Novel Compounds for use as HIV Protease Inhibitors

This invention is concerned with novel HIV protease inhibitors or prodrugs thereof, a process for their manufacture, pharmaceutical compositions and the use of such compounds in medicine. In particular, the compounds are hydroxyethylamine tripeptide mimetics which act as inhibitors of the HIV aspartyl protease, an essential enzyme in the replicative life cycle of HIV. Consequently, the compounds of this invention may be advantageously used in the treatment of HIV infection, either alone or in combination with other inhibitors of HIV viral replication or with pharmacoenhancers such as cytochrome P450 inhibitors.

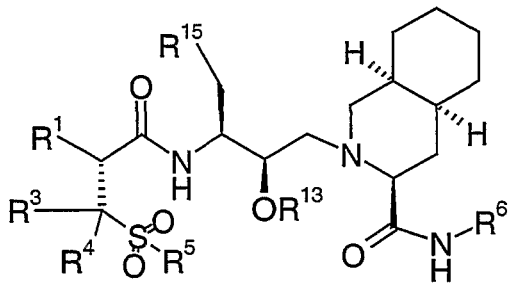
The human immunodeficiency virus HIV is the causative agent of acquired immunodeficiency syndrome (AIDS), a disease characterised by the destruction of the immune system, particularly of the $CD4^+$ T-cell, with attendant susceptibility to opportunistic infections. HIV infection is also associated with a precursor AIDs-related complex (ARC), a syndrome characterised by symptoms such as persistent generalised lymphadenopathy, fever and weight loss.

In common with other retroviruses, the HIV genome encodes protein precursors known as gag and gag-pol which are processed by the viral protease to afford the protease, reverse transcriptase (RT), endonuclease/integrase and mature structural proteins of the virus core. Interruption of this processing prevents the production of normally infectious virus. Considerable efforts have been directed towards the control of HIV by inhibition of virally encoded enzymes. In particular, much effort has been directed towards the inhibition of HIV protease and the HIV protease inhibitors (PIs) saquinavir, ritonavir, nelfinavir, indinavir, amprenavir and lopinavir have been approved for treatment of HIV infections. Because of the emergence of resistant virus during monotherapy, current clinical practice is to use such protease inhibitors in combination therapy, typically with RT inhibitors.

The emergence of resistant virus can be attributed to errors introduced by the HIV reverse transcriptase, in conjunction with a high virus replication rate. It is likely that mutations that lead to resistant virus occur spontaneously but remain undetectable until initiation of therapy leads to a selective pressure for the emergence of virus with replicative advantage over the wildtype population. In the context of HIV protease inhibition, accumulation of mutations that lead to a reduction in inhibitor binding while maintaining sufficient substrate turnover can lead to drug resistance. Although the onset of drug resistance can be delayed to some extent by the use of combinations of drugs, there remains a need for more effective HIV protease inhibitors that retain activity against PI-resistant and multi-PI resistant viruses.

The object of the invention therefore is to provide novel compounds which are potent inhibitors of the HIV aspartyl protease and which accordingly show a potential to be efficacious in the treatment of HIV related diseases. Compounds of the invention may also therefore show the potential to inhibit the replication of virus that is resistant to commonly used protease inhibitors.

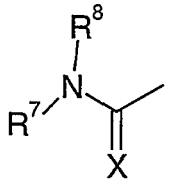
This object could be achieved with the novel compounds of general formula I



I

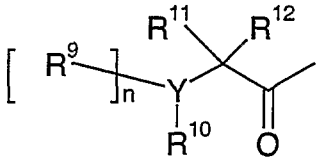
wherein R^1 is H, hydroxy or NHR^2

wherein R^2 is H, alkyl, alkenyl, alkynyl, arylalkyl, heterocyclylalkyl, cycloalkyl alkyl carbonyl, cycloalkyl carbonyl, aryl carbonyl, heterocyclyl carbonyl, heterocyclyl alkyl carbonyl, aryl alkyl carbonyl, alkyl oxy carbonyl, aryl alkyl oxy carbonyl, heterocyclyl alkyl oxy carbonyl, aryl heterocyclyl sulfonyl, alkyl sulfonyl, aryl sulfonyl, heterocyclyl sulfonyl or a group of the formula



wherein X is O or S and

R^7 and R^8 independently are H, alkyl, aryl, heterocyclyl, aryl alkyl, heterocyclyl alkyl or R^7 and R^8 together with the nitrogen atom to which they are attached form a saturated ring optionally containing a further hetero atom or a group



wherein when n=0, Y represents O or S and R^{10} is H, alkyl, aryl alkyl, heterocyclyl alkyl, aryl, heterocyclyl or when n=1, Y represents N, R^9 is H or alkyl and R^{10} H, alkyl, aryl alkyl, heterocyclyl alkyl, aryl, heterocyclyl or R^9 and R^{10} taken together with the heteroatom to which they are attached form a heterocycle, R^{11} and R^{12} independently are H or alkyl or R^{11} and R^{12} taken together with the carbon atom to which they are attached form a cycle, R^3, R^4 independently are alkyl or taken together with the carbon atom to which they are attached form a carbocycle, R^5 is alkyl, aryl alkyl, heterocyclyl alkyl or R^4 and R^5 taken together with the carbon and sulfur atom to which they are attached form a heterocycle and R^6 is alkyl, aryl alkyl, heterocyclyl alkyl, alkyl oxy alkyl, hydroxy alkyl, amino alkyl, fluoro alkyl and R^{13} is H or the residue of an inorganic or an organic ester and R^{15} is aryl and pharmaceutically acceptable salts thereof, with the proviso that, if R^3, R^4 and R^5 are methyl, R^6 is tert.-butyl, R^{13} is H and if R^{15} is phenyl R^2 is not benzyl oxycarbonyl and not 2-quinoline carbonyl.

The term alkyl defines an optionally substituted straight or branched alkyl chain carrying 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms.
The term alkenyl defines an optionally substituted straight or branched alkenyl chain carrying 2 to 6 carbon atoms, preferably 2 to 4 carbon atoms.

The term alkynyl defines an optionally substituted straight or branched alkynyl chain carrying 2 to 6 carbon atoms, preferably 2 to 4 carbon atoms.

Alkyl accordingly preferably stands for methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl and tert.-butyl.

Alkenyl accordingly preferably is vinyl, 1-propenyl, 2-propenyl, i-propenyl, and butenyl and its isomers.

Alkynyl accordingly preferably is ethynyl, propynyl and its isomers, and butynyl and its isomers.

Suitable substituents of alkyl, alkenyl or alkynyl can be selected from one or more of
aryl, heterocyclyl,
carboxy, cyano, alkoxy, cycloalkyl oxy, aryl oxy, heterocyclyl oxy, hydroxy,
alkyl carbonyl, cycloalkyl carbonyl, aryl carbonyl, heterocyclyl carbonyl,
alkoxy carbonyl, cycloalkyl oxy carbonyl, aryl oxy carbonyl, heterocyclyl oxy carbonyl,
amino carbonyl, alkyl amino carbonyl, dialkyl amino carbonyl, cycloalkyl amino carbonyl, aryl amino carbonyl, heterocyclyl amino carbonyl,
amino, alkyl amino, dialkyl amino, alkenyl amino, alkynyl amino, cycloalkyl amino, aryl amino, heterocyclyl amino,
alkyl carbonyl amino, dialkyl carbonyl amino, cycloalkyl carbonyl amino, aryl carbonyl amino, heterocyclyl carbonyl amino,
alkoxy carbonyl amino, cycloalkyl oxy carbonyl amino, aryloxy carbonyl amino, heterocylyl oxy carbonyl amino,
alkyl amino carbonyl amino, dialkyl amino carbonyl amino, cycloalkyl amino carbonyl amino, aryl amino carbonyl amino, heterocyclyl amino carbonyl amino
alkyl sulfonyl amino, cycloalkyl sulfonyl amino, aryl sulfonyl amino, heterocyclyl sulfonyl amino, nitro,
alkyl sulfonyl, cycloalkyl sulfonyl, aryl sulfonyl, heterocyclyl sulfonyl,
thio, alkyl thio, cycloalkyl thio, aryl thio, heterocyclyl thio or
halogen.

In all cases above where there are NH groups, the free hydrogen may also be substituted , preferably with lower alkyl.

Cycloalkyl has the meaning of an optionally substituted cycloalkyl group containing 3 to 8 carbon atoms, preferably 3 to 6 carbon atoms e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl or adamantyl which can also be benz-fused to an optionally substituted saturated, partially unsaturated or aromatic monocyclic, bicyclic or tricyclic heterocycle or carbocycle, e.g. to phenyl.

The term aryl denotes optionally substituted phenyl and naphthyl, both optionally benz-fused to an optionally substituted saturated, partially unsaturated or aromatic monocyclic, bicyclic or tricyclic heterocycle or carbocycle e.g. to cyclohexyl or cyclopentyl.

The term heterocyclyl stands for an optionally substituted saturated, partially unsaturated or aromatic monocyclic, bicyclic or tricyclic heterocycle which contains one or more hetero atoms selected from nitrogen, oxygen and sulfur which can also be benz-fused to an optionally substituted saturated, partially unsaturated or aromatic monocyclic, bicyclic or tricyclic carbocycle or heterocycle.

Examples of suitable heterocycles are oxazolyl, isoxazolyl, furyl, tetrahydrofuryl, 1,3-dioxolanyl, dihydropyranyl, thienyl, pyrazinyl, isothiazolyl, isoquinolinyl, indolyl, indazolyl, quinolinyl, dihydrooxazolyl, pyrimidinyl, benzofuranyl, tetrazolyl, pyrrolidinonyl, (N-oxide)-pyridinyl, pyrrolyl, triazolyl e.g. 1,2,4-triazolyl, pyrazolyl, benzotriazolyl, piperidinyl, morpholinyl, thiazolyl, pyridinyl, dihydrothiazolyl, imidazolidinyl, pyrazolinyl, benzothienyl, piperazinyl, imidazolyl, thiadiazolyl e.g. 1,2,3-thiadiazolyl, and benzothiazolyl.

Suitable substituents for cycloalkyl, aryl, heterocyclyl can be selected from those named for alkyl, in addition, however, alkyl, alkenyl and alkynyl are substituents to be added to the selection.

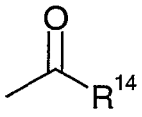
The term halogen stands for fluorine, chlorine, bromine and iodine.

The term residue of an inorganic ester stands for a sulfate of the formula $-SO_2OH$ or a phosphate c the formula $-PO(OH)_2$.

The term residue of an organic ester defines an acyl group as e.g. described in the European Patent Application EP A1 0 594 540 for group R_1.

Suitable residues of an organic ester are defined in R^{13} as being a group of formula

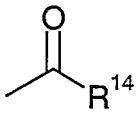
wherein R^{14} is alkyl, alkenyl, cycloalkyl, aryl, aryl alkyl heterocyclyl, a group



$-CH_2$ $(CH_2CH_2O)_mCH_3$, wherein m is an integer from 0 to 10, or a carbonyl group-linked radical of an aminoacid.

With the exception that the alkyl and the alkenyl chain can carry up to 20 carbon atoms the meaning of the terms alkyl, alkenyl, cycloalkyl, aryl, heterocyclyl is the same as outlined above.

The term "carbonyl group-linked radical of an aminoacid" stands for a radical of a natural or unnatural amino acid selected from e.g. glycine, alanine, leucine, isoleucine, phenylalanine, lysine, methionine, threonine, tryptophan, valine, serine, glutamine, etc which is linked to the carbonyl group of



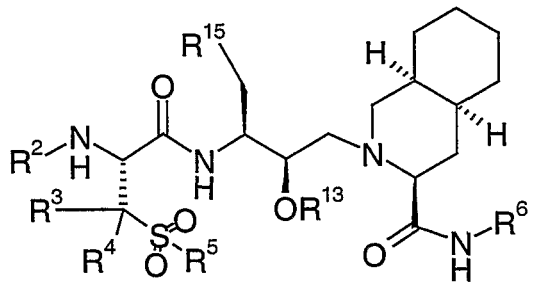
Any functional (i.e. reactive) group present in a side-chain may be protected, with the protecting group being a group which is known per se, for example, as described in "Protective Groups in Organic Synthesis", 2nd Ed., T.W. Greene and P.G.M. Wuts, John Wiley & Sons, New York, NY, 1991. For example, an amino group can be protected by a tert-butoxycarbonyl (BOC), formyl, trityl, benzyloxycarbonyl (Z), 9-fluorenylmethyloxcarbonyl (FMOC), trifluoroacetyl, 2-(biphenylyl)isopropoxycarbonyl or isobornyloxycarbonyl group or in the form of a phthalimido group; or a hydroxyl group can be protected by a tert-butyldimethylsilyl, tetrahydropyranyl, 4-methoxybenzyl, or benzyl or acetate etc; or a carboxyl group can be protected in the form of an ester, for example as a methyl or benzyl or tert. butyl ester. The protecting group may be retained in the final compound or optionally removed by techniques known in the art.

The compounds of this invention are characterized by a core structure with fixed stereochemistry as shown in general formula

The residues R^1 to R^{15} in compounds of this invention may contain one or more asymmetric carbon atoms and may therefore occur as single enantiomers, racemates and racemic mixtures, individual diastereomers and diastereomeric mixtures. Furthermore, where a compound of the invention contains an olefinic double bond, this can have the (E) or (Z) configuration. Also, each chiral centre may be of the R or S configuration. All such isomeric forms of these compounds are embraced by the present invention.

Compounds of formula (I) which are acidic can form pharmaceutically acceptable salts with bases such as alkali metal hydroxides, e.g. sodium hydroxide, potassium hydroxide and the like; alkaline earth metal hydroxides, e.g. calcium hydroxide, barium hydroxide, magnesium hydroxide and the like; with organic bases e.g. N-ethyl piperidine, dibenzylaminen and the like. Those compounds of formula (I) which are basic can form pharmaceutically acceptable salts with inorganic acids, e.g. hydrohalic acids such as hydrochloric acid and hydrobromic acid, sulphuric acid, nitric acid, phosphoric acid and the like; and with organic acids, e.g. acetic acid, tartaric acid, succinic acid, fumaric acid, maleic acid, malic acid, salicylic acid, citric acid, methanesulphonic acid, p-toluene sulphonic acid and the like. The formation and isolation of such salts can be carried out according to methods known in the art.

Preferred compounds of formula (I) are those having the formula

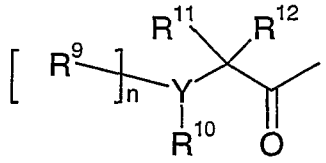


II

wherein R^2, R^3, R^4, R^5,R^6, R^{13} and R^{15} are as above.

In a further preferred embodiment R^3, R^4 and R^5 have the meaning of methyl, R^6 has the meaning of tert-butyl or hydroxy tert-butyl and R^{15} has the meaning of phenyl.

In a further preferred embodiment R^2 is alkyl carbonyl, cycloalkyl carbonyl, aryl carbonyl, heterocyclyl carbonyl, heterocyclyl alkyl carbonyl or a group of the formula



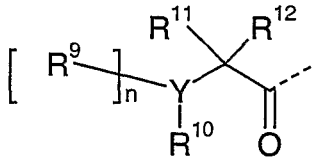
wherein when n=0, Y represents O or S

and R^{10} alkyl, aryl alkyl, heterocyclyl alkyl, aryl, heterocyclyl

or when n=1, Y represents N, R^9 is H and R^{10} is alkyl, aryl alkyl, heterocyclyl alkyl, aryl, heterocyclyl

and wherein R^{11} and R^{12} independently are H.

Still further preferred are compounds wherein R^3, R^4 and R^5 are methyl, R^6 is tert-butyl , R^{15} is phenyl and R^2 is alkyl carbonyl, cycloalkyl carbonyl, aryl carbonyl, heterocyclyl carbonyl, heterocyclyl alkyl carbonyl or a group of the formula



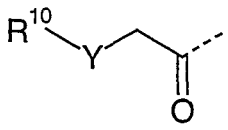
wherein when n=0, Y represents O or S

and R^{10} is alkyl,aryl alkyl, heterocyclyl alkyl, aryl, heterocyclyl

or when n=1, Y represents N, R^9 is H and R^{10} is alkyl, aryl alkyl, heterocyclyl alkyl, aryl, heterocyclyl

and wherein R^{11} and R^{12} independently are H.

Still further preferred are compounds wherein R^3, R^4, R^5 are methyl, R^6 is tert-butyl, R^{15} is phenyl and R^2 is aryl carbonyl, heterocyclyl carbonyl, or a group of the formula

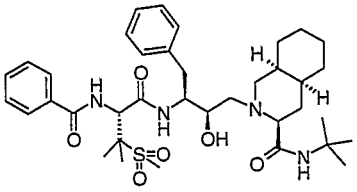
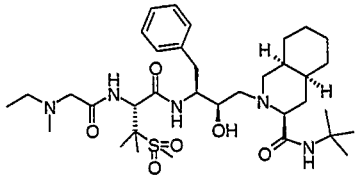
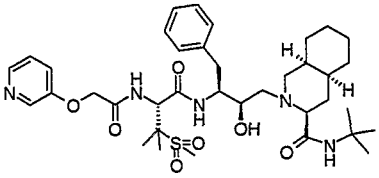
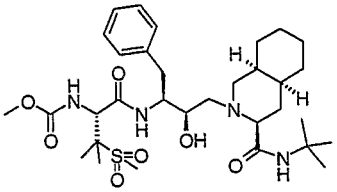
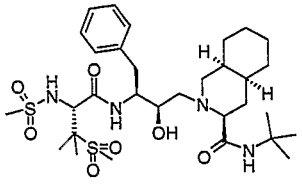
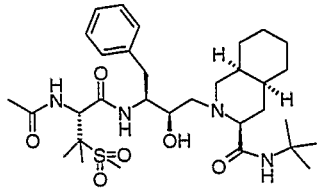


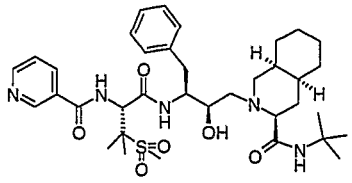
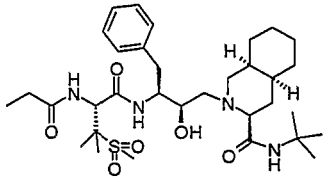
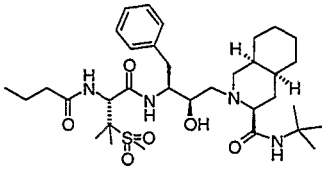
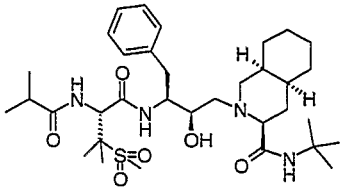
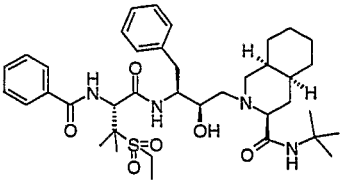
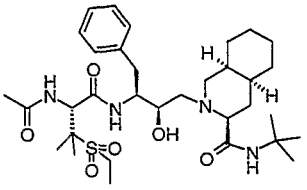
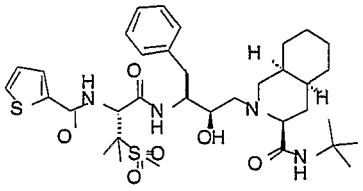
wherein Y represents O, NH, S, CH_2 and R^{10} is aryl, heterocyclyl

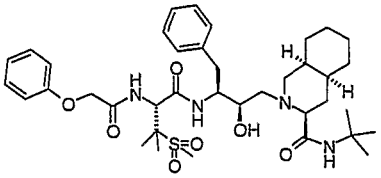
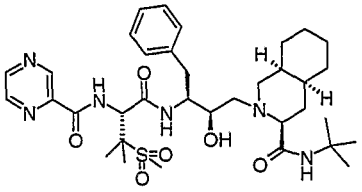
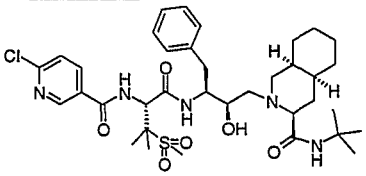
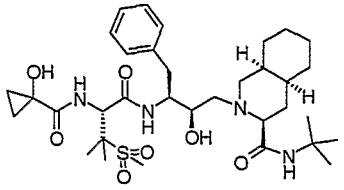
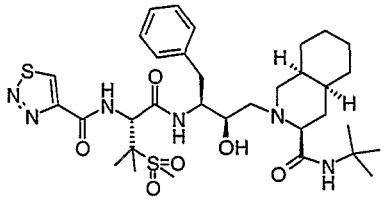
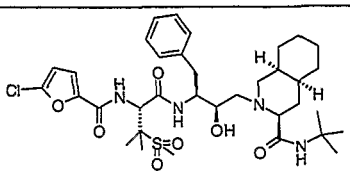
In a still further preferred embodiment R^{13} has the meaning of H.

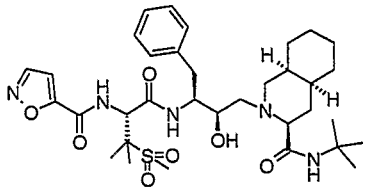
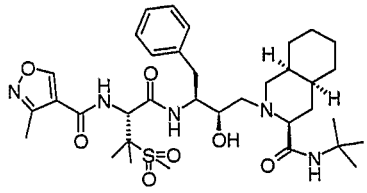
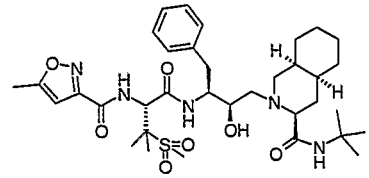
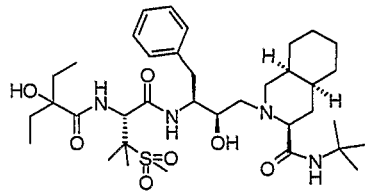
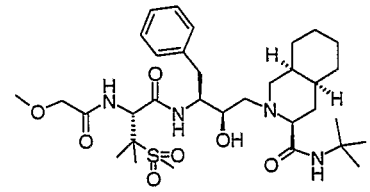
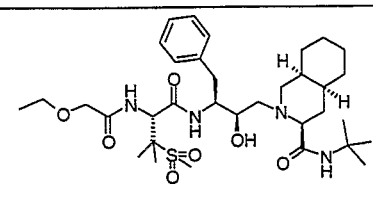
Examples of compounds of formula I or II with the meaning of R^{13} is H are set out in table A below.

