptable salt, prodrug or ester thereof.

11. A compound of claim 1 for use in inhibiting a retroviral protease by administration to a mammal in need of such treatment.

12. The compound of claim 11 wherein the retroviral protease is HIV-1 protease of HIV-2 protease.

13. A compound of claim 1 for use in treating a retroviral infection by administration to a mammal in need of such treatment.

14. A pharmaceutical composition for treating a retroviral infection comprising a pharmaceutical carrier and a therapeutically effective amount of the compound of Claim 1.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application number

EP 90109319.5
- page 1 -

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A,D	US-A-4562552 (CH.A. KETTNER et al.) * column 1, line 5 - column 2, line 62 *	6,11	C07D213/40 C07D213/56 C07D211/44 C07D215/14 C07D211/34 C07D215/18 C07D295/26 C07D295/145 C07D303/04 C07D303/23 C07D303/36 // C07D317/12 C07K5/06 C07C31/125 C07C31/20 C07C49/11 C07C49/175 C07C43/23 C07C233/11 C07C247/12
A,D	BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS vol. 159, no. 2, 15 March 1989, pages 420-425, London, GB; M.L. MOORE et al.: "Peptide Substrates and Inhibitors of the HIV-1 Protease" * pages 423,424 *	6,11	
A,D	FEBS LETTERS vol. 247, no. 1, April 1989, pages 113-117, Amsterdam, NL; A.D. RICHARDS et al.: "Effec-	6,11	

.../2

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

C07D213/00
C07K
C07C
A61K

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.

Claims searched completely: 6-14
Claims searched incompletely: 1-5
Claims not searched:
Reason for the limitation of the search:

Lack of clarity

Place of search	Date of completion of the search	Examiner
Berlin	28.08.1990	G. KYRIAKAKOU

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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PARTIAL EUROPEAN SEARCH REPORT

Application number
EP 90109319.5
- page 2 -

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
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EPO Form 1503.3 06.78