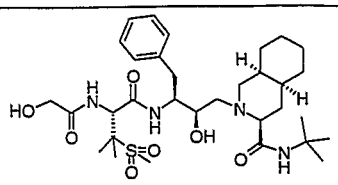
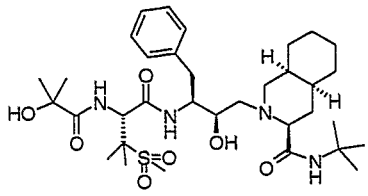
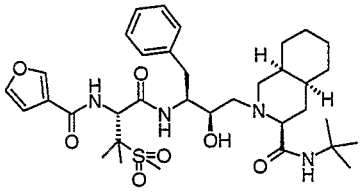
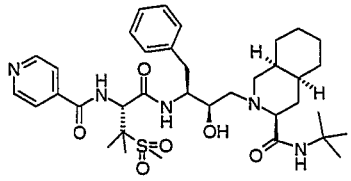
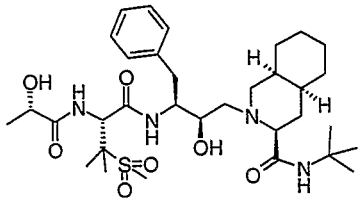
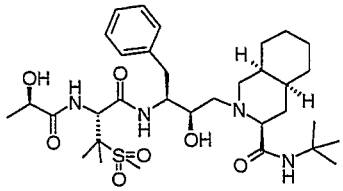
Table A

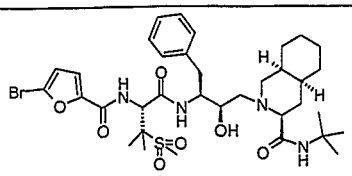
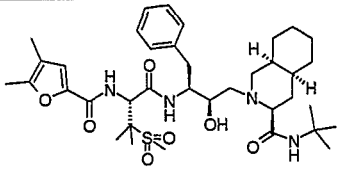
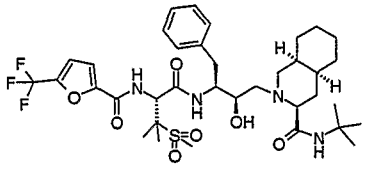
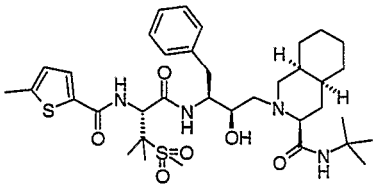
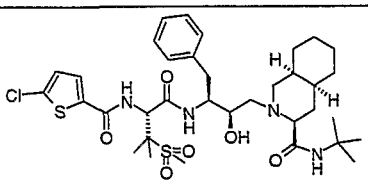
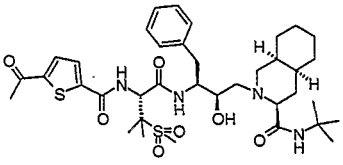
Ex	Name	Structures
1	2-[3(S)-[[N-Benzoyl-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-benzyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
2	N-tert-Butyl-2-[3(S)-[[N-[(9-fluorenyl)methoxycarbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
3	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[2-(3-pyridyloxy)acetyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
4	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(methoxycarbonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinlinecarboxamide	
5	2-[3(S)-[[N,3-Bis(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
6	2-[3(S)-[[N-Acetyl-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	

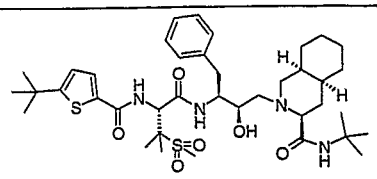
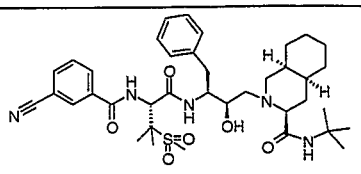
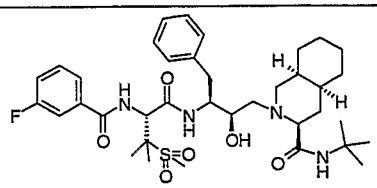
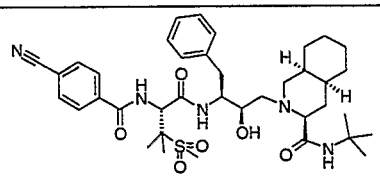
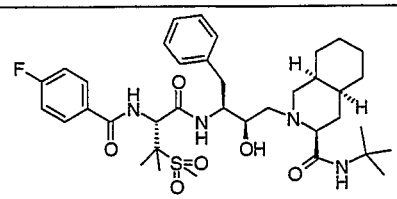
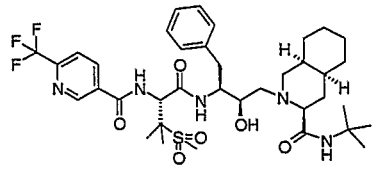
7	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(3-pyridyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
8	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-propionyl-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
9	2-[3(S)-[[N-Butyryl-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
10	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-isobutyryl-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
11	2-[3(S)-[[N-Benzoyl-3-(ethanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
12	2-[3(S)-[[N-Acetyl-3-(ethanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
13	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(2-thenoyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	

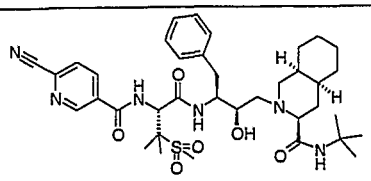
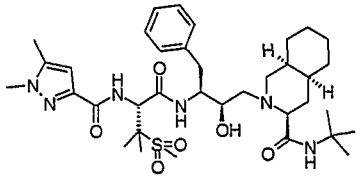
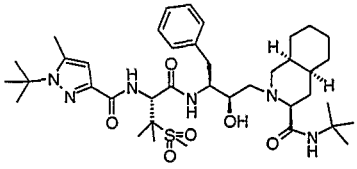
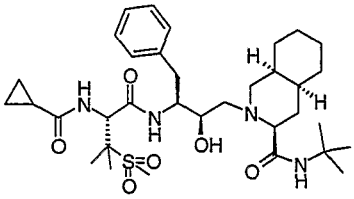
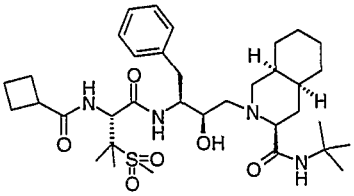
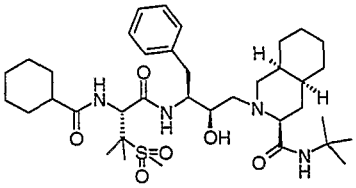
14	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(2-phenoxyacetyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
15	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(2-pyrazinyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
16	N-tert-Butyl-2-[3(S)-[[N-[(6-chloro-3-pyridyl)carbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
17	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-[(1-hydroxy-1-cyclopropyl)carbonyl]-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
18	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(1,2,3-thiadiazol-4-yl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
19	N-tert-Butyl-2-[3(S)-[[N-(5-chloro-2-furoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	

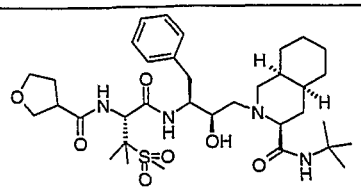
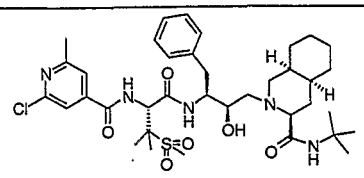
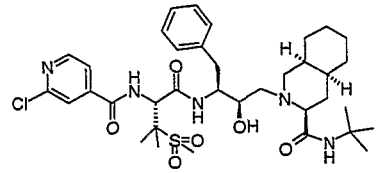
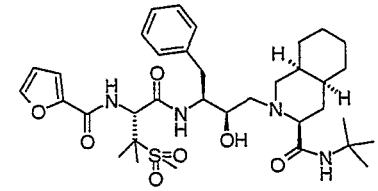
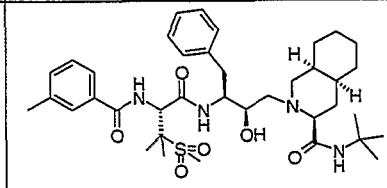
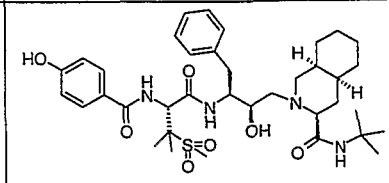
20	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(5-isoxazolyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
21	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(3-methyl-4-isoxazolyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
22	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(5-methyl-3-isoxazolyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
23	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-(2-hydroxy-2-ethylbutyryl)-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
24	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(2-methoxyacetyl))-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
25	N-tert-Butyl-2-[3(S)-[[N-(2-ethoxyacetyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	

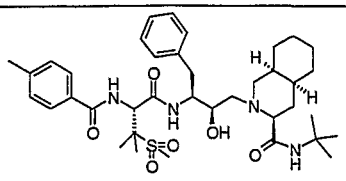
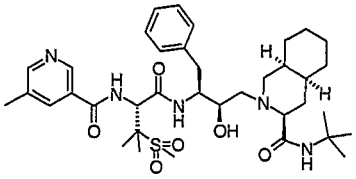
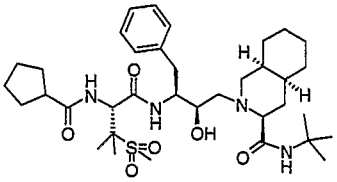
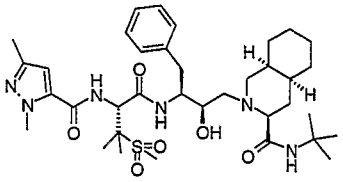
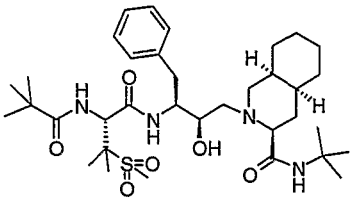
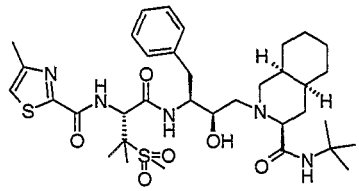
26	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-(2-hydroxyacetyl)-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
27	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-(2-hydroxy-2-methylpropionyl)-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
28	N-tert-Butyl-2-[3(S)-[[N-(3-furoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
29	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(4-pyridyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
30	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-(2(S)-hydroxypropionyl)-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
31	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-(2(R)-hydroxypropionyl)-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	

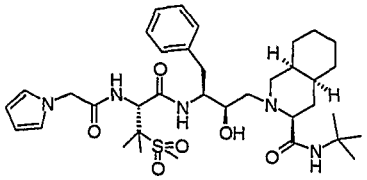
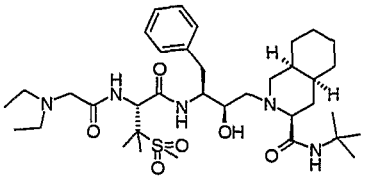
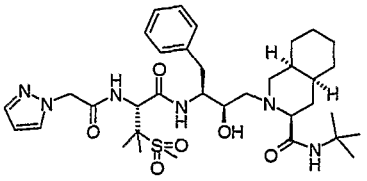
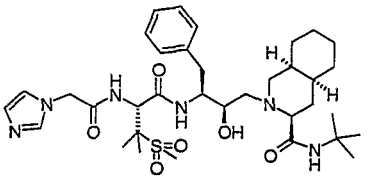
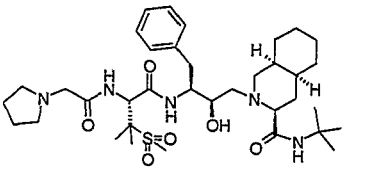
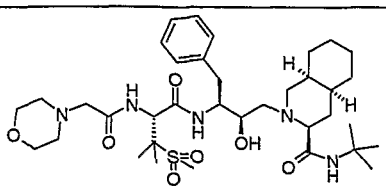
32	2-[3(S)-[[N-(5-Bromo-2-furoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
33	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(4,5-dimethyl-2-furoyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
34	N-tert-Butyl-2-[3(S)-[[N-[5-(trifluoromethyl)-2-furoyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
35	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(5-methyl-2-thenoyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
36	N-tert-Butyl-2-[3(S)-[[N-(5-chloro-2-thenoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
37	2-[3(S)-[[N-(5-Acetyl-2-thenoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	

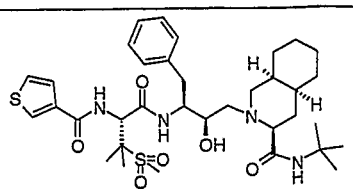
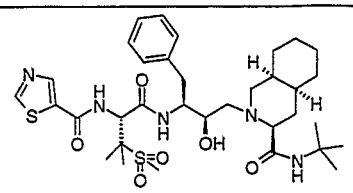
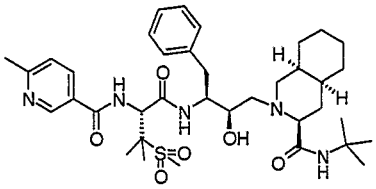
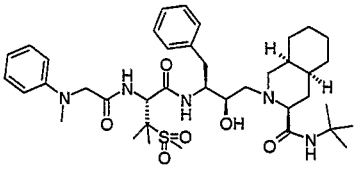
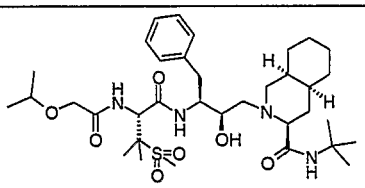
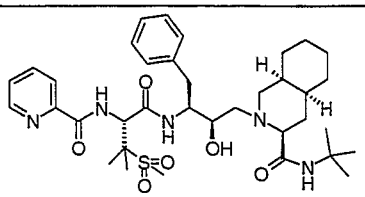
38	N-tert-Butyl-2-[3(S)-[[N-(5-tert-butyl-2-thenoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
39	N-tert-Butyl-2-[3(S)-[[N-(3-cyanobenzoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
40	N-tert-Butyl-2-[3(S)-[[N-(3-fluorobenzoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
41	N-tert-Butyl-2-[3(S)-[[N-(4-cyanobenzoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
42	N-tert-Butyl-2-[3(S)-[[N-(4-fluorobenzyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
43	N-tert-Butyl-2-[3(S)-[[N-[[6-(trifluoromethyl)-3-pyridyl]carbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	

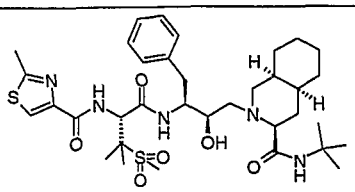
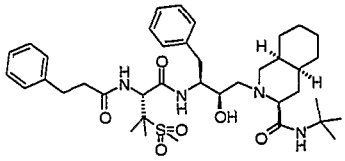
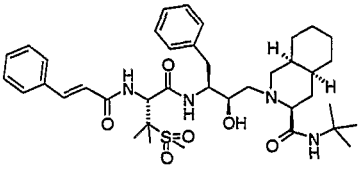
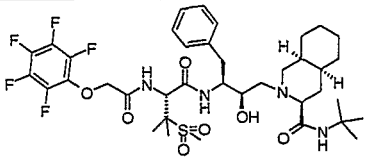
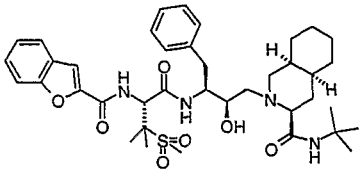
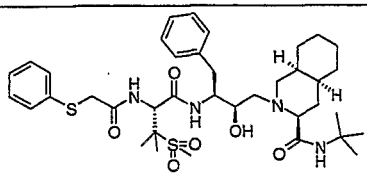
44	N-tert-Butyl-2-[3(S)-[[N-[(6-cyano-3-pyridyl)carbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
45	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(1,5-dimethyl-3-pyrazolyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
46	N-tert-Butyl-2-[3(S)-[[N-[(1-tert-butyl-5-methyl-3-pyrazolyl)carbonyl]3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
47	N-tert-Butyl-2-[3(S)-[[N-(cyclopropylcarbonyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
48	N-tert-Butyl-2-[3(S)-[[N-(cyclobutylcarbonyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
49	N-tert-Butyl-2-[3(S)-[[N-(cyclohexylcarbonyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	

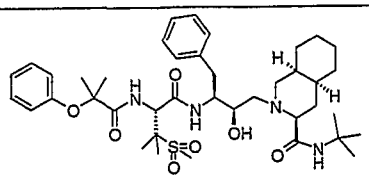
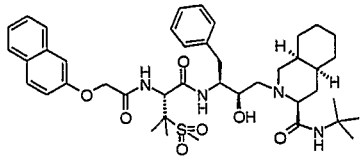
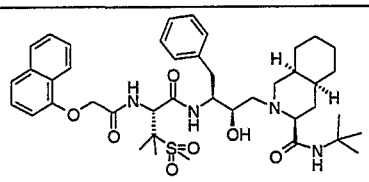
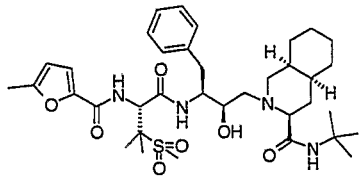
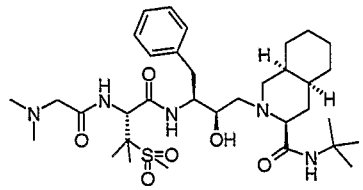
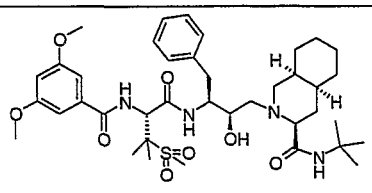
50	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[3(S)-[[N-(tetrahydro-3(RS)-furoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-3(S)-isoquinolinecarboxamide (1:1 mixture of diastereoisomers)	
51	N-tert-Butyl-2-[N-[(2-chloro-6-methyl-4-pyridyl)carbonyl]-3(S)-[[3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
52	N-tert-Butyl-2-[3(S)-[[N-[(2-chloro-4-pyridyl)carbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
53	N-tert-Butyl-2-[N-(2-furoyl)-3(S)-[[3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
54	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(3-methylbenzoyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
55	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(4-methoxybenzoyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	

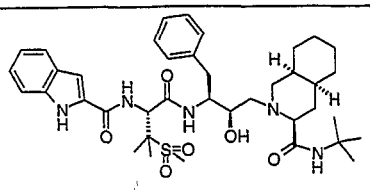
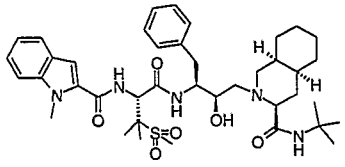
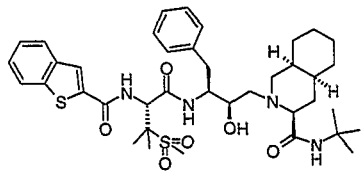
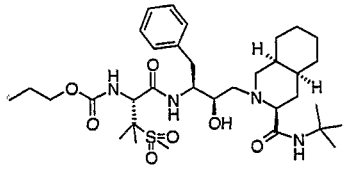
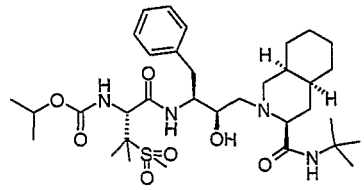
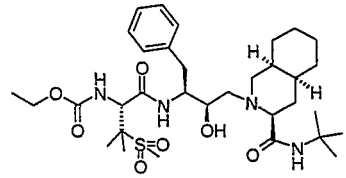
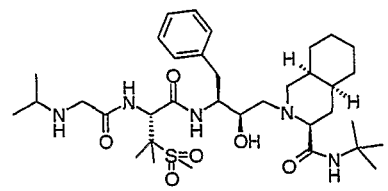
56	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(4-methylbenzoyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
57	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(5-methyl-3-pyridyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
58	N-tert-Butyl-2-[3(S)-[[N-(cyclopentylcarbonyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
59	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(2,5-dimethyl-3-pyrazolyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
60	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-pivaloyl-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
61	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(4-methyl-2-thiazolyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	

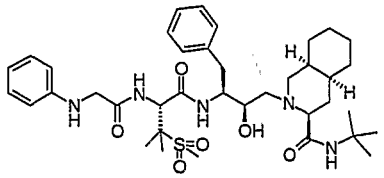
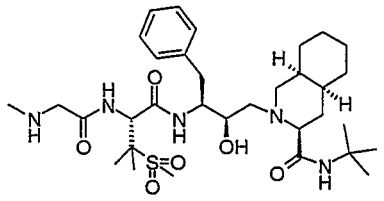
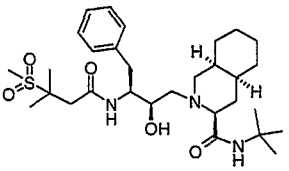
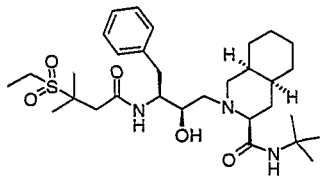
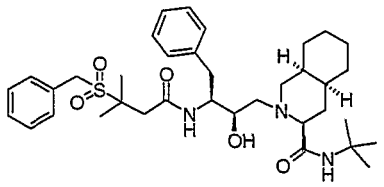
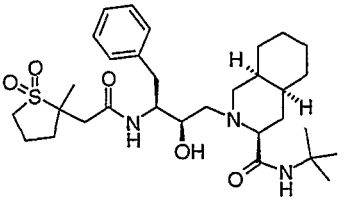
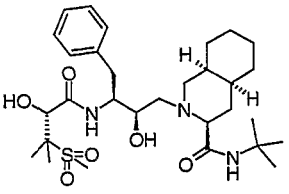
62	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-3-methyl-N-[2-(1-pyrrolyl)acetyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
63	N-tert-Butyl-2-[3(S)-[[N-[2-(diethylamino)acetyl]-3-(methanesulfonyl)-3-methyl-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro3(S)-isoquinolinecarboxamide	
64	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-3-methyl-N-[2-(1-pyrazolyl)acetyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
65	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-[2-(1-imidazolyl)acetyl]-3-(methanesulfonyl)-3-methyl-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
66	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[2-(1-pyrrolidinyl)acetyl]-L-valyl]amino]-4-phenylbutyl-3(S)-isoquinolinecarboxamide	
67	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(2-morpholinoacetyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	

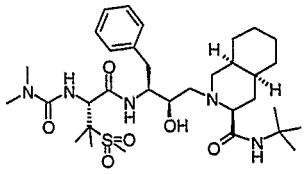
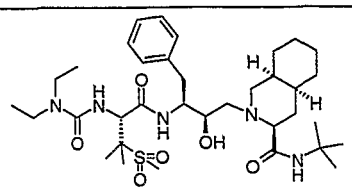
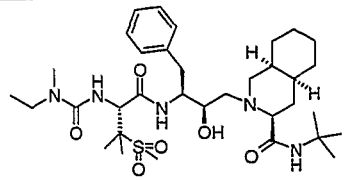
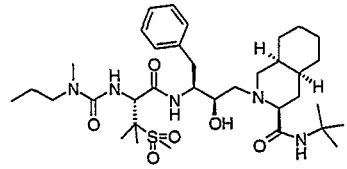
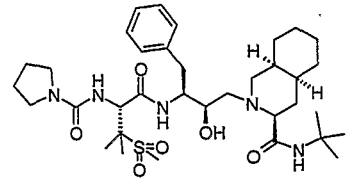
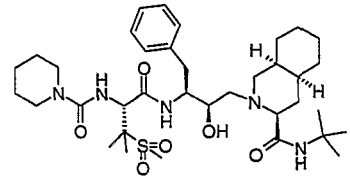
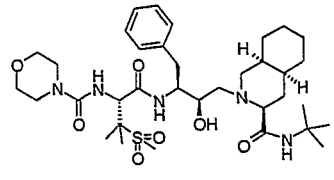
68	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(3-thenoyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
69	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(5-thiazolyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
70	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(6-methyl-3-pyridyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
71	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[N-methyl-N-phenylglycyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
72	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-(2-isopropoxyacetyl)-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
73	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(2-pyridyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	

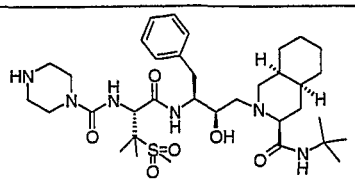
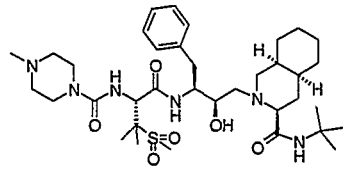
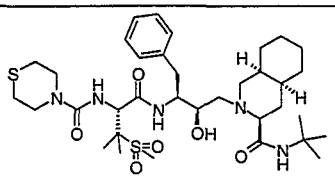
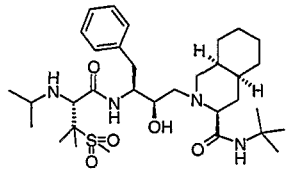
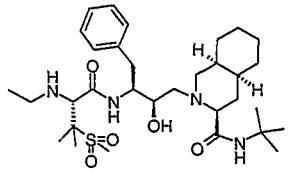
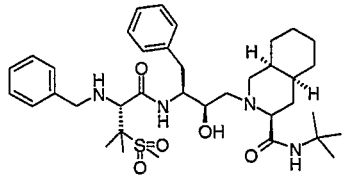
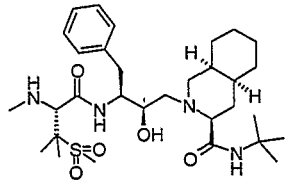
74	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(2-methyl-4-thiazolyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
75	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(3-phenylpropionyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
76	(E)-N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(3-phenylacryloyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
77	N-tert-Butyl-2-[3(S)-[[N-[2-(pentafluorophenoxy)acetyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
78	2-[3(S)-[[N-[[(2-Benzofuryl)carbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
79	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[2-(phenylthio)acetyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	

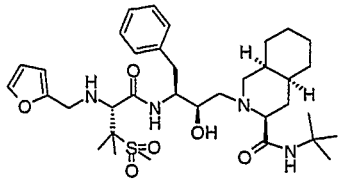
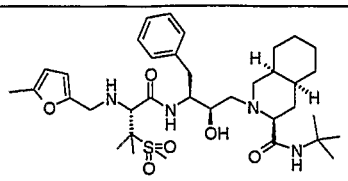
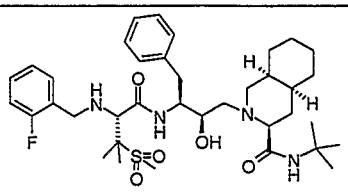
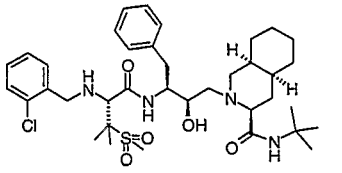
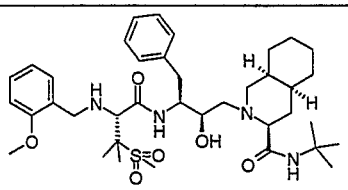
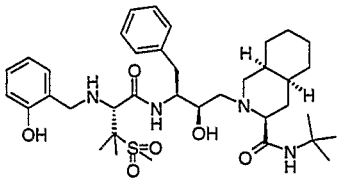
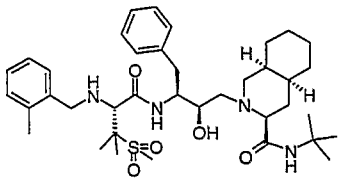
80	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(2-methyl-2-phenoxypropionyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
81	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[2-(2-naphthyloxy)acetyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
82	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[2-(1-naphthyloxy)acetylamino]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
83	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(5-methyl-2-furoyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
84	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[2-[2-(dimethylamino)acetyl]-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
85	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(3,5-dimethoxybenzoyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	

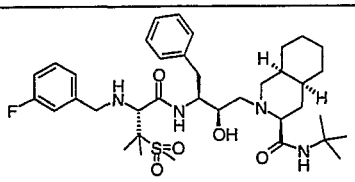
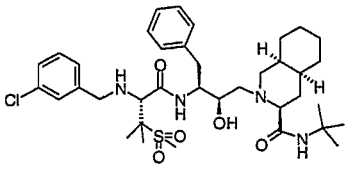
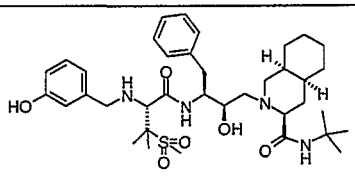
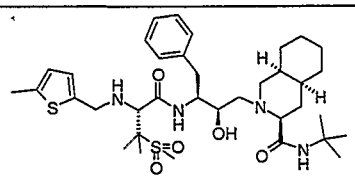
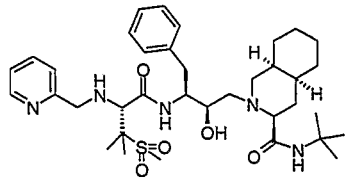
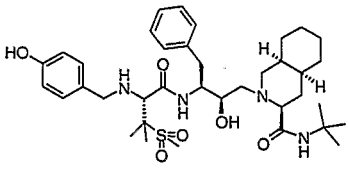
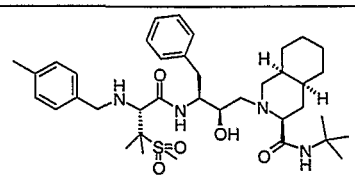
86	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-N-[(2-indolyl)carbonyl]-3(S)-[[3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
87	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[-3-(methanesulfonyl)-N-[1-methyl-2-indolyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
88	2-[3(S)-[[N-[(1-Benzothiophen-2-yl)carbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
89	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(propoxycarbonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
90	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-(isopropoxycarbonyl)-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
91	N-tert-Butyl-2-[3(S)-[[N-(ethoxycarbonyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
92	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-[2-(isopropylamino)acetyl]-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]--3(S)-isoquinolinecarboxamide	

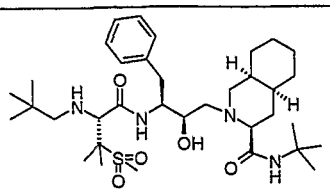
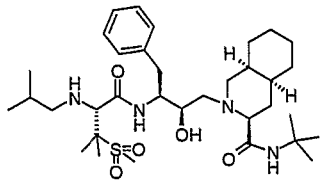
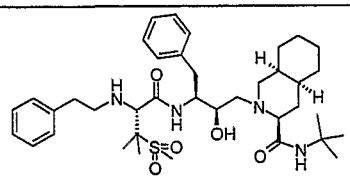
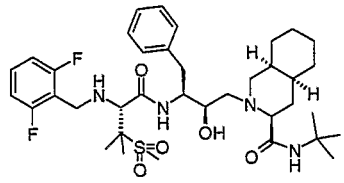
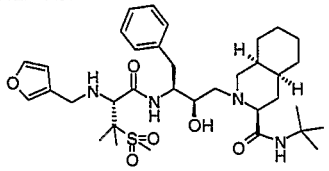
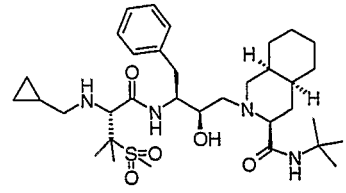
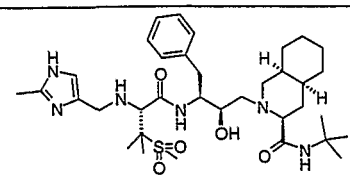
93	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(N-phenylglycyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
94	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(N-methylglycyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
95	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-1-[2(R)-hydroxy-3(S)-[3-(methanesulfonyl)butyramido]-4-phenylbutyl]-2(S)-piperazinecarboxamide	
96	2-[3(S)-[3-(Ethanesulfonyl)-3-methylbutyramido]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
97	2-[3(S)-[3-(Benzenesulfonyl)-3-methylbutyramido]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
98	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[3(S)-[[N-[2-(tetrahydro-2(RS)-methyl-1,1-dioxo-2-thienyl)acetyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-3(S)-isoquinolinecarboxamide (mixture of diastereoisomers)	
99	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[2(R)-hydroxy-3-(methanesulfonyl)-3-methylbutyramido]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	

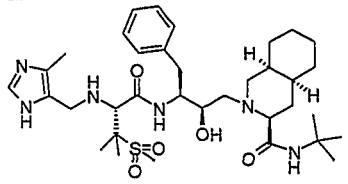
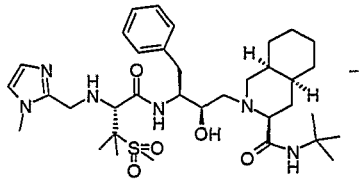
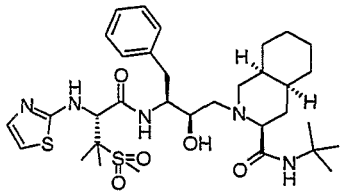
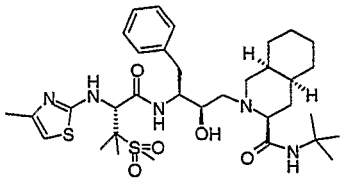
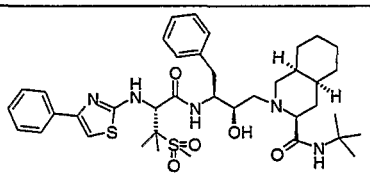
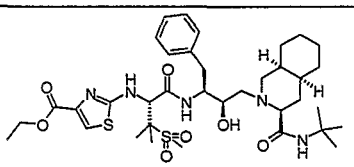
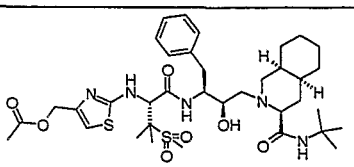
100	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-(dimethylcarbamoyl-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
101	N-tert-Butyl-2-[3(S)-[[N-(diethylcarbamoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
102	N-tert-Butyl-2-[3(S)-[[N-(N-ethyl-N-methylcarbamoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
103	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(N-methyl-N-propylcarbamoyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
104	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(1-pyrrolidinyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
105	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(piperidinocarbonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
106	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(morpholinocarbonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	

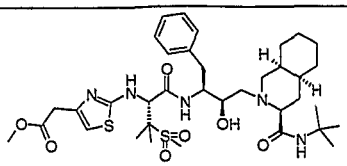
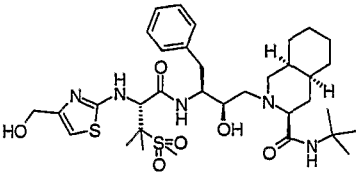
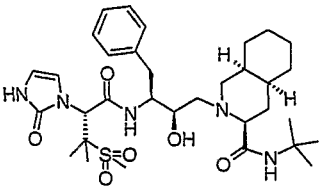
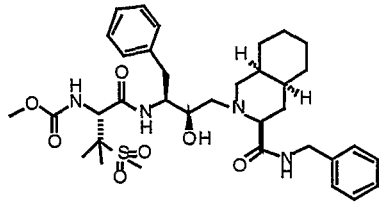
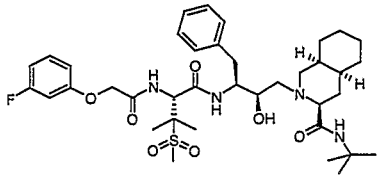
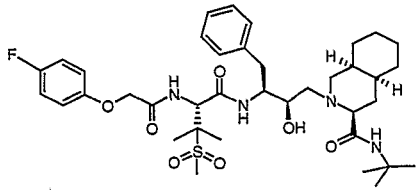
107	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(1-piperazinyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
108	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(4-methyl-1-piperazinyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
109	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[3(S)-[[N-[(tetrahydro-1,4-thiazin-4-yl)carbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
110	N-tert-Butyl-1,2,3,4,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-isopropyl-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
111	N-tert-Butyl-2-[3(S)-[[N-ethyl-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
112	2-[3(S)-[[N-Benzyl-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
113	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-methyl-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	

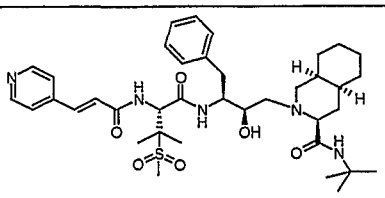
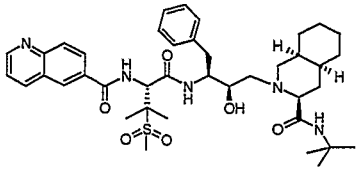
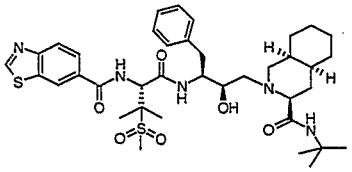
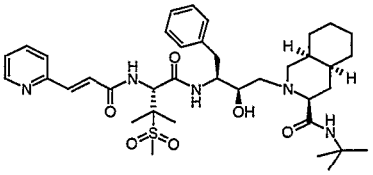
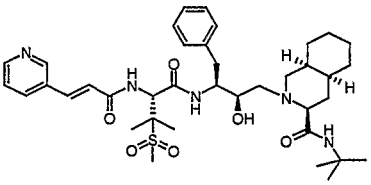
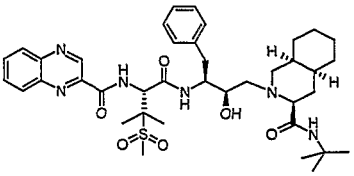
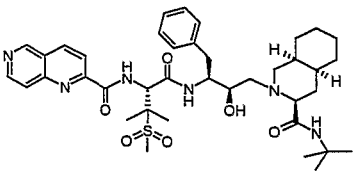
114	N-tert-Butyl-2-[3(S)-[[N-(2-furfuryl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
115	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(5-methyl-2-furfuryl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
116	N-tert-Butyl-2-[3(S)-[[N-(2-fluorobenzyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
117	N-tert-Butyl-2-[3(S)-[[N-(2-chlorobenzyl)-3-(methanesulfonyl)-L-valyl]amino]-3(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
118	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(2-methoxybenzyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
119	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-(2-hydroxybenzyl)-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
120	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(2-methylbenzyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	

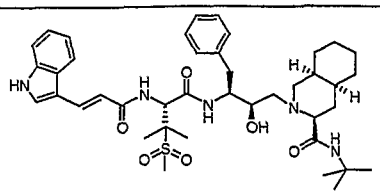
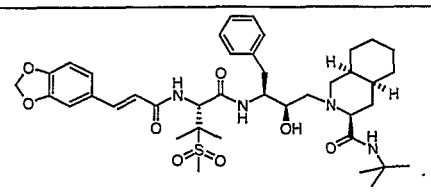
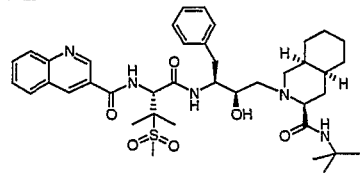
121	N-tert-Butyl-2-[3(S)-[[N-(3-fluorobenzyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
122	N-tert-Butyl-2-[3(S)-[[N-(3-chlorobenzyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
123	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-(3-hydroxybenzyl)-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
124	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(5-methyl-2-thenyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
125	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(2-pyridyl)methyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
126	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-(4-hydroxybenzyl)-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
127	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(4-methylbenzyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	

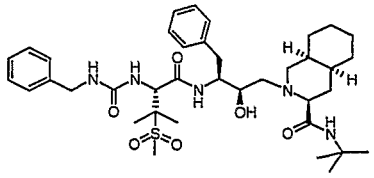
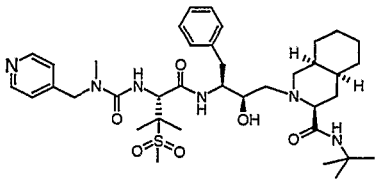
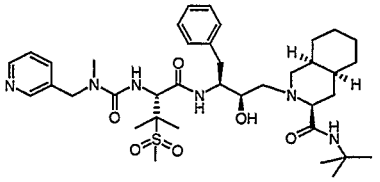
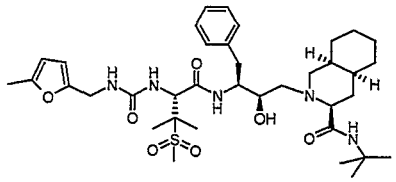
128	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(2,2-dimethylpropyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
129	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-isobutyl-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
130	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(2-phenylethylyl))-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
131	N-tert-Butyl-2-[3(S)-[[N-(2,6-difluorobenzyl)-3-(methanesulfonyl)-N-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
132	N-tert-Butyl-2-[3(S)-[[N-(3-furfuryl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
133	N-tert-Butyl-2-[3(S)-[[N-(cyclopropylmethyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
134	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(2-methyl-4-imidazolyl)methyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	

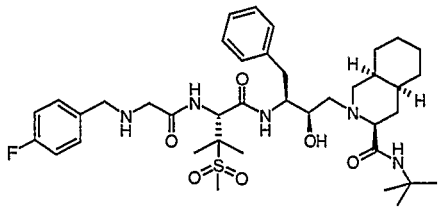
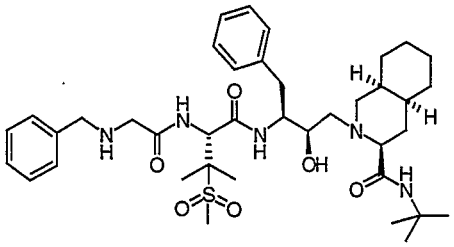
135	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(5-methyl-4-imidazolyl)methyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
136	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(1-methyl-2-imidazolyl)methyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
137	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(2-thiazolyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
138	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(4-methyl-2-thiazolyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
139	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(4-phenyl-2-thiazolyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
140	N-tert-Butyl-2-[3(S)-[[N-[4-(ethoxycarbonyl)-2-thiazolyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro3(S)-isoquinolinecarboxamide	
141	2-[3(S)-[[N-[4-(Acetoxymethyl)-2-thiazolyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	

142	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[4-[(methoxycarbonyl)methyl]-2-thiazolyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
143	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-[4-(hydroxymethyl)-2-thiazolyl]-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
144	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[3(S)-[2(R)-(2,3-dihydro-2-oxo-1H-imidazol-2-yl)-3-(methanesulfonyl)-3-methylbutyramido]-2(R)-hydroxy-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
145	N-Benzyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(methoxycarbonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
156	N-tert-Butyl-2-[3(S)-[[N-[2-(3-fluorophenoxy)acetyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
157	N-tert-Butyl-2-[3(S)-[[N-[2-(4-fluorophenoxy)-acetyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	

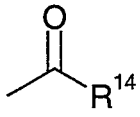
158	(E)-N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[3-(4-pyridyl)acroyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
159	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(6-quinolinyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
160	2-[3(S)-[[N-[(6-Benzothiazolyl)carbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
161	(E)-N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[3-(2-pyridyl)acroyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
162	(E)-N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[3-(3-pyridyl)acroyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
163	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(2-quinoxalinyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
164	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(pyrido[4,3-b]pyridin-2-yl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	

165	(E)-N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-[3-(3-indolyl)acroyl]-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
166	(E)-2-[3(S)-[[N-[3-(1,3-Benzodioxol-5-yl)acroyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
167	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(3-quinolyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	

168	2-[3(S)-[[N-(Benzylcarbamoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
169	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[N-methyl-N-[(4-pyridyl)methyl]carbamoyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
170	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[N-methyl-N-[(3-pyridyl)methyl]carbamoyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
171	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(5-methyl-2-furfuryl)carbamoyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	

172	N-tert-Butyl-2-[3(S)-[[N-[2-(4-fluorobenzylamino)acetyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S).5.6.7.8.8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
173	2-[3(S)-[[N-[2-(Benzylamino)acetyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S).5.6.7.8.8a(S)-decahydro-3(S)-isoquinolinecarboxamide	

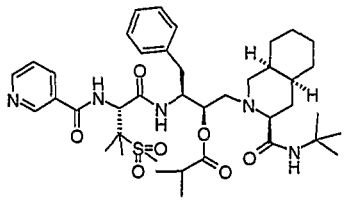
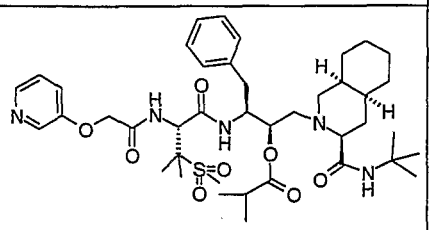
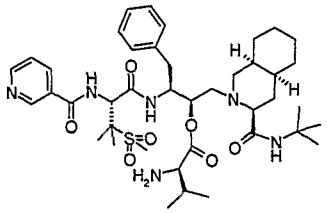
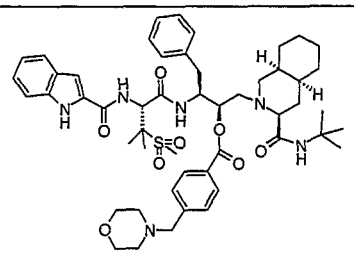
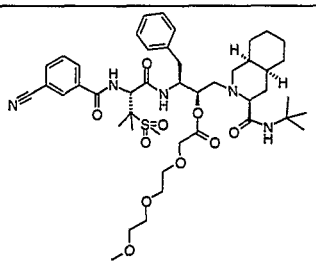
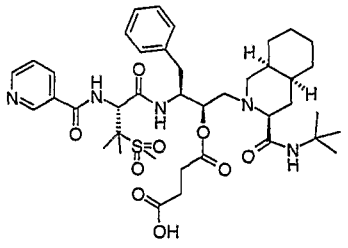
In another preferred embodiment R^{13} has the meaning of $-SO_2OH$, $-PO(OH)_2$ or of a group



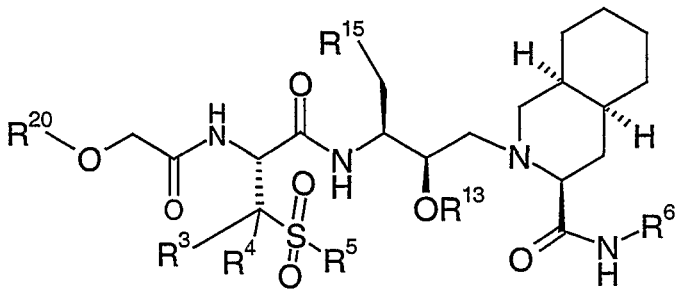
wherein R^{14} is alkyl, alkenyl, cycloalkyl, aryl, aryl alkyl, heterocyclyl, a group $-CH_2(CH_2CH_2O)_mCH_3$, wherein m is an integer from 0 to 10, or a carbonyl group-linked radical of an aminoacid.

Examples of compounds of formula I or II with R^{13} not being H are set out in Table B below.

Table B

Ex	Name	Structures
146	N-tert-Butyl-1,2,3,4,4s(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-(isobutyryloxy)-3(S)-[[3-(methanesulfonyl)-N-[(3-pyridyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
147	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-(isobutyryloxy)-3(S)-[[3-(methanesulfonyl)-N-[2-(3-pyridyloxy)acetyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
148	N-tert-Butyl-1,2,3,4,4a(S),4,5,6,8,8(a)-decahydro-2-[3(S)-[[3-(methanesulfonyl)-N-[(3-pyridyl)carbonyl]-L-valyl]amino]-4-phenyl-2(R)-(L-valyloxy)butyl]-3(S)-isoquinolinecarboxamide	
149	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[3(S)-[[N-[(2-indolyl)carbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-[4-(morpholinomethyl)benzoyloxy]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
150	N-tert-Butyl-2-[3(S)-[[N-(3-cyanobenzoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-[2-[2-(2-methoxyethoxy)ethoxy]acetoxy]-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
151	N-tert-Butyl-2-[2(R)-(3-carboxypropionyloxy)-3(S)-[[3-(methanesulfonyl)-N-[(3-pyridyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)decahydro-3(S)-isoquinolinecarboxamide	

Further preferred compounds of formula (I) are those having the formula



X

wherein R^3, R^4, R^5, R^6, R^{13} and R^{15} are as above and R^{20} is heterocyclyl.

More preferred compounds of formula (X) are those where R^3, R^4 and R^5 are methyl, R^6 is tert-butyl , R^{13} is H and R^{15} is phenyl.

Examples of such preferred compounds of formula (X) are listed below.

- N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[2-(3-pyridyloxy)acetyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide
- N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[2-(2-pyridyloxy)acetyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide
- N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[2-(6-methyl-3-pyridyloxy)acetyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide
- N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[2-(3-pyrazinyloxy)acetyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide
- 2-(2-Hydroxy-3-{3-methanesulfonyl-3-methyl-2-[2-(pyrimidin-2-yloxy)-acetylamino]-butyrylamino}-4-phenyl-butyl)-decahydro-isoquinoline-3-carboxylic acid tert-butylamide

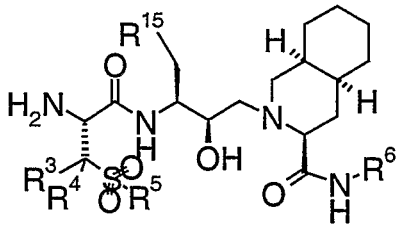
Most preferred compound is

N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[2-(3-pyridyloxy)acetyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide its pharmaceutically acceptable salts and esters .

The hydroxyethylamine compounds provided by the present invention are potent inhibitors, or prodrugs thereof, of the HIV aspartyl protease, an essential enzyme in the replicative cycle of the HIV virus. They accordingly are therapeutically active substances in the treatment of HIV- mediated diseases and therefore can be used as medicaments, either alone or combined with other therapeutically active agents.

The hydroxyethylamine compounds provided by the present invention are, in particular, useful in combating HIV disease states such as AIDS.

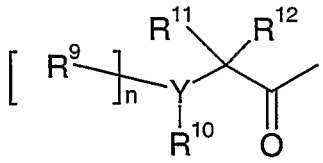
Compounds of the invention with formula I wherein R^1 is NHR^2 can be prepared from a compound o formula III



III

wherein R^3, R^4, R^5, R^6 and R^{15} are as above.

a) For a compound of formula I wherein R^1 is NHR^2 in which R^2 is alkyl carbonyl, cycloalkyl carbonyl, aryl carbonyl, heterocyclyl carbonyl, heterocyclyl alkyl carbonyl, aryl alkyl carbonyl, alkyl oxy carbonyl, aryl alkyl oxy carbonyl, heterocyclyl alkyl oxy carbonyl, sulfonyl, alkyl sulfonyl, aryl sulfonyl, heterocyclyl sulfonyl, or a group of formula



wherein R^9, R^{10}, R^{11}, and R^{12} are as above.

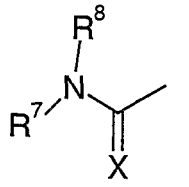
the compound of formula III is reacted with an appropriate acid derivative such as an acyl halide, mixed anhydride etc.

Alternatively when n=1, Y represents N, R^9 is H and R^{10} is alkyl, aryl alkyl, heterocyclyl alkyl, the compound of formula III is reacted with N-protected glycine, deprotected and reacted with

an aldehyde or ketone under reductive conditions as described in embodiment b) of the process

b) For a compound of formula I wherein R^1 is NHR^2 in which R^2 is, alkyl, alkenyl, alkynyl, arylalkyl, heterocyclylalkyl, cycloalkyl, a compound of formula III is reacted with an aldehyde or ketone under reductive conditions.

c) For a compound of formula I wherein R^1 is NHR^2 in which R^2 is a group of formula

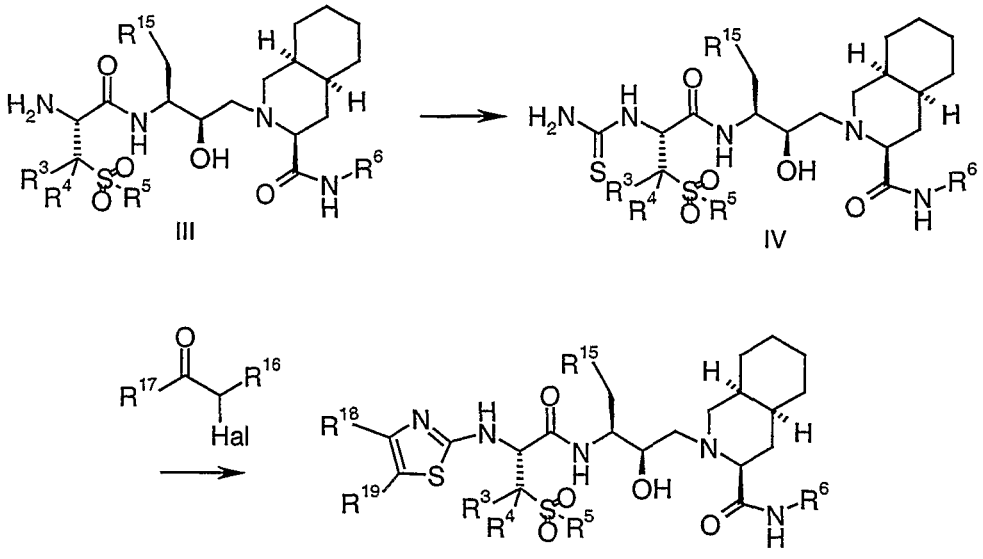


,

in which X, R^7 and R^8 have the same meaning as described previously, a compound of formula III is reacted with reagents described in the art for the formation of ureas and thioureas.

d) For a compound of formula I wherein R^1 is NHR^2 in which R^2 is a heterocycle a compound of formula III is reacted according to methods described in the art for the formation of heterocycles. For example, in the case where R^2 is thiazole, by using the Hansch synthesis according to Scheme 1, by converting a compound of formula III into the thiourea IV followed by reaction of IV with the required α-haloketone or α-haloaldehyde

Scheme 1

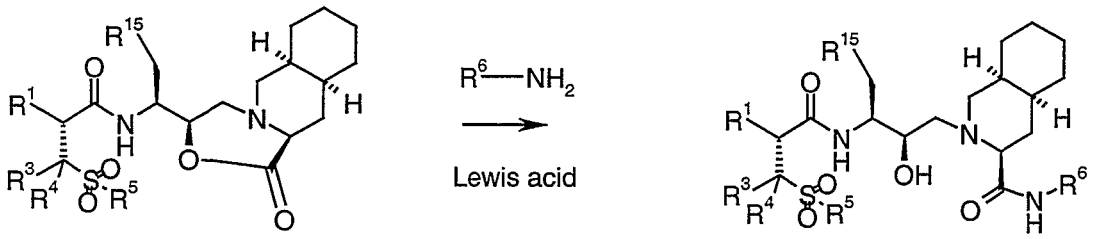


in said scheme, R^2, R^3, R^4, R^5, R^6 and R^{15} are as previously described; R^{16} has the meaning of H, alkyl, alkoxy carbonyl, aryl, heterocyclyl; R^{17} has the meaning of H, alkyl, aryl, heterocyclyl; R^{18} is the same as R^{16}; and R^{19} is the same as R^{17}. Hal has the meaning of a halogen atom selected of , chlorine, bromine and iodine.

e) For a compound of formula I wherein R^1 is NHR^2 in which R^2 is aryl, a compound of formula III is reacted with aryl halides under transition metal catalysed conditions known in the art. Alternatively the amino acid derived from deprotection of compounds V (Scheme 3) can be reacted with aryl halides under similar conditions prior to coupling with compounds of formula VI (Scheme 3).

f) For a compound of formula I in which R^6 is alkyl, aryl alkyl, heterocyclyl alkyl, alkyl oxy alkyl, hydroxy alkyl,amino alkyl, fluoro alkyl, a compound of formula IVa (Scheme 2) is reacted with the appropriate amine under conditions of Lewis acid catalysis

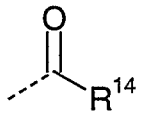
Scheme 2



IVa

in said scheme R^1, R^3, R^4, R^5, R^6 and R^{15} are as previously described.

g) For a compound of formula I in which R^{13} has the meaning of–SO_2OH, -$PO(OH)_2$,or a group

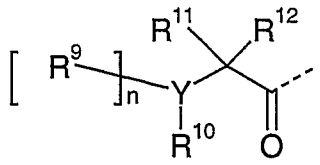


wherein R^{14} is as previously described,

a compound of formula I in which R^{13} is H is reacted with the appropriate activated acid derivative or, in the case of an amino acid, an amino-protected form thereof, according to methods described in the art for the formation of esters.

In accordance with embodiment a) of the process, suitable reagents which yield alkyl carbonyl, cycloalkyl carbonyl, aryl carbonyl, heterocycly carbonyl, aryl alkyl carbonyl, heterocycly alkyl carbonyl, alkyl oxy carbonyl, aryl alkyl oxy carbonyl, heterocyclyl alkyl oxy

carbonyl, sulfonyl, alkyl sulfonyl, aryl sulfonyl, or heterocyclyl sulfonyl amines or a group of formula



wherein R^9, R^{10}, R^{11} and R^{12} are as previously described,

are the corresponding acids or reactive derivatives thereof, such as the corresponding acid halides (e.g. acid chlorides), acid anhydrides, mixed anhydrides, activated esters etc. The reaction of III with the aforementioned reagents is carried out in accordance with methods described in the art for example in text books on organic chemistry such as J. March (1992) "Advanced Organic Chemistry : Reactions, Mechanisms and Structure", 4th ed. John Wiley & Sons. Thus when an acid is used, the reaction is preferably carried out in the presence of condensation agents such as N-ethyl-N'(3-dimethylaminopropyl)carbodiimide hydrochloride (EDAC.HCl) in the presence of hydroxybenzotriazole (HOBT). This reaction is conveniently carried out in an inert organic solvent such as tetrahydrofuran (THF), dichloromethane or dimethylformamide at a temperature from –10°C to +25°C. When a reactive derivative is used the reaction can be carried out in an inert solvent such as dichloromethane or tetrahydrofuran in the presence of an organic base (e.g. N-ethylmorpholine, triethylamine etc) at a temperature from –10°C to 25°C.

In accordance with embodiment b) of the process, reaction of compounds of formula III with an aldehyde or ketone can be carried out according to methods described in the art for the reductive amination of aldehydes and ketones. For example, text books on organic chemistry such as J. March (1992) "Advanced Organic Chemistry : Reactions, Mechanisms and Structure", 4th ed. John Wiley & Sons can be consulted. Thus, for example, the reaction is conveniently carried out with sodiumtriacetoxyborohydride in an inert halogenated solvent such as dichloroethane in the presence of acetic acid according to the method described by A.F. Abdel-Magid et al; Tetrahedron Letters 1990, 31, 5595.

In accordance with embodiment c) of the process, the reaction can be carried out according to methods known in the art, for example in text books on organic chemistry such as J. March (1992) "Advanced Organic Chemistry : Reactions, Mechanisms and Structure", 4th ed. John Wiley & Sons. Thus, for example, for a compound in which X is O, the reaction can be carried out by reaction of compounds of formula III with para-nitrophenylchloroformate in the presence of an inorganic base such as sodium hydrogen carbonate followed by reaction with an amine R^7R^8NH in the presence of an organic base such as triethylamine where R^7 and R^8 have the significance given earlier. (See for example N. Choy et al. Org. Prep. Proced. Int. 1996, 28(2), 173-7). The reaction is conveniently carried out in an inert polar solvent such as

acetonitrile at a temperature between 0°C and 25°C. When X is O or S and one of R^7 or R^8 is H the reaction can be conveniently carried out by the reaction of a compound of formula III with an isocyanate ($R^7N=C=O$ or $R^8N=C=O$) or isothiocyanate ($R^7N=C=S$ or $R^8N=C=S$) according to methods described in the art.

In accordance with embodiment d) of the process, the reaction can be carried out according to methods described in text books on heterocyclic chemistry such as T.L. Gilchrist (1992) "Heterocyclic Chemistry", 2nd ed. John Wiley and Sons. For example when R^2 is thiazole, the reaction can be carried out by heating a mixture of compound IV and the α-halocarbonyl compound in an appropriate solvent such as an alkanol (e.g. ethanol). Compound IV can be readily prepared from compound III according to known methods, for example by reaction with benzoyl isothiocyanate in refluxing acetone followed by hydrolysis with an inorganic base such as potassium carbonate in a mixture of a polar organic solvent and water. (See for example N.M. Olken et al J. Med. Chem. 1992, 35, 1137).

In accordance with embodiment e) of the process, the reaction of amino acids (derived from compounds of formula V by deprotection) with aryl halides, e.g. bromobenzene, can be carried out in the presence of copper salts, e.g copper iodide in dimethyl acetamide. See for example D. Ma et al, J. Amer. Chem. Soc 1998, 120, 12467.

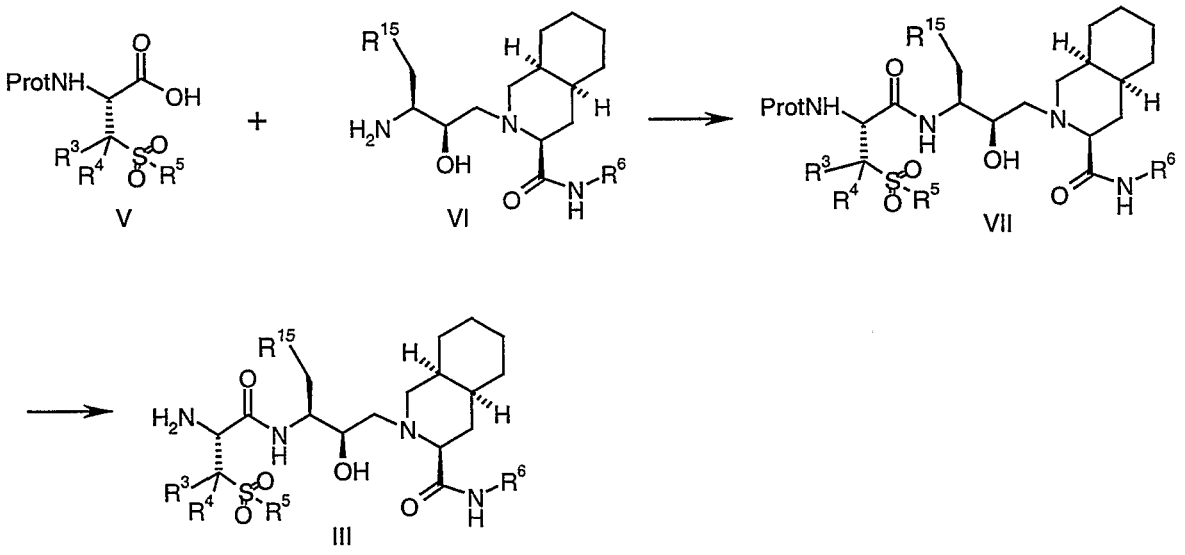
In accordance with embodiment f) of the process, the reaction of compounds of formula IVa with amines R^6NH_2 is carried out using methods described in the art for example using a reagent derived from the amine and an aluminium derived Lewis acid, e.g. trimethylaluminium, at ambient temperature in an inert solvent such as dichloromethane or toluene. (See for example S. M. Weinreb et al, Tetrahedron Letters 1977, 4171)

In accordance with embodiment g) of the process, the reaction can be carried out according to methods known in the art for the formation of esters, see for example text books on organic chemistry such as J. March (1992) "Advanced Organic Chemistry : Reactions, Mechanisms and Structure", 4th ed. John Wiley & Sons. For example the reaction is conveniently carried out at ambient temperature using the carboxylic acid derivative and a peptide coupling reagent such as EDAC.HCl in an inert solvent such as dichloromethane in the presence of 4-dimethylaminopyridine as a catalyst. Alternatively the acyl halide can be used in an inert solvent in the presence of pyridine and 4-dimethylaminopyridine as a catalyst at a temperature between 0°C and 25°C.

Compounds of formula III which are used as starting materials in embodiments a-e are either known as can be prepared according to Scheme 3. Thus reaction of a compound of formula V with a compound of formula VI can be carried out in accordance with methods known in peptide chemistry to give a compound of formula VII (see J. Jones (1994), "The Chemical Synthesis of Peptides", Oxford University Press). The term "amino protecting group" (Prot) as used herein refers to groups employed in peptide chemistry such as a tert-butoxycarbonyl

group (BOC) or a 9-fluorenylmethyloxycarbonyl group (FMOC). The preferred amino protecting group (Prot) for this reaction is a 9-fluorenylmethyloxycarbonyl group. This reaction is preferably carried out by reaction of a compound of formula V with a chloroformate (e.g. isobutylchloroformate) in the presence of an organic base such as N-ethylmorpholine to generate a mixed anhydride which is subsequently reacted with compounds of formula VI. The reaction is conveniently carried out in an inert solvent such as an ether (e.g. diethyl ether, tetrahydrofuran, etc) or an aliphatic halogenated solvent (e.g. dichloromethane) at a low temperature, suitably at about –10°C to 5°C. Conversion of compounds of formula VII into compounds of formula III is carried out using known methods employed in peptide chemistry for the deprotection of the amino group of amino acids. For example when the amino protecting group is FMOC the reaction is conveniently conducted by reaction of compounds of formula VII with piperidine in dimethylformamide or dichloromethane at room temperature.

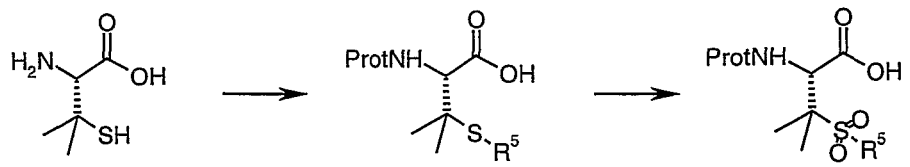
Scheme 3



in said scheme R^3, R^4, R^5, R^6 and R^{15} have the meaning previously described.

Compounds of formula V where R^3 and R^4 are methyl can be prepared from penicillamine according to Scheme 4.

Scheme 4



in said scheme R^5 is as previously described.

Thus reaction of L-penicillamine with an alkyl halide R^5X, where R^5 has the significance given earlier and X is a halogen (e.g. bromide), in the presence of an inorganic base such as potassium carbonate, followed by reaction with a reagent for introducing amino acid protecting groups (e.g. FMOCONSu or BOC_2O) gives compounds of formula VIII. The reaction can be carried out at room temperature in a mixed solvent system consisting of water and an organic solvent preferably dioxane. Compounds of formula VIII are oxidized to compounds of formula Va according to known procedures preferably by reaction with Oxone (K.S. Webb, Tetrahedron Lett. 1994, 35(21), 3457-60).

Other compounds of formula V can be prepared by analogous routes from penicillamine analogues described in the art.

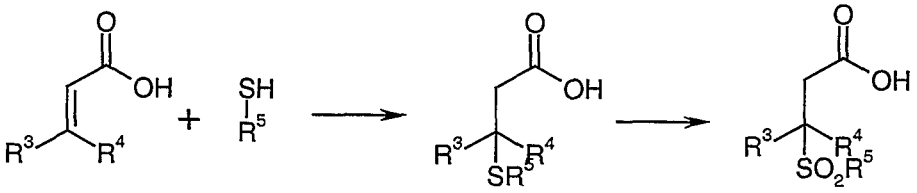
Compounds of formula VI can be prepared according to the known procedures described in the art, for example EP 432695 A2.

Compounds of formula I in which R^1 is hydroxy can be prepared according to methods described in the art, for example A.N. Cook et al; J. Chem. Soc. 1949, 1022. For example, deprotection of the amino acids V followed by diazotization, hydrolysis, and coupling to compounds of formula VI according to the methods described above gives compounds of formula I in which R^1 is hydroxy .

Compounds of formula I in which R^1 is H can be prepared from compounds of formula VI and compounds of formula IX (Scheme 5) in a manner analogous to that already described.

Compounds of formula IX can be prepared from the appropriate acrylic acid and thiol according to methods decribed in the art and outlined in Scheme 5 (See for example G. Pattenden et al, J. Chem. Soc., Perkin Trans. 1, 1992, (10), 1215-21)

Scheme 5

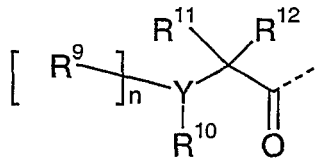


IX

in said scheme R^3, R^4 and R^5 are as previously described.

The starting materials of formula V, VI, IX and their reactive derivatives, insofar as they are not known compounds or analogues of known compounds, can be prepared in a similar manner to the known compounds or as described in the examples hereinafter or by analogy thereto. Moreover, the reagents used in embodiments a-g are generally known compounds.

Reagents required for the introduction of groups of formula



wherein R^9, R^{10}, R^{11} and R^{12} are as previously described.

are the corresponding carboxylic acids, or activated derivatives thereof, which themselves are known compounds or can be readily prepared by analogy to known compounds. For example when n=0, Y represents O or S and R^{10} is aryl or heterocyclyl the reagent is prepared by reaction of the appropriate alcohol (e.g. 3-hydroxypyridine) with tert-butylbromoacetate under basic conditions (e.g. sodium hydride in dimethylformamide or potassium carbonate in acetone) followed by acid-catalysed deprotection (e.g. hydrochloric acid in ether, hydrobromic acid in acetic acid or trifluoroacetic acid in dichloromethane). Similarly, when n=1 and Y represents N, the reagent can be prepared by similar methods in which the amine $R^9R^{10}NH$ is used instead of the alcohol and without added base. Alternatively, glycine t-butyl ester can be reductively aminated with an aldehyde or ketone under analogous conditions to those described above in embodiment b) of the process, followed by acid catalysed deprotection of the carboxylic acid group; preferably with HBr in acetic acid.

Assay Methods:

HIV protease inhibition assay

HIV protease inhibitory activity was assessed using an adaptation of the method of Matayoshi. et al. [Matayoshi E.D. et al (1990). Science. 247. 954-958]

Crude HIV-1 protease was prepared from E. coli pPTΔN. Cultures were grown at 30° in M9 medium supplemented with 0.2% casamino acids, 100 μg/ml ampicillin and 25 μg/ml thiamine until OD_{600} = 0.5-0.6, and the temperature was raised to 42° to induce expression of the protease. After 1.5 hours, the cells were harvested and the pellets stored at -70° until required.

The protease was prepared by lysis of the cells in a French pressure cell followed by precipitation of the enzyme with ammonium sulfate at 30% saturation.

The assay was based on intramolecular fluorescence energy transfer using a quenched fluorogenic substrate DABCYL-Ser.Gln.Asn.Tyr.Pro.Ile.Val.Gln.-EDANS, the peptide sequence of which was derived from one of the natural polypeptide processing sites of HIV-1 protease.

The peptide substrate was dissolved in spectroscopic grade dimethyl sulphoxide (DMSO) to give a stock solution of 500 μM. Inhibitors were dissolved in a 1:9 mixture of DMSO : 0.1% aqueous Tween 20 to give inhibitor concentrations 20x more concentrated than the desired final concentration. The assay buffer comprised 0.1M sodium acetate pH 4.7, 8 mM EDTA, 0.2 M NaCl.

10 μl HIV-1 protease diluted in a 1:1 mixture of 0.1% Tween:assay buffer (concentration adjusted to give approximately 20% substrate turnover) was added to a mixture comprising 455μl assay buffer, 25μl inhibitor solution, 10μl substrate solution.

Tubes were incubated for 2 hours at 37° and the reaction was terminated by the addition of 500 μl of a 2:1 mixture of DMSO: 50 mM Tricine pH 8.5. Fluorescence was measured in a fluorescence spectrophotometer, excitation λ = 340 nm, emission λ = 492 nm.

Antiviral assay method

Anti-HIV antiviral activity was assessed using an adaptation of the method of Pauwels et al. [Pauwels et al., 1988, J. Virol. Methods 20: 309-321]. The method is based on the ability of compounds to protect HIV-infected T lymphoblastoid cells (MT4 cells) from cell-death mediated by the infection. The endpoint of the assay was calculated as the concentration of compound at which the cell viability of the culture was preserved by 50% ('50% inhibitory concentration', IC_{50}). The cell viability of a culture was determined by the uptake of soluble, yellow 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) and its reduction to a purple insoluble formazan salt. After solubilization, spectrophotometric methods were employed to measure the amount of formazan product.

MT4 cells were prepared to be in logarithmic-phase growth and a total of 2 x 10^6 cells infected with either the wild type or site directed mutant clones of HIV-HXB2 at a multiplicity of approximately 0.0001 infectious units of virus per cell in a total volume of between 200-500 μl. The cells were incubated with virus for one hour at 37°C then washed in 0.01 M phosphate buffered saline, pH 7.2, and resuspensed in culture medium for incubation in culture with serial dilutions of test compound. The culture medium used was RPMI 1640 without phenol red, supplemented with penicillin, streptomycin, L-glutamine and 10% fetal calf serum (GM10).

Test compounds were prepared as 2 mM solutions in dimethyl sulphoxide (DMSO). Four replicate, serial 2-fold dilutions in GM10 were then prepared and 50 microlitre amounts placed in 96-well plates over a final concentration range of 625 – 1.22nm. Fifty microlitres GM10 and 3.75 x 10^4 infected cells were then added to each well. Control cultures

containing no cells (blank), uninfected cells (100% viability; 4 replicates) and infected cells without compound (total virus-mediated cell death; 4 replicates) were also prepared. The cultures were then incubated at 37 °C in a humidified atmosphere of 5% CO_2 in air for 5 days.

A fresh solution of 5 mg/mL MTT was prepared in 0.01 M phosphate buffered saline, pH 7.2 and 20 µL added to each culture. The cultures were further incubated as before for 2 hours. They were then mixed by pipetting up and down, and 170 microlitres of Triton X-100 in acidified isopropanol (10% v/v Triton X-100 in 1:250 mixture of concentrated HCl in isopropanol) were added and the cultures were mixed again by pipetting up and down. When the formazan deposit was fully solubilized by further mixing, the absorbance (OD) of the cultures was measured at 540nm and 690nm wavelength (690nm readings were used as blanks for artefacts between wells). The percen protection for each treated culture was then calculated from the equation:

$$\% \text{ Protection} = \frac{(\text{OD drug-treated cultures}) - (\text{OD untreated virus control cultures})}{(\text{OD uninfected cultures}) - (\text{OD untreated virus control cultures})} \times 100\%$$

The IC_{50} was then obtained from graph plots of percentage protection versus $\log_{10}$ drug concentration.

The IC_{50} of the compounds of the present invention is as a rule in the range of 1 nM to 10,000nM, preferably in the range of 1 nM to 60 nM.

Some representative activity data is given in table 9 below.

Table 9

Example number	Enzyme inhibitory IC_{50}(nM)	Antiviral IC_{50}(nM)
3	0.6	17
4	2.8	14
7	2.3	21
16	1.0	12
28	1.0	21
40	1.4	19
92	4.0	33
93	0.5	8
95	61.0	250
106	10.7	60
112	7.5	94

138	7.8	65
152	1.2	17
154	0.5	16
168	0.5	16
170	1.0	13

Enzyme inhibitory IC_{50}s have been rounded up to 1 decimal point, antiviral IC_{50}s have been rounded up to nearest whole number.

The compounds of the present invention, as well as their pharmaceutically usable acid addition salts, can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatin capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The compounds of the present invention and their pharmaceutically usable acid addition salts can be processed with pharmaceutically inert, inorganic or organic excipients for the production of tablets, coated tablets, dragees and hard gelatin capsules. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc. can be used as such excipients e.g. for tablets, dragées and hard gelatine capsules.

Suitable excipients for soft gelatine capsules are e.g. vegetable oils, waxes, fats, semi-solid and liquid polyols etc.

Suitable excipients for the manufacture of solutions and syrups are e.g. water, polyols, saccharose, invert sugar, glucose etc.

Suitable excipients for injection solutions are e.g. water, alcohols, polyols, glycerol, vegetable oils etc.

Suitable excipients for suppositories are e.g. natural or hardened oils, waxes, fats, semi-liquid or liquid polyols etc.

Moreover, the pharmaceutical preparations can contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily dosage of about 10 to 2500 mg per person of a compound of formula I should be appropriate, although the above upper limit can also be exceeded when necessary.

The daily dosage can be administered as a single dosage or in divided dosages. The treatment may be in conjunction with the administration of one or more additional therapeutically active substance(s), and such administration may be concurrent or sequential with respect to that of the compounds of formula I. Thus, concurrent administration, as used herein, includes administration of the agents in conjunction or combination, together, or before or after each other.

Examples

Mass spectra were recorded under electrospray ionization conditions on one of the following instruments:

a) THERMOQUEST SSQ 7000 [Solvent 0.085% TFA in 90% acetonitrile/water; flow rate 100 microlitres/minute; capillary 250°C; spray voltage 5KV; sheath gas 80 psi], or

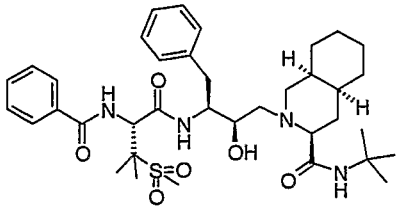
b) LC-MS system (liquid chromatograph coupled to mass spectrum) THERMOQUEST 7000 ELECTROSPRAY or MICROMASS PLATFORM ELECTROSPRAY [gradient of 0.1% TFA in water to 0.085% TFA in acetonitrile]

With regard to the starting materials that are known compounds some of these may be purchased from commercial suppliers. Other known starting materials and their analogues can be prepared by methods well known in the art. Examples of the compounds available from commercial suppliers, and citations to the synthesis of other compounds and their analogues are provided in the following.

The following examples illustrate the present invention:

Example 1

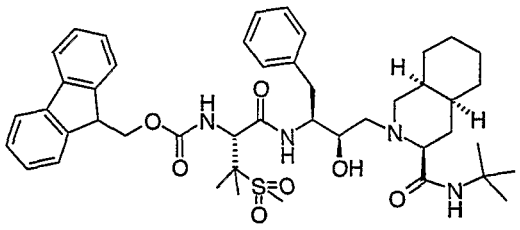
2-[3(S)-[[N-Benzoyl-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-benzyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide



A stirred solution of 105mg (0.13mmol) of N-tert-butyl-2-[3(S)-[[N-[(9-fluorenyl)methoxycarbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide in 4ml of dry dimethylformamide at room temperature was treated with 0.4ml (4mmol) of piperidine. After 2.5 hours the volatiles were evaporated and the residue triturated with hexane to give N-tert-butyl-1,2,3,4,4a(S),5,5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide as a gum which was dissolved in 3ml of dichloromethane and cooled to 0°C. 0.035ml (0.26mmol) of N-Ethylmorpholine (NEM) was added followed by 0.016ml (0.13mmol) of benzoyl chloride (Aldrich 24,054-0). After 2 hours the solution was diluted with 20ml of dichloromethane and washed in sequence with 10% aqueous citric acid solution, saturated sodium hydrogen carbonate and brine. The solution was dried over magnesium sulfate and evaporated under reduced pressure to give a solid which was chromatographed on silica eluting with dichloromethane/methanol (37:3) to give the product 60mg (67%) as a white solid, mp 212-18°C, $[M+H]^+$ 683.2.

The starting material was prepared as follows:

N-tert-Butyl-2-[3(S)-[[N-[(9-fluorenyl)methoxycarbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide



(A) A stirred solution of 596mg (4mmol) of L-penicillamine (Aldrich 19,631-2) in 40ml of water/dioxane (1:1) was treated at room temperature with 11.04g (80mmol) of potassium carbonate followed by 710mg (5mmol) of iodomethane followed, after 1 hour, by 5.39g (20mmol) of N-(9-fluorenylmethyloxycarbonyl)-oxysuccinimide (Advanced Chemtech RC8015). After a further 2 hours the volatiles were evaporated and the residue partitioned between water and ether. The solution was acidified with 2N hydrochloric acid, extracted with ether and the combined organic phase dried over magnesium sulfate. Evaporation to dryness afforded a yellow foam which was chromatographed on silica eluting with dichloromethane/methanol (9:1) to give 4.8g (78%) of N-[(9-fluorenyl)methoxycarbonyl]-3-(methylthio)-L-valine as a white foam, $[M+H]^+$ 385.9.

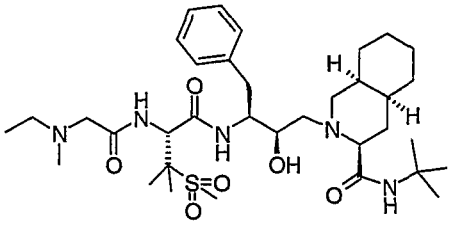
(B) A vigorously stirred solution of 4.8g (12.4mmol) of N-[(9-fluorenyl)methoxycarbonyl]-3-(methylthio)-L-valine, obtained from (A) above, in 36ml of water containing 600mg (15mmol)

of sodium hydroxide was treated with 8.43g (99mmol) of sodium hydrogen carbonate and 12ml of acetone. 10.26g (16.68mmol) of OXONE® (Aldrich 22,803-6) in 36ml of (0.0004M) EDTA solution was added dropwise and the solution stirred vigorously for 2 hours. A solution of 6.3g of sodium metabisulfite in 12.6ml of water was then added and the solution stirred for a further 15 minutes. Ethyl acetate was added and the aqueous phase was acidified to pH 2 with 6N hydrochloric acid, saturated with sodium chloride and extracted with ethyl acetate. The combined organic phase was washed in sequence with water and brine, dried over magnesium sulfate and evaporated under reduced pressure to give a yellow gum. Trituration with petroleum ether (bp 40-60°C)/ether afforded a cream solid which was washed further with ether to give 3.18g (61%) of N-[(9-fluorenyl)methoxycarbonyl]-3-(methanesulfonyl)-L-valine as a white solid, mp 189-92°C, $[M+H]^+$ 417.8.

C) A solution of 8.34g (20mmol) of N-[(9-fluorenyl)methoxycarbonyl]-3-(methanesulfonyl)-L-valine, obtained from (B) above, in dry tetrahydrofuran was cooled to -10°C and 2.8ml (20mmol) of triethylamine was added followed by 2.6ml (20mmol) of isobutyl chloroformate (Aldrich 17,798-9). 8.02g (20mmol) of 2-(3(S)-amino-2(R)-hydroxy-4-phenylbutyl)-N-tert-butyl-1,2,3,4,4a(S),4,5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide (prepared according to known methods, e.g. Martin, Joseph Armstrong; Redshaw, Sally; EP 432695 A2) was then added and the mixture stirred at -10°C for a further 2 hours and then allowed to warm to room temperature overnight. The volatiles were evaporated and the residue partitioned between 100ml of dichloromethane and 100ml of 10% citric acid solution. The aqueous phase was extracted with dichloromethane and the combined organic phase was washed with saturated sodium hydrogen carbonate and brine, dried over magnesium sulfate and evaporated under reduced pressure to give a solid which was triturated with ether followed by ether/ethyl acetate (10:1) to give 10.84g (68%) of N-tert-butyl-2-[3(S)-[[N-[(9-fluorenyl)methoxycarbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide as a white solid, $[M+H]^+$ 801.4.

Example 2

N-tert-Butyl-2-[3(S)-[[N-(N-ethyl-N-methylglycyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide

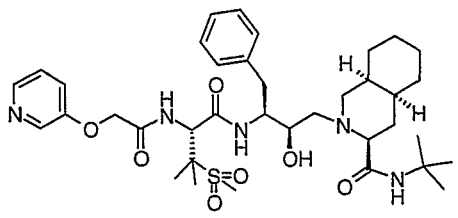


A solution of 38mg (0.2mmol) of N-ethyl-N-methylglycine hydrobromide and 116mg (0.2mmol) of N-tert-butyl-1,2,3,4,4a(S),5,5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide in 5ml of dichloromethane was treated with 28mg (0.2mmol) of 1-hydroxy-7-azabenzotriazole (HOAT), 0.05ml (0.4mmol) of N-ethylmorpholine (NEM) and 38mg (0.2mmol) of N-ethyl-N'(3-dimethylaminopropyl)carbodiimide hydrochloride (EDAC.HCl) at 0°C and allowed to warm to room temperature overnight. The reaction mixture was diluted with dichloromethane, washed with saturated sodium hydrogen carbonate and brine, dried over magnesium sulfate and evaporated under reduced pressure to give a gum which was chromatographed on silica eluting with dichloromethane/methanol (19:1) to give 65mg of N-tert-butyl-2-[3(S)-[[N-(N-ethyl-N-methylglycyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide as a white foam, $[M+H]^+$ 678.4.

The starting material N-ethyl-N-methylglycine hydrobromide (1:1) was prepared as follows
A) A stirred solution of 0.6ml (7mmol) of N-ethylmethylamine and 0.97ml (7mmol) of triethylamine in 7ml of dichloromethane was treated with 1ml (7mmol) of tert-butyl bromoacetate (Aldrich 12,423-0) and stirred overnight. The volatiles were evaporated and the residue triturated with ethyl acetate and the solid was removed by filtration. The solvent was evaporated to give 459mg of a yellow oil which was treated at room temperature with 2ml of 45% hydrobromic acid in acetic acid, and stirred for 6 hours. The volatiles were evaporated under reduced pressure and the residue was triturated extensively with ethyl acetate to give 413mg N-ethyl-N-methylglycine hydrobromide as a white solid.

Example 3

N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[2-(3-pyridyloxy)acetyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide



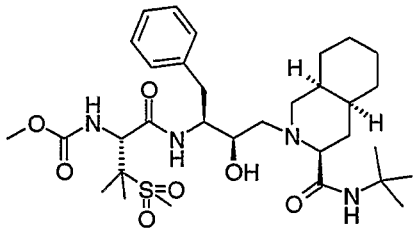
Example 3, $[M+H]^+$ 714.4, was prepared in a manner analogous to that described in Example 2 but starting from 2-(3-pyridyloxy)acetic acid trifluoroacetate.

The starting material 2-(3-pyridyloxy)acetic acid trifluoroacetate was prepared as follows:

A) A solution of 9.5g (0.1mol) of 3-hydroxypyridine in 50ml of dry dimethylformamide at 0°C was treated portionwise with a slurry of sodium hydride in hexane (prepared by washing 4g of sodium hydride (60% dispersion of in mineral oil) with hexane). After 30 minutes 19.4g (0.1mol) of tert-butyl bromoacetate was added dropwise and the solution stirred overnight. The volatiles were evaporated and the residue partitioned between dichloromethane and water. The organic phase was washed with water, dried over magnesium sulfate and evaporated under reduced pressure to give an oil which was chromatographed on silica eluting with dichloromethane to give 8.9g of a green-brown oil. The oil was dissolved in dichloromethane, cooled to 0°C and treated with 18ml of trifluoroacetic acid and allowed to warm to room temperature overnight. The volatiles were evaporated and the residue triturated with ether to give 9.2g of 2-(3-pyridyloxy)acetic acid trifluoroacetate as a light brown solid.

Example 4

N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(methoxycarbonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide

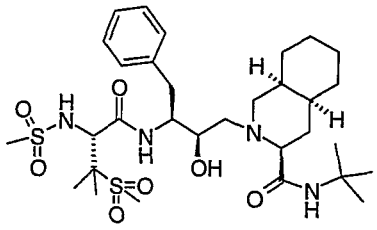


A stirred solution of 200mg (0.25mmol) of N-tert-butyl-2-[3(S)-[[N-[(9-fluorenyl)methoxycarbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide in 5ml of dry dimethylformamide at room temperature was treated with 0.63ml (6.3mmol) of piperidine. After 2.5 hours the volatiles were evaporated and the residue triturated with hexane to give N-tert-butyl-1,2,3,4,4a(S),5,5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide as a gum which was dissolved in 5ml of dichloromethane and treated with 0.2ml (1.5mmol) of N-

ethylmorpholine (NEM) and 0.02ml (0.25mmol) of methylchloroformate (Aldrich, M3,530-4) and stirred overnight. A further 0.02ml (0.25mmol) of methylchloroformate was added and the reaction stirred for a further 3 hours. The solution was diluted with dichloromethane, and then washed with 10% citric acid solution, saturated sodium hydrogen carbonate and brine. The citric acid solution was made basic by the addition of solid sodium hydrogen carbonate and extracted with dichloromethane. The combined organic phase was dried over magnesium sulfate and evaporated under reduced pressure to give a residue which was chromatographed on silica eluting with dichloromethane/methanol (19:1) and triturated with ether to give 75mg of N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(methoxycarbonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide as a white solid, mp 190-194°C, $[M+H]^+$ 637.4.

Example 5

2-[3(S)-[[N,3-Bis(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8a(S)-decahydro-3(S)-isoquinolinecarboxamide

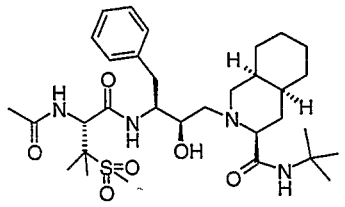
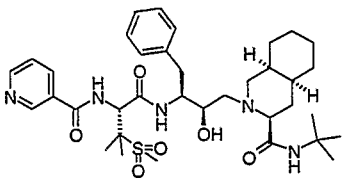
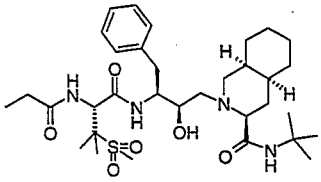
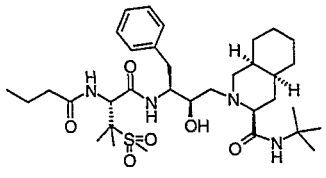


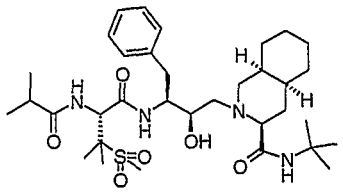
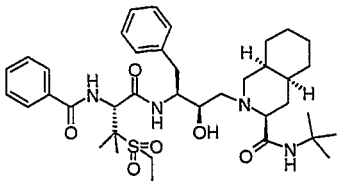
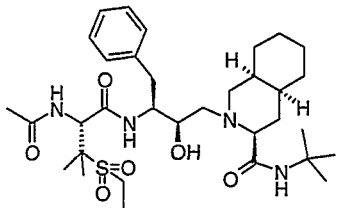
A stirred solution of 200mg (0.25mmol) of N-tert-butyl-2-[3(S)-[[N-[(9-fluorenyl)methoxycarbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide in 5ml of dry dimethylformamide at room temperature was treated with 0.63ml (6.3mmol) of piperidine. After 2.5 hours the volatiles were evaporated and the residue triturated with hexane to give N-tert-butyl-1,2,3,4,4a(S),5,5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide as a gum which was dissolved in 5ml of dichloromethane and treated with 0.12ml (1.5mmol) of pyridine followed by 0.02ml (0.25mmol) of methanesulfonyl chloride. After 2 hours the solution was diluted with dichloromethane, washed with saturated sodium hydrogen carbonate and brine, dried over magnesium sulfate and evaporated under reduced pressure to give a gum which was triturated with ether and then chromatographed on silica eluting with dichloromethane/methanol (19:1) to give 105mg of 2-[3(S)-[[N,3-bis(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8a(S)-decahydro-

3(S)-isoquinolinecarboxamide as a white solid, mp 135-160°C foams, re-melts 230-235°C (dec.), $[M+H]^+$ 657.2.

In a manner analogous to that described for Example 1, the compounds shown in Table 1 were also prepared. Examples 6, 7, 8, 9, 10 were prepared from N-tert-butyl-2-[3(S)-[[N-[(9-fluorenyl)methoxycarbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide and examples 11 and 12 were prepared in an analogous manner to Example 1 but using iodoethane in place of iodomethane in part A). The acid chlorides used as starting materials were all purchased from commercial sources such as Aldrich and Lancaster.

Table 1

name	structure	$[M+H]^+$	Ex. No.
2-[3(S)-[[N-Acetyl-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		621.1	6
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(3-pyridyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		684.2	7
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-propionyl-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		635.3	8
2-[3(S)-[[N-Butyryl-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		649.3	9

N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-isobutyryl-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		649.3	10
2-[3(S)-[[N-Benzoyl-3-(ethanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		697.2	11
2-[3(S)-[[N-Acetyl-3-(ethanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		635.2	12

In a manner analogous to that described for Examples 2 and 3, the compounds in Table 2 were prepared starting from N-tert-butyl-2-[3(S)-[[N-[(9-fluorenyl)methoxycarbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide.

Other reagents used in the synthesis of the compounds in Table 2 were obtained from commercial sources such as Aldrich, Lancaster, and Maybridge Int. or were prepared using methods described in the art or analogous to those described in the art.

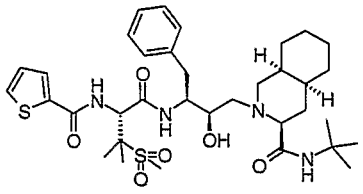
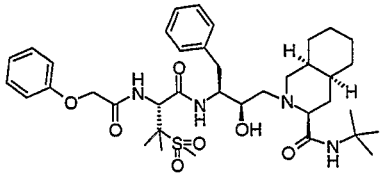
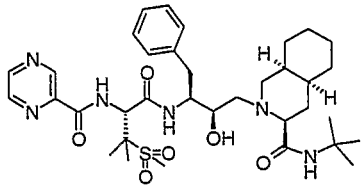
For example phenoxyacetic acid (Example 14), 3-furoic acid (Example 28), 2-ethyl-2-hydroxybutyric acid (Example 23) and 5-bromo-2-furoic acid (Example 32) were purchased from Aldrich (cat. Nos. 15,851-8; 16,339-2; 13,843-6; B6,740-6), 4,5-dimethyl-2-furoic acid (Example 33) and 5-(trifluoromethyl)-2-furoic acid (Example 34) were purchased from Maybridge Int. (cat. Nos. BTB 08890; PC8012) and thiophene-3-carboxylic acid (Example 68) and 5-chlorothiophene-2-carboxylic acid (Example 36) were purchased from Lancaster (cat. Nos. 1089; 5453).

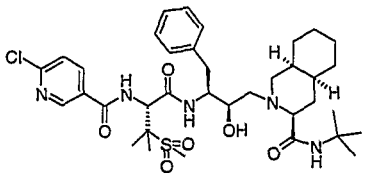
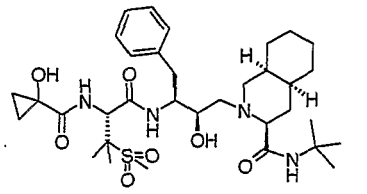
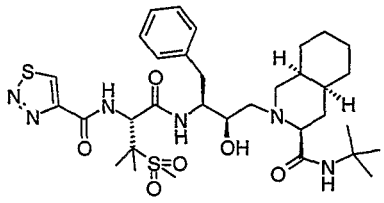
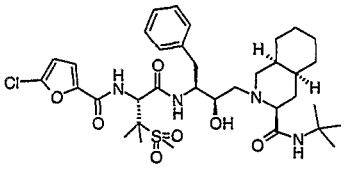
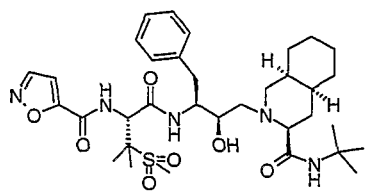
Thiazole-5-carboxylic acid (Example 69) was prepared according to the method described in WO97/14687, and 5-methyl-thiazole-2-carboxylic acid (Example 61) was prepared analogously. 2-Methyl-thiazole-4-carboxylic acid (Example 74) was prepared by analogy to the method of W.R. Tully et al, J. Med. Chem; 1991, 34, 2060. 2-Isopropoxyacetic acid

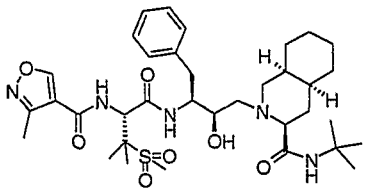
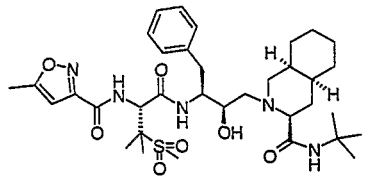
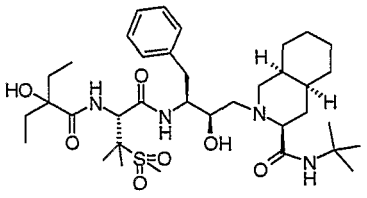
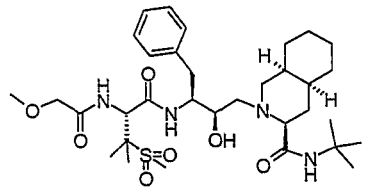
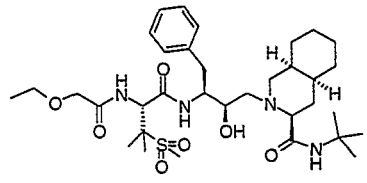
(Example 72) was prepared according to the method described in J. Chem. Soc., 1969, 2698. 2-Methyl-2-phenoxypropionic acid (Example 80) was prepared according to the method described in the Romanian patent RO 69-61256.

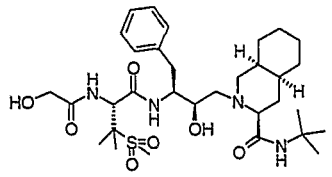
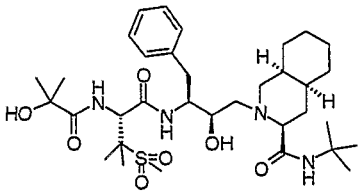
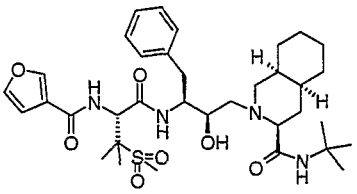
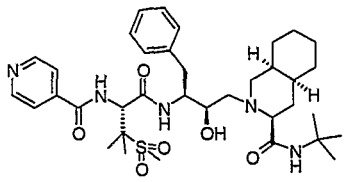
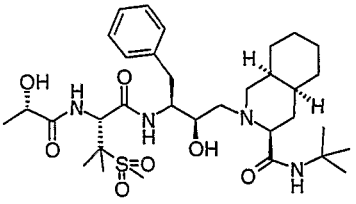
Other aryloxy acetic acids were prepared by analogy to the method of Mertes et al, J. Heterocycl. Chem., 1968, 5, 281, or by the method described for Example 3A for the preparation of 2-(3-pyridyloxy)acetic acid trifluoroacetate. Similarly 2-(1-pyrrolyl)acetic acid (example 62), pyrazole-1-acetic acid (example 64), 1-pyrrolidinylacetic acid (example 66) etc were prepared by analogy to the method described in example 2A for the preparation of N-ethyl-N-methylglycine hydrobromide

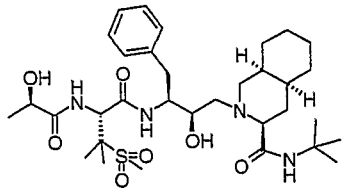
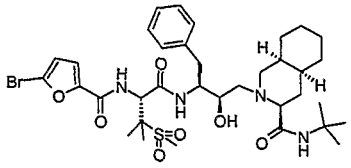
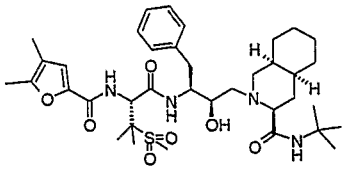
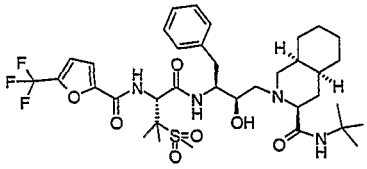
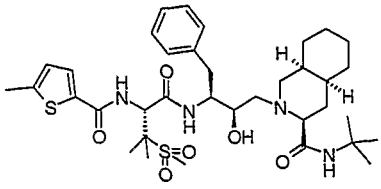
Table 2

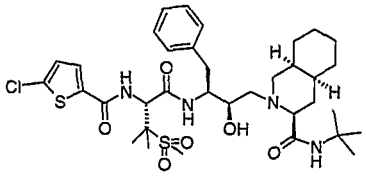
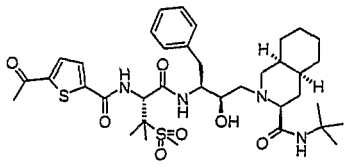
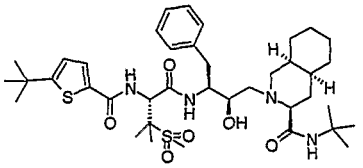
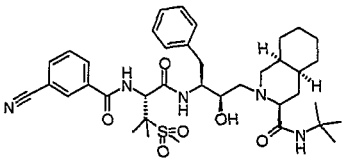
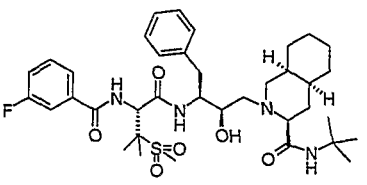
Name	Structure	$[M+H]^+$	Ex. No.
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(2-thenoyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		689.4	13
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(2-phenoxyacetyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		713	14
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(2-pyrazinyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		685.4	15

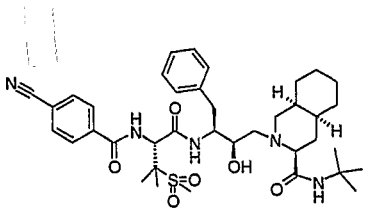
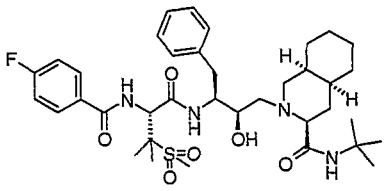
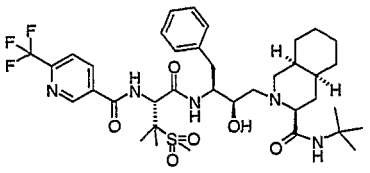
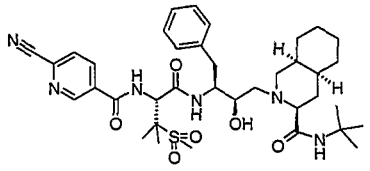
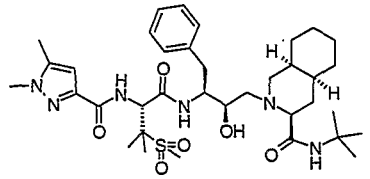
N-tert-Butyl-2-[3(S)-[[N-[(6-chloro-3-pyridyl)carbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		718.3	16
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-[(1-hydroxy-1-cyclopropyl)carbonyl]-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		663.4	17
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(1,2,3-thiadiazol-4-yl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		688.4	18
N-tert-Butyl-2-[3(S)-[[N-(5-chloro-2-furoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		707	19
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(5-isoxazolyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		674.3	20

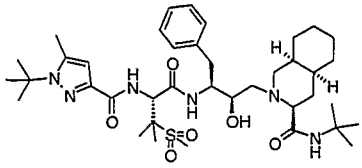
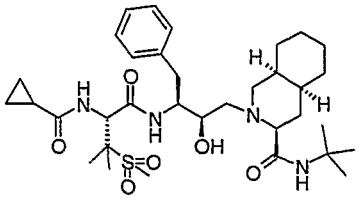
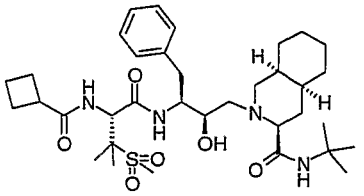
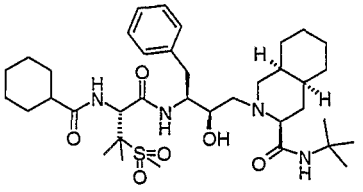
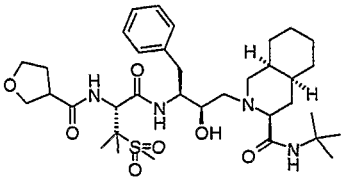
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(3-methyl-4-isoxazolyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		688.4	21
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(5-methyl-3-isoxazolyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		688.4	22
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-(2-hydroxy-2-ethylbutyryl)-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		693.4	23
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(2-methoxyacetyl))-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		651.3	24
N-tert-Butyl-2-[3(S)-[[N-(2-ethoxyacetyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		665.4	25

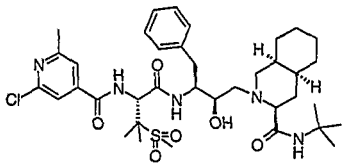
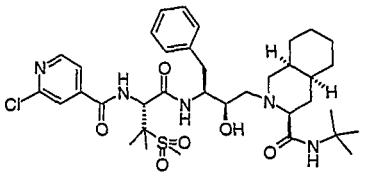
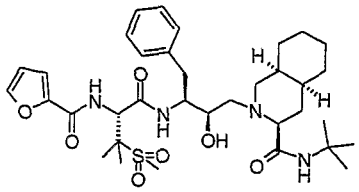
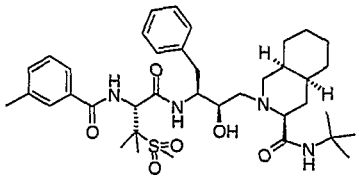
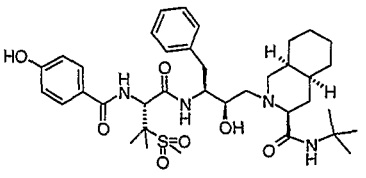
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-(2-hydroxyacetyl)-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		637.2	26
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-(2-hydroxy-2-methylpropionyl)-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		665.4	27
N-tert-Butyl-2-[3(S)-[[N-(3-furoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		673.3	28
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(4-pyridyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		684.3	29
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-(2(S)-hydroxypropionyl)-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		651.4	30

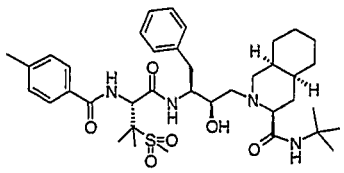
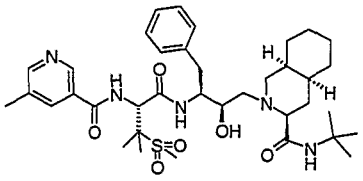
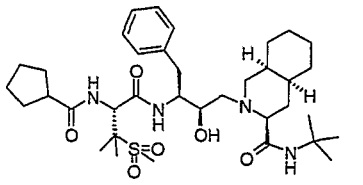
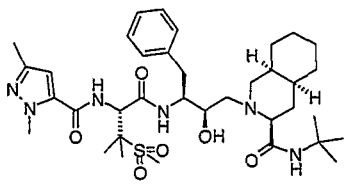
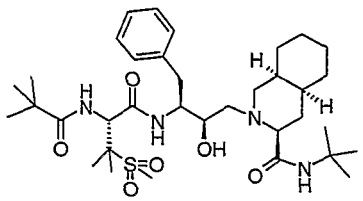
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-(2(R)-hydroxypropionyl)-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		651.3	31
2-[3(S)-[[N-(5-Bromo-2-furoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		751.6	32
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(4,5-dimethyl-2-furoyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		701.6	33
N-tert-Butyl-2-[3(S)-[[N-[5-(trifluoromethyl)-2-furoyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		741.6	34
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(5-methyl-2-thenoyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		703.6	35

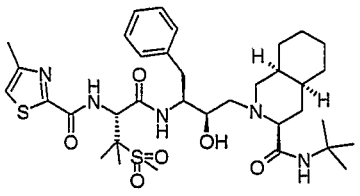
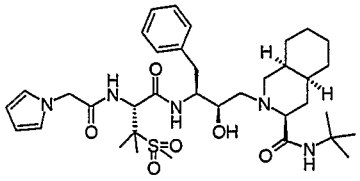
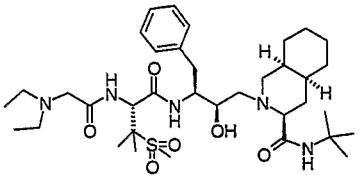
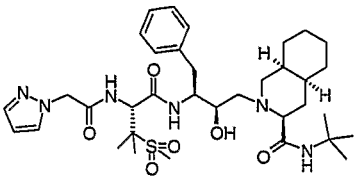
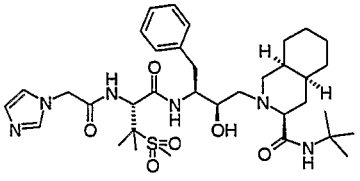
N-tert-Butyl-2-[3(S)-[[N-(5-chloro-2-thenoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		723.4	36
2-[3(S)-[[N-(5-Acetyl-2-thenoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		731.2	37
N-tert-Butyl-2-[3(S)-[[N-(5-tert-butyl-2-thenoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		745.6	38
N-tert-Butyl-2-[3(S)-[[N-(3-cyanobenzoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		708.6	39
N-tert-Butyl-2-[3(S)-[[N-(3-fluorobenzoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		701.4	40

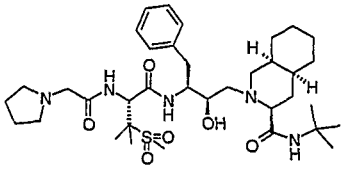
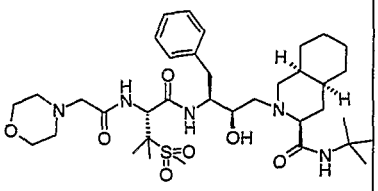
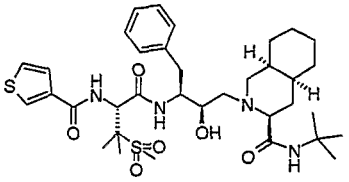
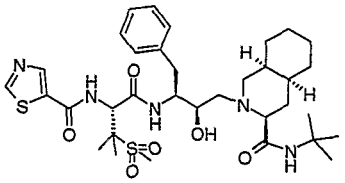
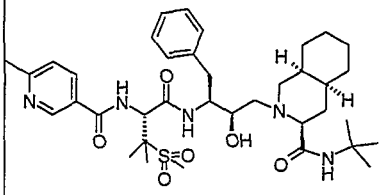
N-tert-Butyl-2-[3(S)-[[N-(4-cyanobenzoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		708.6	41
N-tert-Butyl-2-[3(S)-[[N-(4-fluorobenzyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		701.6	42
N-tert-Butyl-2-[3(S)-[[N-[[6-(trifluoromethyl)-3-pyridyl]carbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		752.8	43
N-tert-Butyl-2-[3(S)-[[N-[(6-cyano-3-pyridyl)carbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		709.6	44
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(1,5-dimethyl-3-pyrazolyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		701.6	45

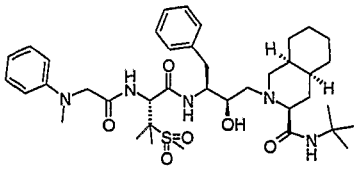
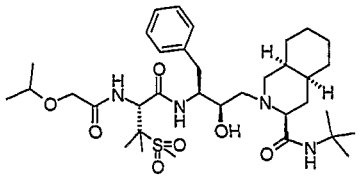
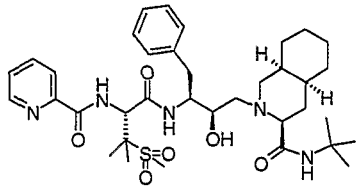
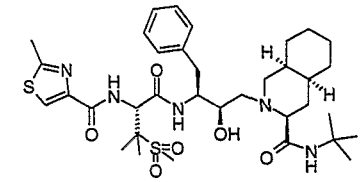
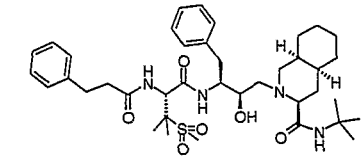
N-tert-Butyl-2-[3(S)-[[N-[(1-tert-butyl-5-methyl-3-pyrazolyl)carbonyl]3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		743.6	46
N-tert-Butyl-2-[3(S)-[[N-(cyclopropylcarbonyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		647.6	47
N-tert-Butyl-2-[3(S)-[[N-(cyclobutylcarbonyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		661.6	48
N-tert-Butyl-2-[3(S)-[[N-(cyclohexylcarbonyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		689.4	49
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[3(S)-[[N-(tetrahydro-3(RS)-furoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-3(S)-isoquinolinecarboxamide (1:1 mixture of diastereoisomers)		677.6	50

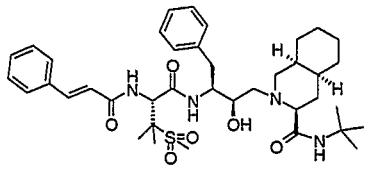
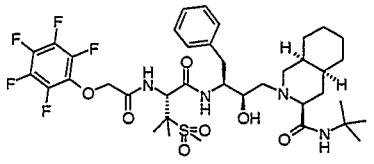
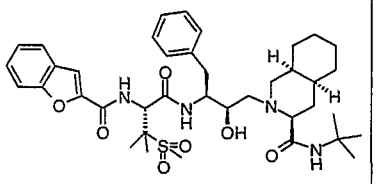
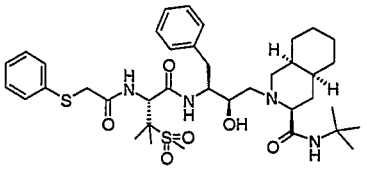
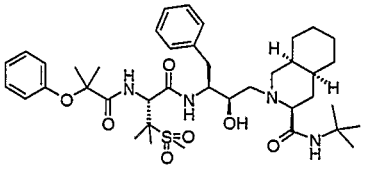
N-tert-Butyl-2-[N-[(2-chloro-6-methyl-4-pyridyl)carbonyl]-3(S)-[[3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		732.4	51
N-tert-Butyl-2-[3(S)-[[N-[(2-chloro-4-pyridyl)carbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		718.4	52
N-tert-Butyl-2-[N-(2-furoyl)-3(S)-[[3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		673.8	53
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(3-methylbenzoyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		697.6	54
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(4-methoxybenzoyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		701.6	55

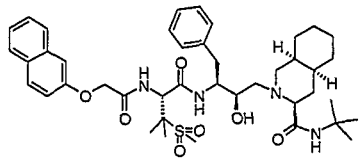
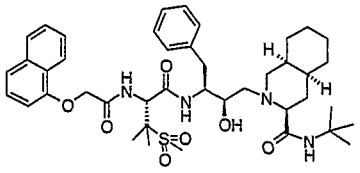
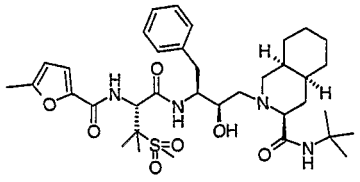
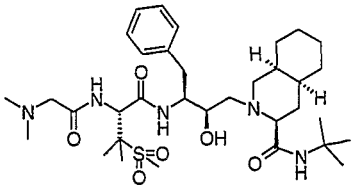
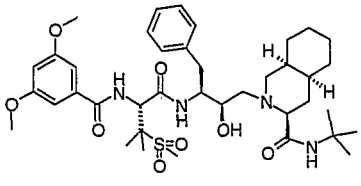
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(4-methylbenzoyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		697.6	56
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(5-methyl-3-pyridyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		698.6	57
N-tert-Butyl-2-[3(S)-[[N-(cyclopentylcarbonyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		675.5	58
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(2,5-dimethyl-3-pyrazolyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		701.6	59
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-pivaloyl-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		663.4	60

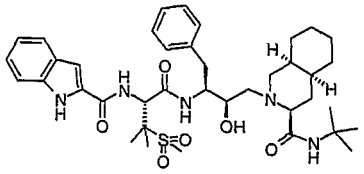
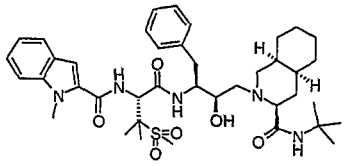
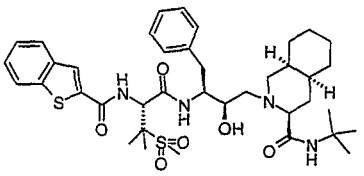
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(4-methyl-2-thiazolyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		704	61
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-3-methyl-N-[2-(1-pyrrolyl)acetyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		686.2	62
N-tert-Butyl-2-[3(S)-[[N-[2-(diethylamino)acetyl]-3-(methanesulfonyl)-3-methyl-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro3(S)-isoquinolinecarboxamide		692.3	63
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-3-methyl-N-[2-(1-pyrazolyl)acetyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		687.3	64
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-[2-(1-imidazolyl)acetyl]-3-(methanesulfonyl)-3-methyl-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		687.2	65

N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[2-(1-pyrrolidinyl)acetyl]-L-valyl]amino]-4-phenylbutyl-3(S)-isoquinolinecarboxamide		690.3	66
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(2-morpholinoacetyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		706.2	67
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(3-thenoyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		689.2	68
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(5-thiazolyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		690.3	69
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(6-methyl-3-pyridyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		698.3	70

N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[N-methyl-N-phenylglycyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		726.4	71
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-(2-isopropoxyacetyl)-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		679.3	72
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(2-pyridyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		684.3	73
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(2-methyl-4-thiazolyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		704	74
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(3-phenylpropionyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		711.4	75

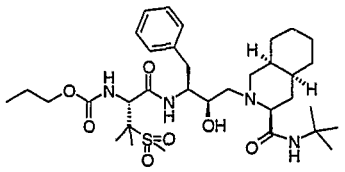
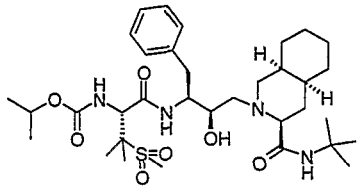
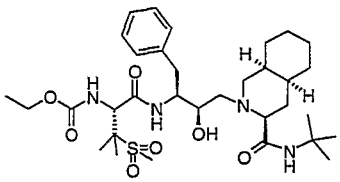
(E)-N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(3-phenylacryloyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		709.4	76
N-tert-Butyl-2-[3(S)-[[N-[2-(pentafluorophenoxy)acetyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		803.3	77
2-[3(S)-[[N-[[(2-Benzofuryl)carbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		723.4	78
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[2-(phenylthio)acetyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		729.4	79
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(2-methyl-2-phenoxypropionyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		741.4	80

N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[2-(2-naphthyloxy)acetyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		763.4	81
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[2-(1-naphthyloxy)acetylamino]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		763.4	82
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(5-methyl-2-furoyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		687.5	83
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[2-[2-(dimethylamino)acetyl]-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		664.5	84
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(3,5-dimethoxybenzoyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		743.4	85

N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-N-[(2-indolyl)carbonyl]-3(S)-[[3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		722.4	86
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[-3-(methanesulfonyl)-N-[1-methyl-2-indolyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		736.4	87
2-[3(S)-[[N-[(1-Benzothiophen-2-yl)carbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		739.3	88

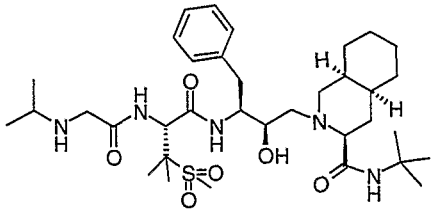
In a manner analogous to that described for Example 4 the compounds in Table 3 were prepared starting from N-tert-butyl-2-[3(S)-[[N-[(9-fluorenyl)methoxycarbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide and commercially available chloroformates.

Table 3

name	structure	$[M+H]^+$	Ex. No.
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(propoxycarbonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		665.3	89
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-(isopropoxycarbonyl)-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		665.3	90
N-tert-Butyl-2-[3(S)-[[N-(ethoxycarbonyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		651.3	91

Example 92

N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-[2-(isopropylamino)acetyl]-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide



A solution of 0.123g of 2-[3(S)-[[N-[N-(benzyloxycarbonyl)-N-isopropylglycyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide in 30ml of ethanol was treated with 10% palladium on carbon and hydrogenated under a hydrogen atmosphere overnight.

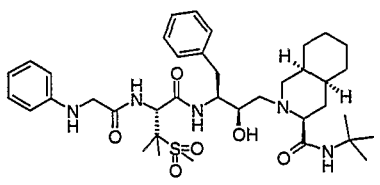
The catalyst was removed by filtration and the volatiles evaporated under reduced pressure to give a colourless glass which was chromatographed on silica eluting with dichloromethane/methanol (25:1) followed by dichloromethane/methanol (10:1) to give an oil. The oil was triturated with petroleum ether/ether (bp 40-60°C) to give 29mg of N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-[2-(isopropylamino)acetyl]-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide as a white solid, $[M+H]^+$ 678.5.

The starting material was prepared as follows:

A solution of 1.04ml (7.6mmol) of glycine tert-butyl ester and 0.11ml (8.38mmol) of acetone in 30ml of ethanol was treated with 10% palladium on carbon (Fluka) and hydrogenated under a hydrogen atmosphere overnight. The catalyst was removed by filtration and the volatiles evaporated under reduced pressure to give 1.08g (82%) a cloudy mobile oil which was treated at 0°C with 7ml of trifluoroacetic acid and allowed to warm to room temperature. After 5 hours the volatiles were evaporated to give 2.65g of a pale yellow oil, a 1.44g portion of which was dissolved in 10ml of 2M sodium hydroxide solution at 0°C and treated simultaneously with 0.89ml (6.23mmol) of benzyl chloroformate and 10ml of 2M sodium hydroxide solution. The reaction mixture was allowed to warm to room temperature overnight and was washed with ether. The solution was acidified and extracted with ethyl acetate and the combined organic phase was washed with water, dried over magnesium sulfate and evaporated under reduced pressure to give 0.338g of N-(benzyloxycarbonyl)-N-isopropylglycine as a colourless oil. A 0.043g portion of the oil was reacted with 0.1g (1.73mmol) of N-tert-butyl-1,2,3,4,4a(S),5,5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide in a manner analogous to that described for Example 2 to give 0.123g of 2-[3(S)-[[N-[N-(benzyloxycarbonyl)-N-isopropylglycyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide as a yellow glass.

Example 93

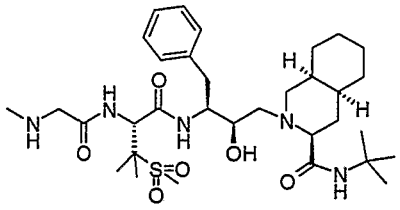
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(N-phenylglycyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide



Example 93, $[M+H]^+$ 712.5, was prepared in a manner analogous to that described for Example 92 starting from N-phenylglycine (Aldrich 33,046-9).

Example 94

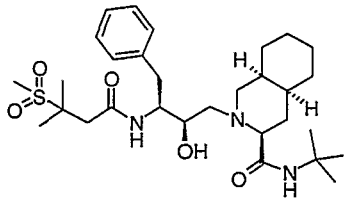
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(N-methylglycyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide



Example 94, $[M+H]^+$ 650.4, was prepared in a manner analogous to that described for Example 92 starting from N-(benzyloxycarbonyl)sarcosine (Bachem C-2570) but omitting the protection step in the preparation of the starting material.

Example 95

N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-1-[2(R)-hydroxy-3(S)-[3-(methanesulfonyl)butyramido]-4-phenylbutyl]-2(S)-piperazinecarboxamide



3-(Methanesulfonyl)-3-methylbutyric acid was reacted with 2-(3(S)-amino-2(R)-hydroxy-4-phenylbutyl)-N-tert-butyl-1,2,3,4,4a(S),4,5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide in a manner analogous to that described for Example 2 to give the product as a white solid, mp 95-110°C (foams), $[M+H]^+$ 564.3.

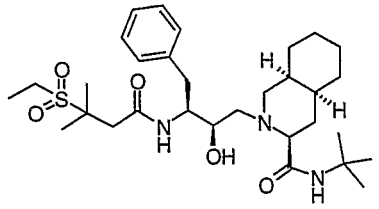
The starting material 3-(methanesulfonyl)-3-methylbutyric acid was prepared as follows:

A stirred solution of 0.81g (6mmol) of 3-mercapto-3-methylbutanoic acid, prepared from 3,3-dimethylacrylic acid (Aldrich D13,860-6) according to the method described by G. Pattenden et al, J. Chem. Soc. Perkin Trans. 1, 1992, 10, 1215-21, in 25ml of dioxane/water (3:2) was treated with 4.14g (30mmol) of potassium carbonate in 5ml of water followed by 1.14g (8mmol) of iodomethane.

After 4 hours the volatiles were evaporated and water added. The aqueous phase was extracted with ether and then acidified. The acidified aqueous phase was then extracted with ether and the organic phase dried over magnesium sulfate and evaporated under reduced pressure to give 0.57g (64%) of 3-methyl-3-(methylthio)butyric acid as a pale orange oil. The oil was dissolved in 12ml of water containing 188mg (4.63mmol) of sodium hydroxide and treated with 2.59g (31mmol) of sodium hydrogen carbonate and 4ml of acetone, followed by 3.16g (5.13mmol) of OXONE® (Aldrich 17,798-9) dissolved in 12ml of 0.0004M EDTA solution by dropwise addition. After 2 hours, 2g of sodium metabisulfite in 4ml of water was added and the solution stirred for 15 minutes. The solution was acidified to pH 2 and extracted with ethyl acetate. The organic phase was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure to give 585mg of a colourless oil, $[M+H]^+$ 181 (Cl $^{+ive}$),

Example 96

2-[3(S)-[3-(Ethanesulfonyl)-3-methylbutyramido]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide

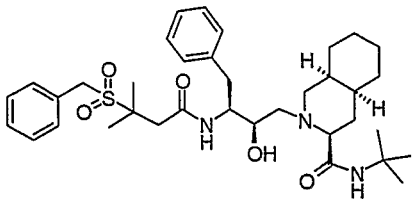


Example 96, $[M+H]^+$ 578.2, was prepared in a manner analogous to that described for Example 2 by reacting 3-(ethanesulfonyl)-3-methylbutyric acid with 2-(3(S)-amino-2(R)-hydroxy-4-phenylbutyl)-N-tert-butyl-1,2,3,4,4a(S),4,5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide.

The starting material 3-(ethanesulfonyl)-3-methylbutyric acid was prepared in a manner analogous to that described for the preparation of 3-(methanesulfonyl)-3-methylbutyric acid, the starting material usedfor Example 95, using iodoethane in place of iodomethane.

Example 97

2-[3(S)-[3-(Benzenesulfonyl)-3-methylbutyramido]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide

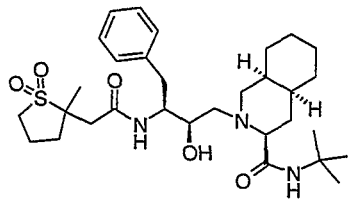


Example 97, $[M+H]^+$ 640, was prepared in a manner analogous to that described for Example 2 by reacting 3-(benzylsulfonyl)-3-methylbutyric acid with 2-(3(S)-amino-2(R)-hydroxy-4-phenylbutyl)-N-tert-butyl-1,2,3,4,4a(S),4,5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide.

The starting material 3-(benzylsulfonyl)-3-methylbutyric acid was prepared from 3-(benzylthio)-3-methylbutyric acid (G. Pattenden et al, J. Chem. Soc., Perkin Trans. 1, 1992, 10, 1215-21 in a manner analogous to that described in the preparation of the starting material for Example 95.

Example 98

N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[3(S)-[[N-[2-(tetrahydro-2(RS)-methyl-1,1-dioxo-2-thienyl)acetyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-3(S)-isoquinolinecarboxamide (mixture of diastereoisomers)

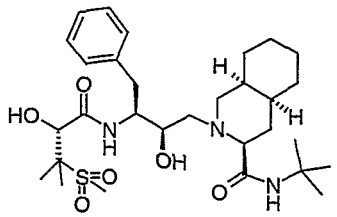


Example 98, $[M+H]^+$ 576.3, was prepared in a manner analogous to that described for Example 2 by reacting tetrahydro-2(RS)-methyl-2-thiopheneacetic acid S,S-dioxide with 2-(3(S)-amino-2(R)-hydroxy-4-phenylbutyl)-N-tert-butyl-1,2,3,4,4a(S),4,5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide.

The starting material tetrahydro-2(RS)-methyl-2-thiopheneacetic acid S,S-dioxide was prepared from tetrahydro-2-methyl-thiopheneacetic acid (R.A. Bunce et al, J. Org. Chem. 1992, 57(6), 1727-33) in a manner analogous to that described in the preparation of the starting material for Example 95.

Example 99

N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[2(R)-hydroxy-3-(methanesulfonyl)-3-methylbutyramido]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide



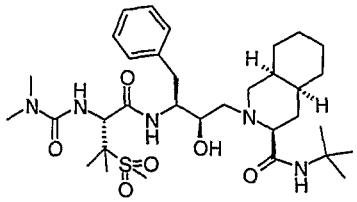
Example 99, $[M+H]^+$ 580.4, was prepared in a manner analogous to that described for Example 2 by reacting 2(R)-Hydroxy-3-(methanesulfonyl)-3-methylbutyric acid with 2-(3(S)-amino-2(R)-hydroxy-4-phenylbutyl)-N-tert-butyl-1,2,3,4,4a(S),4,5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide.

The starting material 2(R)-hydroxy-3-(methanesulfonyl)-3-methylbutyric acid was prepared as follows:

A stirred solution of 2.25g (5.3mmol) of the protected amino acid from example 1 part (B), in 20ml dry dimethylformamide was treated with 1.1ml (11mmol) piperidine. After 1 hour the volatiles were evaporated and the residue triturated with ether followed by ethyl acetate to give 1g of a gum which was dissolved in 8ml of 10%v/v sulfuric acid and heated to 50°C. 1.3g of sodium nitrite in 3ml of water was added dropwise and, after 30 minutes, a further 0.7g of sodium nitrite in 2ml of water was added. The reaction mixture was cooled and extracted with ethyl acetate and the combined organic phase was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure to give 200mg of 2(R)-hydroxy-3-(methanesulfonyl)-3-methylbutyric acid as a gum.

Example 100

N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-(dimethylcarbamoyl-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide

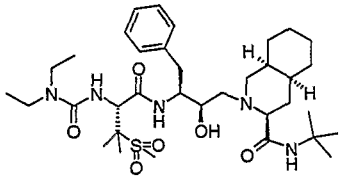
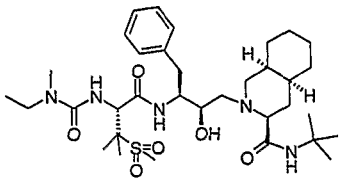
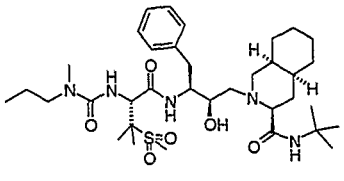


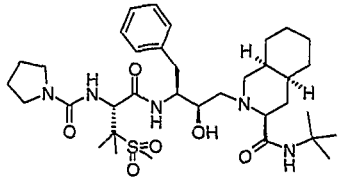
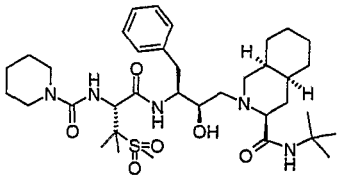
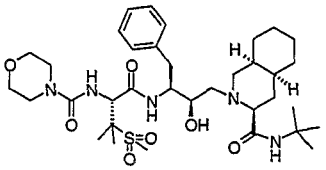
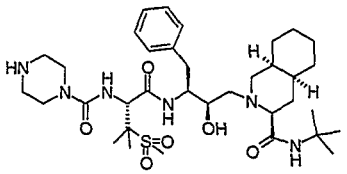
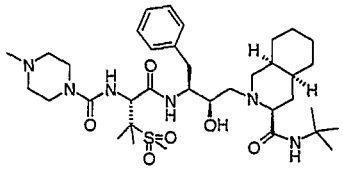
A stirred solution of 0.4g (0.5mmol) of N-tert-butyl-2-[3(S)-[[N-[(9-fluorenyl)methoxycarbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide in 10ml dry dimethylformamide at room temperature was treated with 1ml (10mmol) of piperidine. After 1 hour the volatiles were evaporated and the residue triturated with hexane to give N-tert-butyl-1,2,3,4,4a(S),5,5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide as a gum which was dissolved in 5ml of acetonitrile and treated with 100mg (0.5mmol) of p-nitrophenylchloroformate (Aldrich 16,021-0) followed by 84mg (1mmol) of solid sodium hydrogen carbonate. After 15 minutes, 0.25ml of 2M dimethylamine in tetrahydrofuran (Aldrich 39,195-6) and 0.14ml of triethylamine were added and the reaction mixture was stirred for 2 hours. The volatiles were evaporated

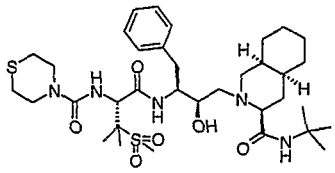
under reduced pressure and the residue was partitioned between water and dichloromethane and the aqueous phase extracted with dichloromethane. The combined organic phase was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give an oil which was chromatographed on silica eluting with dichloromethane/methanol (19:1) to give 62mg (20%) of N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-(dimethylcarbamoyl-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide as a white solid, $[M+H]^+$ 650.4.

In a manner analogous to that described for Example 100, starting from N-tert-butyl-2-[3(S)-[[N-[(9-fluorenyl)methoxycarbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide the compounds shown in Table 4 were also prepared. Other reagents used in the synthesis of the compounds in Table 4 were obtained from commercial sources such as Aldrich and Lancaster.

Table 4

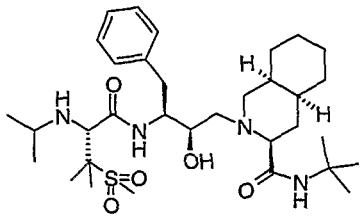
Name	Structure	$[M+H]^+$	Ex. No.
N-tert-Butyl-2-[3(S)-[[N-(diethylcarbamoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		678.4	101
N-tert-Butyl-2-[3(S)-[[N-(N-ethyl-N-methylcarbamoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		664.3	102
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(N-methyl-N-propylcarbamoyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		678.3	103

N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(1-pyrrolidinyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		676.3	104
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(piperidinocarbonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		690.3	105
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(morpholinocarbonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		692.2	106
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(1-piperazinyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		691.3	107
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(4-methyl-1-piperazinyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		705.3	108

N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[3(S)-[[N-[(tetrahydro-1,4-thiazin-4-yl)carbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		708	109

Example 110

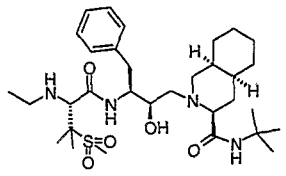
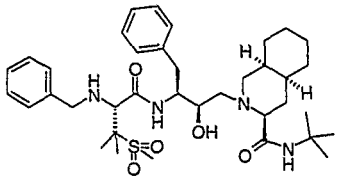
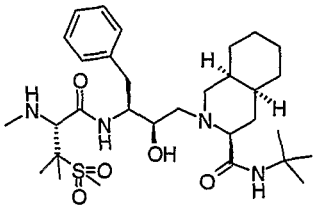
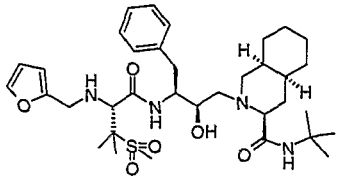
N-tert-Butyl-1,2,3,4,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-isopropyl-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide

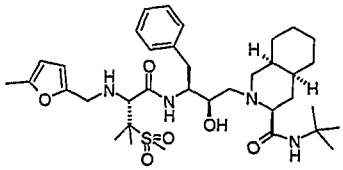
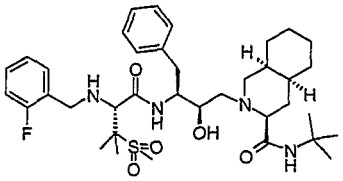
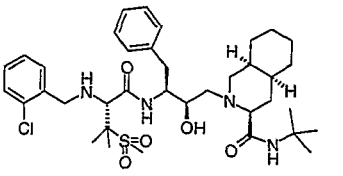
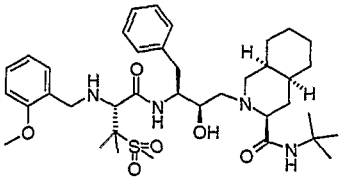
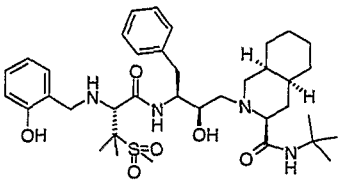


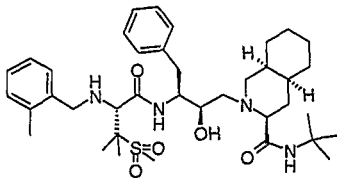
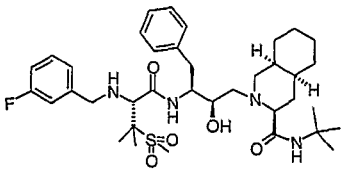
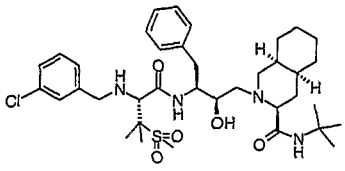
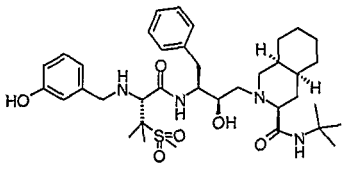
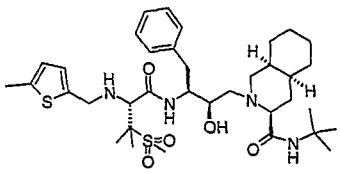
A stirred solution of 0.4g (0.5mmol) of N-tert-butyl-2-[3(S)-[[N-[(9-fluorenyl)methoxycarbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide in 10ml dry dimethylformamide at room temperature was treated with 1ml (10mmol) of piperidine. After 1 hour the volatiles were evaporated and the residue triturated with hexane to give N-tert-butyl-1,2,3,4,4a(S),5,5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide as a gum which was dissolved in 8ml dichloroethane and treated under nitrogen with 0.037ml (0.5mmol) of acetone, 0.028ml (0.5mmol) glacial acetic acid and 160mg (0.75mmol) sodium triacetoxyborohydride. The reaction mixture was stirred overnight and the volatiles were then evaporated. The residue was partitioned between dichloromethane and water and extracted with dichloromethane. The combined organic phase was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give a gum which was chromatographed on silica eluting with ethyl acetate/hexane (4:1) and then triturated with hexane to give 127mg (41%) of N-tert-butyl-1,2,3,4,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-isopropyl-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide as a white solid. $[M+H]^+$ 621.3

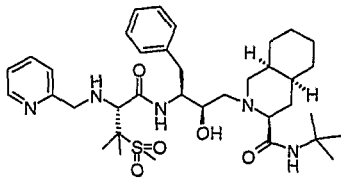
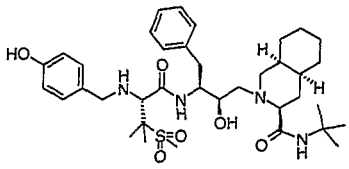
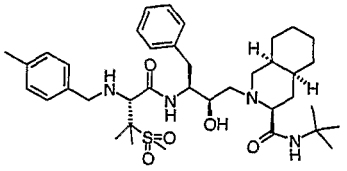
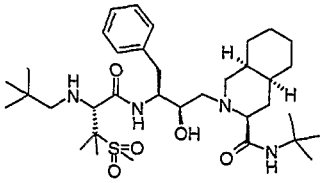
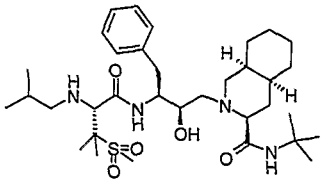
In a manner analogous to that described for example 110, starting from N-tert-butyl-2-[3(S)-[[N-[(9-fluorenyl)methoxycarbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide the compounds shown in Table 5 were also prepared. Other reagents used in the synthesis of the compounds in Table 5 were obtained from commercial sources such as Aldrich, Lancaster and Maybridge Int, for example e.g. furfural (example 114) and 2-fluorobenzaldehyde (example 116) were purchased from Aldrich, cat. nos.(31,991-0), (F480-7), 4(5)-formyl-2-methylimidazole (example 134) was purchased from Maybridge Int. (SB 01361)

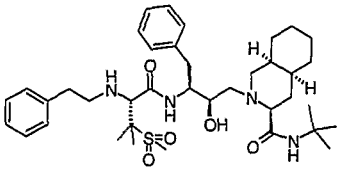
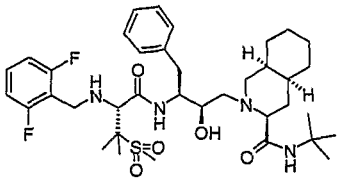
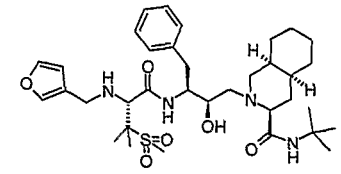
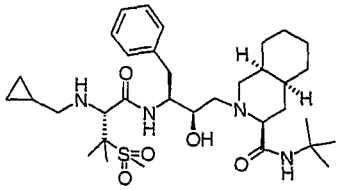
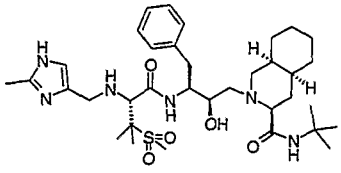
Table 5

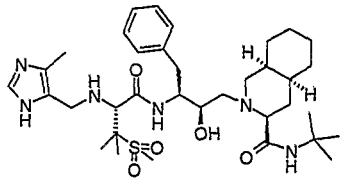
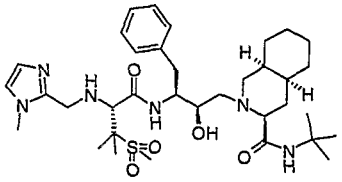
name	structure	$[M+H]^+$	Ex. No.
N-tert-Butyl-2-[3(S)-[[N-ethyl-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		607.3	111
2-[3(S)-[[N-Benzyl-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		669.3	112
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-methyl-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		593.2	113
N-tert-Butyl-2-[3(S)-[[N-(2-furfuryl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		659.2	114

N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(5-methyl-2-furfuryl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		673.3	115
N-tert-Butyl-2-[3(S)-[[N-(2-fluorobenzyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		687.2	116
N-tert-Butyl-2-[3(S)-[[N-(2-chlorobenzyl)-3-(methanesulfonyl)-L-valyl]amino]-3(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		703.2	117
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(2-methoxybenzyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		699.2	118
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-(2-hydroxybenzyl)-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		685.2	119

N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(2-methylbenzyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		683.3	120
N-tert-Butyl-2-[3(S)-[[N-(3-fluorobenzyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		687.2	121
N-tert-Butyl-2-[3(S)-[[N-(3-chlorobenzyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		703.2	122
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-(3-hydroxybenzyl)-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		685.3	123
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(5-methyl-2-thenyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		689.2	124

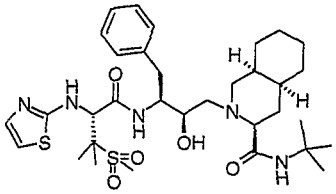
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(2-pyridyl)methyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		670.3	125
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-(4-hydroxybenzyl)-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		685.2	126
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(4-methylbenzyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		683.3	127
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(2,2-dimethylpropyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		649.3	128
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-isobutyl-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		635.2	129

N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(2-phenylethylyl))-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		683.3	130
N-tert-Butyl-2-[3(S)-[[N-(2,6-difluorobenzyl)-3-(methanesulfonyl)-N-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		705.2	131
N-tert-Butyl-2-[3(S)-[[N-(3-furfuryl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		659.2	132
N-tert-Butyl-2-[3(S)-[[N-(cyclopropylmethyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		633.3	133
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(2-methyl-4-imidazolyl)methyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		673.3	134

N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(5-methyl-4-imidazolyl)methyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		673.3	135
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(1-methyl-2-imidazolyl)methyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		673.3	136

Example 137

N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(2-thiazolyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide



A stirred solution of 255mg (0.4mmol) of N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(thiocarbamoyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide in 5ml of ethanol was treated with 0.1ml of chloroacetaldehyde (50% solution in water) and heated at reflux for 4 hours. The volatiles were evaporated and the residue partitioned between dichloromethane and saturated aqueous sodium hydrogen carbonate. The aqueous phase was extracted with dichloromethane and the combined organic phase was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give a solid which was chromatographed on silica eluting with dichloromethane/methanol (19:1) to give 100mg (38%) of N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(2-thiazolyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide as a white solid, $[M+H]^+$ 662.2.

The starting material N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(thiocarbamoyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide was prepared as follows:

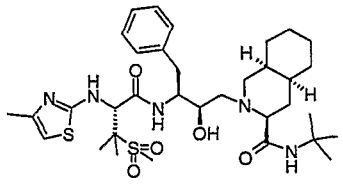
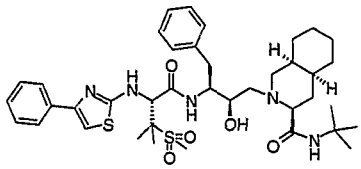
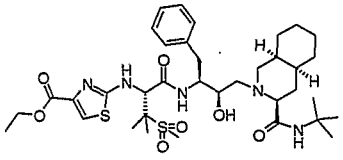
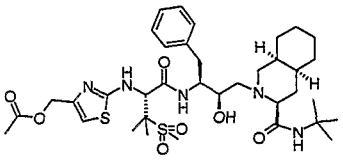
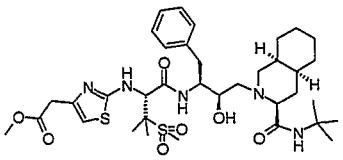
(A) A stirred solution of 1.6g (2mmol) of N-tert-butyl-2-[3(S)-[[N-[(9-fluorenyl)methoxycarbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide in 40ml of dry dimethylformamide at room temperature was treated with 4ml (40mmol) of piperidine. After 1 hour the volatiles were evaporated and the residue triturated with hexane to give N-tert-butyl-1,2,3,4,4a(S),5,5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide as a gum which was dissolved in 5ml of acetone and treated with 0.28ml (2.1mmol) of benzoyl isothiocycanate (Aldrich 26,165-3). The stirred reaction mixture was heated at reflux for 4 hours and then cooled. The volatiles were evaporated under reduced pressure and the residue was triturated with hexane to give a gum which was then chromatographed on silica eluting with ethyl acetate/hexane (2:1) to give 765mg (52%) of 2-[3(S)-[[N-(benzoylthiocarbamoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide as a fawn foam, $[M+H]^+$ 742.3, which was combined with another batch of material and used in the next step.

(B) A stirred solution of 850mg (1.15mmol) of 2-[3(S)-[[N-(benzoylthiocarbamoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide from (A) above, in 6ml of methanol/acetone (1:1) was treated with 115mg (1.15mmol) of potassium hydrogen carbonate and 0.5ml of water. After 5 hours 1ml of acetic acid was added and the mixture stirred for a further 10 minutes.

The volatiles were evaporated under reduced pressure and the remaining water was removed by repeated re-evaporation with ethanol to give a gummy oil which was chromatographed on silica eluting with dichloromethane/methanol (19:1) to give 710mg (97%) of N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(thiocarbamoyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide as a white foam, $[M+H]^+$ 638.

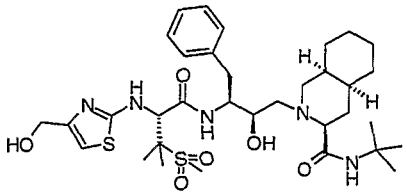
In a manner analogous to that described for Example 137, starting from N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(thiocarbamoyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide, the compounds shown in Table 6 were also prepared. Other reagents were obtained from commercial sources.

Table 6

Name	Structure	$[M+H]^+$	Ex. No.
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(4-methyl-2-thiazolyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		676	138
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(4-phenyl-2-thiazolyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		738	139
N-tert-Butyl-2-[3(S)-[[N-[4-(ethoxycarbonyl)-2-thiazolyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro3(S)-isoquinolinecarboxamide		734	140
2-[3(S)-[[N-[4-(Acetoxymethyl)-2-thiazolyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		734	141
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[4-[(methoxycarbonyl)methyl]-2-thiazolyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		734	142

Example 143

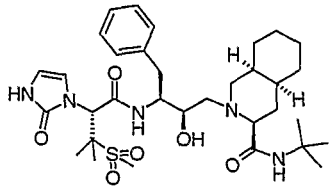
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-[4-(hydroxymethyl)-2-thiazolyl]-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide



A stirred solution of 73mg (0.1mmol) of 2-[3(S)-[[N-[4-(acetoxymethyl)-2-thiazolyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide (Example 141) in 7ml of methanol/water (5:2) was treated with 700mg of potassium carbonate. After 1.5 hours the volatiles were evaporated and the residue partitioned between ethyl acetate and water. The aqueous phase was extracted with ethyl acetate and the combined organic phase was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give a gum which was chromatographed on silica eluting with dichloromethane/methanol (40:3) to give 32mg (48%) of N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-[4-(hydroxymethyl)-2-thiazolyl]-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide as a solid, mp 126°C,$[M+H]^+$ 692.

Example 144

N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[3(S)-[2(R)-(2,3-dihydro-2-oxo-1H-imidazol-2-yl)-3-(methanesulfonyl)-3-methylbutyramido]-2(R)-hydroxy-4-phenylbutyl]-3(S)-isoquinolinecarboxamide

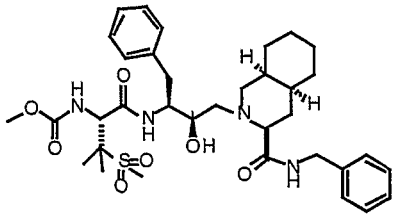


A stirred solution of 0.578g (1mmol) of N-tert-butyl-1,2,3,4,4a(S),5,5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide was dissolved in 20ml of acetonitrile and treated with 201mg (1mmol) of p-nitrophenyl chloroformate followed by 168mg (21mmol) of sodium hydrogen

carbonate. After 15 minutes, 0.11ml of aminoacetaldehyde dimethyl acetal (Lancaster 7520) and 0.28ml (2mmol) of triethylamine were added and the reaction mixture was stirred for 2 hours. The volatiles were evaporated under reduced pressure and the residue partitioned between water and dichloromethane. The aqueous phase was extracted with dichloromethane and the combined organic phase was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give a yellow gum which was triturated with hexane followed by ethyl acetate to give 466mg (66%) of a cream solid mp 228-30°C, $[M+H]^+$ 710. 420mg (0.59mmol) Of the solid was dissolved in 20ml of acetone and treated with 5ml of 10% hydrochloric acid solution and stirred overnight. The solution was treated with saturated sodium hydrogen carbonate solution and partially evaporated. The solution was extracted with dichloromethane and the combined organic phase washed with brine, dried over magnesium sulfate and evaporated to give a cream solid which was chromatographed on silica eluting with dichloromethane/methanol (38:1) to give 50mg (13%) of N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[3(S)-[2(R)-(2,3-dihydro-2-oxo-1H-imidazol-2-yl)-3-(methanesulfonyl)-3-methylbutyramido]-2(R)-hydroxy-4-phenylbutyl]-3(S)-isoquinolinecarboxamide as a white solid, $[M+H]^+$ 646.

Example 145

N-Benzyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(methoxycarbonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide



A solution of 0.13ml (1.2mmol) of benzylamine in 5ml of dichloromethane was treated with 0.6ml of trimethylaluminium (2M in toluene) and stirred at room temperature for 15 minutes. A solution of 68mg of the lactone N1-[1(S)-(1,3,4,6,6a(S),7,8,9,10,10a(S),11,11a(S)-dodecahydro-1-oxo-1,4-oxazino[4,3-b]isoquinolin-3(R)-yl)-2-phenylethyl]-3-(methanesulfonyl)-N2-(methoxycarbonyl)-L-valinamide, dissolved in 5ml of dichloromethane was added dropwise followed by 5ml of toluene and the solution was stirred overnight. Dilute hydrochloric acid was added dropwise and the solution was extracted with dichloromethane. The combined organic phase was washed with dilute hydrochloric acid and brine, dried over magnesium sulphate and evaporated under reduced pressure to give a residue which was crystallised from dichloromethane/hexane to give 15mg of N-benzyl-

1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(methoxycarbonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide as a white solid, $[M+H]^+$ 671.

The starting material N1-[1(S)-(1,3,4,6,6a(S),7,8,9,10,10a(S),11,11a(S)-dodecahydro-1-oxo-1,4-oxazino[4,3-b]isoquinolin-3(R)-yl)-2-phenylethyl]-3-(methanesulfonyl)-N2-(methoxycarbonyl)-L-valinamide was prepared as follows:

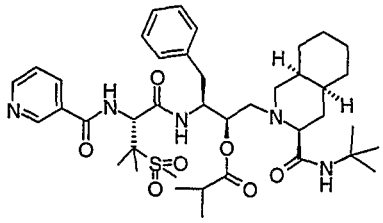
(A) 23.8g (0.1M) of N-tert-butyl-1,2,3,4,4a(S),4,5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide prepared according to known procedures e.g. Martin, Joseph Armstrong; Redshaw, Sally, EP 432695 A2, was suspended in 100ml of 6N hydrochloric acid and stirred at reflux for 23 hours. The reaction mixture was evaporated to dryness to give 23.1g of a white solid which was dissolved in 200ml of water and treated with 30ml of 4N sodium hydroxide solution. The solution was cooled to 4°C and stirred vigorously as 15.5ml (0.11mol) of benzyl chloroformate and 4.4g (0.11mol) of sodium hydroxide in 15ml of water were added simultaneously. The reaction was stirred for a further 1 hour adjusting the pH to pH 9 by the addition of 4N sodium hydroxide and was then warmed to room temperature. After a further 2 hours the solution was diluted with water and extracted with hexane. The aqueous phase was acidified with concentrated hydrochloric acid and extracted with ethyl acetate. The combined organic phase was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure to give 29.6g of a gum which was dissolved in 300ml of ethyl acetate and stirred vigorously as 10.7ml (0.093mol) of cyclohexylamine was added dropwise. A further 200ml of ethyl acetate was added and the mixture stirred overnight and then filtered to give a 28.9g of a solid which was combined with another 10.4g batch of the same material and partitioned between 400ml of ethyl acetate and 250ml of 2N hydrochloric acid. The organic phase was washed with water and brine, dried over magnesium sulfate and evaporated to give a gum. A stirred solution of the gum in 50ml of dichloromethane was treated with a solution of 41.3g (0.18mol) of tert-butyl trichloroacetimidate (Aldrich) in 400ml of cyclohexane followed by 1.9ml of borontrifluoride diethyl etherate (Fluka). The mixture was stirred overnight and sodium hydrogen carbonate was added and the solution filtered after 30 minutes. The volatiles were evaporated to give a gum which was dissolved in 500ml of ethyl acetate and washed with 2N sodium carbonate, water and brine, dried over magnesium sulfate and evaporated under reduced pressure to give 28g of a gum. A solution of 18.8g of the gum in 500ml of ethanol was hydrogenated over 1.9g of 5% palladium on carbon (Fluka). The catalyst was removed by filtration and the volatiles evaporated under reduced pressure to give a white solid which was partitioned between 300ml of methyl tert-butyl ether and 250ml of saturated sodium hydrogen carbonate solution. The organic phase was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure to give 10g (0.042mol) of a pale yellow gum

which was dissolved in 200ml of ethanol. 12.43g (0.042mol) of 2(S)-[1(S)-(Benzyloxyformamido)-2-phenylethyl]oxirane (prepared according to known methods (EP 346847 A2)) was added and the mixture heated at reflux for 10 hours. The volatiles were evaporated and the residue was chromatographed on silica eluting with ethyl acetate/hexane (1:2) to give 19.5g of a cream solid, 1.072g (2.0mmol) of which was dissolved in 5ml glacial acetic acid and treated with 10ml 45% hydrogen bromide in acetic acid and stirred for 1.5 hours. The volatiles were evaporated almost to dryness and the solid filtered and washed with glacial acetic acid followed by ether. The solid was partitioned between ethyl acetate and aqueous sodium carbonate and the organic phase was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure to give 493mg of 3(R)-(1(S)-amino-2-phenylethyl)-3,4,6a(S),7,8,9,10,10a(S),11,11a(S)-decahydro-1,4-oxazino[4,3-b]isoquinolin-1(6H)-one hydrobromide as a white foam, $[M+H]^+$ 329.0.

(B) A stirred suspension of 417mg (1mmol) of N-[(9-fluorenyl)methoxycarbonyl]-3-(methanesulfonyl)-L-valine obtained in example 1 (B) above, in 5ml of tetrahydrofuran was treated with 115mg (1mmol) of N-ethylmorpholine (NEM) and cooled to 0°C under nitrogen. 0.13ml (1mmol) of isobutyl chloroformate was added and the reaction mixture stirred for 15 minutes. A solution of 295mg (0.9mmol) of 3(R)-(1(S)-amino-2-phenylethyl)-3,4,6a(S),7,8,9,10,10a(S),11,11a(S)-decahydro-1,4-oxazino[4,3-b]isoquinolin-1(6H)-one hydrobromide, from (A) above, in 5ml of tetrahydrofuran was added and the solution was allowed to warm to room temperature overnight. The solution was partitioned between ethyl acetate and water and the organic phase was washed with 10% citric acid solution, aqueous sodium hydrogen carbonate and brine, dried over magnesium sulfate and evaporated under reduced pressure to give a yellow gum. The gum was chromatographed on silica eluting with ethyl acetate/hexane (1:1) to give 281mg of a product, $[M+H]^+$ 729, which was dissolved in 5ml of dichloromethane and treated with 1ml of piperidine and stirred at room temperature for 2 hours. The solution was diluted with hexane and filtered and the filtrate evaporated under reduced pressure. The residue was chromatographed on silica eluting with dichloromethane/methanol (19:1) and then crystallised from ether/hexane to give 120mg (0.24mmol) of a white solid, $[M+H]^+$ 506, which was dissolved in 4ml dioxane/water (1:1) and treated with 66mg of potassium carbonate and 0.19ml of methyl chloroformate. The solution was stirred overnight and then partitioned between ethyl acetate and water. The organic phase was washed with aqueous sodium hydrogen carbonate and brine, dried over magnesium sulfate and evaporated under reduced pressure to give the 68mg of N1-[1(S)-(1,3,4,6,6a(S),7,8,9,10,10a(S),11,11a(S)-dodecahydro-1-oxo-1,4-oxazino[4,3-b]isoquinolin-3(R)-yl)-2-phenylethyl]-3-(methanesulfonyl)-N2-(methoxycarbonyl)-L-valinamide as a white solid, $[M+H]^+$ 564.

Example 146

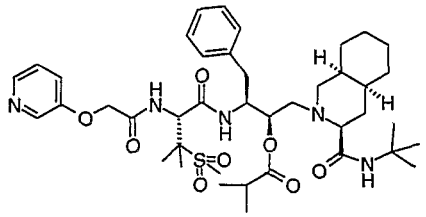
N-tert-Butyl-1,2,3,4,4s(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-(isobutyryloxy)-3(S)-[[3-(methanesulfonyl)-N-[(3-pyridyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide



A solution of 0.15g (0.21mmol) of N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(3-pyridyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide (Example 7) in 1ml of pyridine was treated with 0.092ml (0.21mmol) of isobutyryl chloride at 0°C and allowed to reach room temperature overnight. The volatiles were evaporated and the residue partitioned between dichloromethane and saturated sodium hydrogen carbonate solution. The organic phase was dried over sodium sulfate and evaporated under reduced pressure to give a gum which was chromatographed on silica eluting with dichloromethane/methanol (25:1) and triturated with ether/petroleum ether bp 40-60°C to give 83mg of N-tert-butyl-1,2,3,4,4s(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-(isobutyryloxy)-3(S)-[[3-(methanesulfonyl)-N-[(3-pyridyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide as a white solid, $[M+H]^+$ 754.5.

Example 147

N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-(isobutyryloxy)-3(S)-[[3-(methanesulfonyl)-N-[2-(3-pyridyloxy)acetyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide

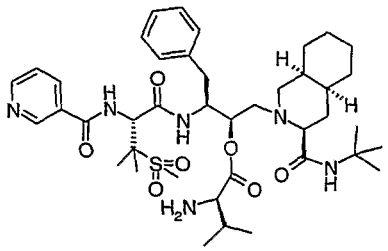


A stirred solution of 190mg (2.66mmol) of N-tert-butyl-1,2,3,4,4a(S),5,6,7,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[2-(3-pyridyloxy)acetyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide (Example 3) and 26mg (2.66mmol) of isobutyric

acid in 3ml of dichloromethane was treated with 36mg (2.92mmol) of 4-(dimethylamino)pyridine (DMAP) and 56mg (2.92mmol) of EDAC.HCl and left at room temperature overnight. A further 26mg of isobutyric acid, 36mg of DMAP and 56mg of EDAC.HCl were added and the reaction stirred for a further 2 hours. The solution was diluted with dichloromethane and the organic phase was washed with saturated sodium hydrogen carbonate solution and brine, dried over magnesium sulfate and evaporated under reduced pressure to give a colourless glass which was chromatographed on silica eluting with dichloromethane/methanol (97:3) to give 153mg of N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-(isobutyryloxy)-3(S)-[[3-(methanesulfonyl)-N-[2-(3-pyridyloxy)acetyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide as a white foam, $[M+H]^+$ 784.6.

Example 148

N-tert-Butyl-1,2,3,4,4a(S),4,5,6,8,8(a)-decahydro-2-[3(S)-[[3-(methanesulfonyl)-N-[(3-pyridyl)carbonyl]-L-valyl]amino]-4-phenyl-2(R)-(L-valyloxy)butyl]-3(S)-isoquinolinecarboxamide

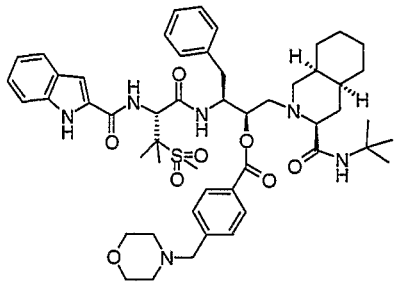


A stirred solution of 150mg (2.19mmol) of N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(3-pyridyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide (Example 7), 61mg (2.41mmol) of carbobenzyloxy-L-valine (BACHEM C-2805) and 33mg (2.41mmol) of HOBT in 2ml of dichloromethane was treated with 0.026ml (2.1mmol) of NEM and 46mg (2.41mmol) of EDAC.HCl. Further equivalent portions of carbobenzyloxy-L-valine, HOBT, NEM and EDAC.HCl were added daily over a period of 11 days. The solution was diluted with dichloromethane and washed with saturated sodium hydrogen carbonate solutionand brine, dried over magnesium sulfate and evaporated under reduced pressure to give an orange gum which was chromatographed on silica eluting with dichloromethane/methanol (97:3) to give 137mg of an off white foam. The foam was dissolved in 20ml of ethanol and treated with 10% palladium on carbon and hydrogenated under a hydrogen atmosphere for 1 hour. The catalyst was removed by filtration and the volatiles were evaporated under reduced pressure to give a white solid which was chromatographed on silica eluting with

dichloromethane/methanol (47:2) and triturated with ether/petroleum ether bp 40-60°C to give 14mg of N-tert-butyl-1,2,3,4,4a(S),4,5,6,8,8(a)-decahydro-2-[3(S)-[[3-(methanesulfonyl)-N-[(3-pyridyl)carbonyl]-L-valyl]amino]-4-phenyl-2(R)-(L-valyloxy)butyl]-3(S)-isoquinolinecarboxamide as a white solid, $[M+H]^+$ 783.5.

Example 149

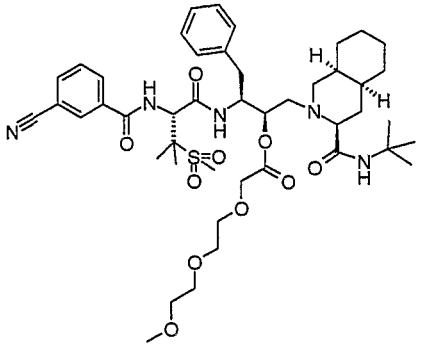
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[3(S)-[[N-[(2-indolyl)carbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-[4-(morpholinomethyl)benzoyloxy]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide



Example 159, $[M+H]^+$ 925.6, was prepared in a manner analogous to Example 157 starting from N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-N-[(2-indolyl)carbonyl]-3(S)-[[3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide (Example 86) and 4-(morpholinomethyl)benzoic acid which was prepared according to the method described by H. Bundgaard et al, J. Med. Chem. 1989, 32, 2503.

Example 150

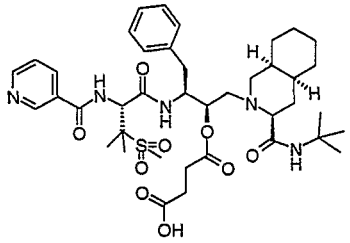
N-tert-Butyl-2-[3(S)-[[N-(3-cyanobenzoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-[2-[2-(2-methoxyethoxy)ethoxy]acetoxy]-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide



Example 160, $[M+H]^+$ 868.5, was prepared in a manner analogous to Example 147 starting from N-tert-butyl-2-[3(S)-[[N-(3-cyanobenzoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide (Example 39) and 2-[2-(2-methoxyethoxy)ethoxy]acetic acid (Aldrich 40,7000-3).

Example 151

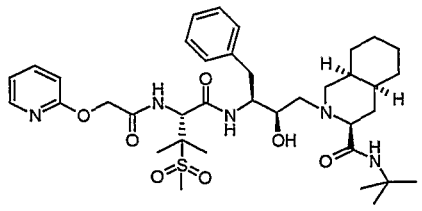
N-tert-Butyl-2-[2(R)-(3-carboxypropionyloxy)-3(S)-[[3-(methanesulfonyl)-N-[(3-pyridyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)decahydro-3(S)-isoquinolinecarboxamide



A solution of 68mg (0.1mmol) of N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(3-pyridyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide (example 7) in 10ml of tetrahydrofuran was treated with 10mg (1mmol) of succinic anhydride (Aldrich 23,960-0) and heated at reflux overnight. The volatiles were evaporated under reduced pressure and the residue chromatographed on silica eluting with dichloromethane/methanol (19:1) to give 53mg of N-tert-butyl-2-[2(R)-(3-carboxypropionyloxy)-3(S)-[[3-(methanesulfonyl)-N-[(3-pyridyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)decahydro-3(S)-isoquinolinecarboxamide as a foam, $[M+H]^+$ 784.5.

Example 152

N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[2-(2-pyridyloxy)acetyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide

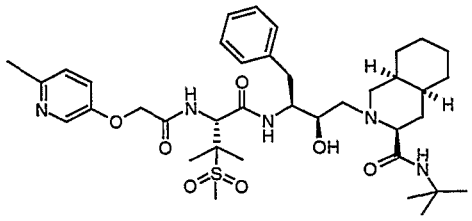


Example 152, $[M+H]^+$ 714 was prepared in a manner analogous to that described in Example 2 but starting from 2-(2-pyridyloxy)acetic acid.

The starting material 2-(2-pyridyloxy)acetic acid was prepared by methods described in the art. For example following the methods of Hill and Mc Graw, J. Org.Chem., 1949, 14, 783-787 and Maas et al, Red. Trav. Chim. Pays-Bas, 1955, 74, 175 - 179.

Example 153

N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[2-(6-methyl-3-pyridyloxy)acetyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide



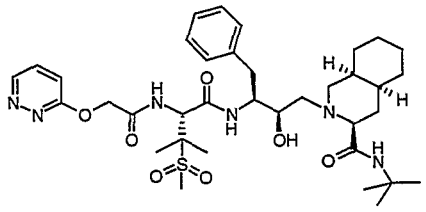
Example 153, $[M+H]^+$ 728 was prepared in a manner analogous to that described in Example 2 but starting from 2-(6-methyl-3-pyridyloxy)acetic acid hydrobromide.

The starting material 2-(6-methyl-3-pyridyloxy)acetic acid hydrobromide was prepared as follows:

1.09g (0.01mol) of 3-hydroxy-6-methylpyridine was added to a stirred suspension of 440mg sodium hydride (60% dispersion in mineral oil) in 20ml of dry dimethylformamide at 0°C under nitrogen. After effervescence had subsided 1.94g (0.01mol) of tert-butyl bromoacetate was added dropwise and the solution stirred overnight. The volatiles were evaporated and the residue partitioned between dichloromethane and 10% citric acid solution. The organic phase was washed with saturated sodium hydrogen carbonate and brine. The combined organic phase was dried over magnesium sulfate and evaporated under reduced pressure to give 1.8g of a gum, $[M+H]^+$ 224 which was treated with 3ml of 45% hydrobromic acid in acetic acid at 0°C. 5ml of acetic acid was added and the suspension was stirred overnight. The volatiles were evaporated and the residue was triturated with petroleum ether bp 40-60°C to give 1.5g of 2-(6-methyl-3-pyridyloxy)acetic acid hydrobromide as a fawn solid.

Example 154

N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[2-(3-pyrazinyloxy)acetyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide



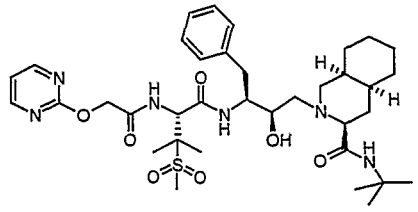
Example 154, $[M+H]^+$ 715 was prepared in a manner analogous to that described in Example 2 but starting from 2-(3-pyrazinyloxy)acetic acid trifluoroacetate.

The starting material 2-(3-pyrazinyloxy)acetic acid trifluoroacetate was prepared as follows:

A stirred suspension of 88mg (2.2mmol) sodium hydride (60% dispersion in mineral oil) in 5ml of dry dimethylformamide at -5°C under nitrogen was treated with 264mg (2mmol) tert-butylglycolate. After 10 minutes 298mg (2mmol) of 3,6-dichloropyridazine (Aldrich D7, 320-0) was added and the solution was allowed to warm to room temperature and was stirred overnight. The volatiles were evaporated under reduced pressure and the residue was chromatographed on silica eluting with ethyl acetate/hexane (1:2) to give 210mg of a gum that was dissolved in 20ml of ethanol and treated with 10% palladium on carbon (Fluka) and hydrogenated under a hydrogen atmosphere overnight. The catalyst was removed by filtration and the volatiles were evaporated under reduced pressure to give a gum that was chromatographed on silica eluting with ethyl acetate/hexane (1:2) followed by ethyl acetate to give 50mg of a gum $[M+H+MeCN]^+$ 252. The gum was dissolved in 2ml of dichloromethane and treated with 1ml of trifluoroacetic acid. After 10 minutes the volatiles were evaporated and the residue triturated with toluene and re-evaportated to give a gum that was further triturated with petroleum ether bp 40-60°C to give 2-(3-pyrazinyloxy)acetic acid trifluoroacetate.

Example 155

N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[2-(2-pyrimidinyloxy)acetyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide



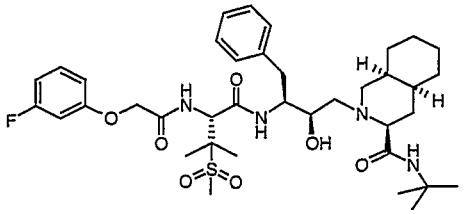
Example 155, $[M+H]^+$ 715 was prepared in a manner analogous to that described in Example 2 but starting from 2-(pyrimidin-2-yloxy)acetic acid trifluoroacetate.

The starting material 2-(pyrimidin-2-yloxy)acetic acid trifluoroacetate was prepared as follows:

A stirred suspension of 88mg (2.2mmol) sodium hydride (60% dispersion in mineral oil) in 5ml of dry dimethylformamide at -5°C under nitrogen was treated with 264mg (2mmol) tert-butylglycolate. After 30 minutes 318mg (2mmol) of 2-bromopyrimidine was added and the solution was allowed to warm to room temperature and was stirred overnight. The volatiles were evaporated and the residue partitioned between dichloromethane and 10% citric acid solution. The organic phase was washed with saturated sodium hydrogen carbonate and brine. The combined organic phase was dried over magnesium sulfate and evaporated under reduced pressure to give 360mg of a gum. The gum was chromatographed on silica eluting with ethyl acetate/hexane (1:1) to give 105mg of a gum that was dissolved in 3ml of dichloromethane and treated with 1.5ml of trifluoroacetic acid. After 1 .5 hours the volatiles were evaporated and the residue triturated with toluene and re-evaportated to give a gum that was further triturated with petroleum ether bp 40-60°C to give 60mg of 2-(pyrimidin-2-yloxy)acetic acid trifluoroacetate as an of white solid.

Example 156

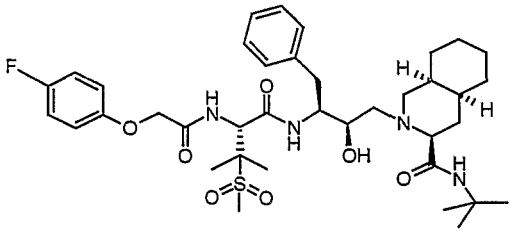
N-tert-Butyl-2-[3(S)-[[N-[2-(3-fluorophenoxy)acetyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide



Example 156, $[M+H]^+$ 731.6 mp 197-199°C was prepared in a manner analogous to that described in Example 3 but starting from 3-fluorophenol in place of 3-hydroxypyridine.

Example 157

N-tert-Butyl-2-[3(S)-[[N-[2-(4-Fluorophenoxy)-acetyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide

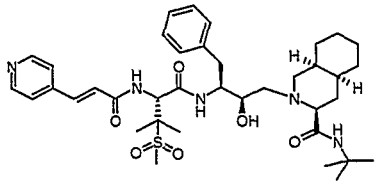
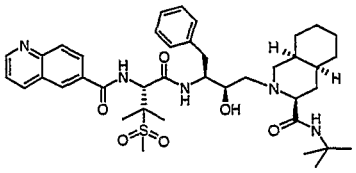
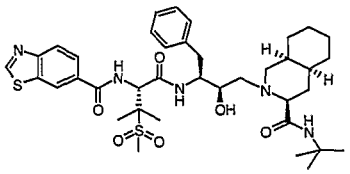
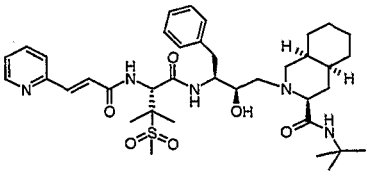
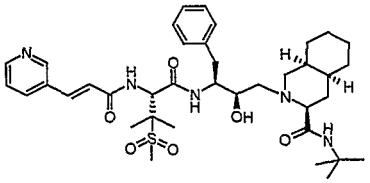


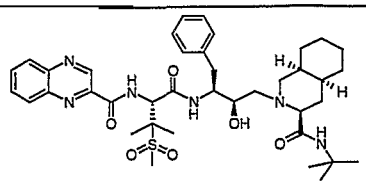
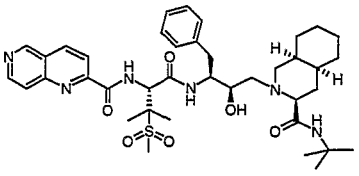
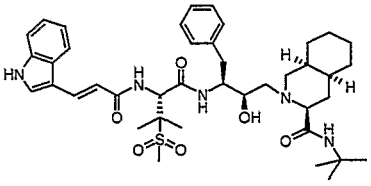
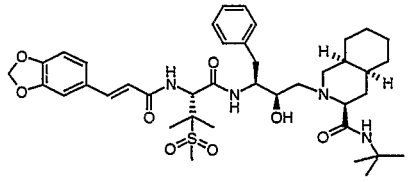
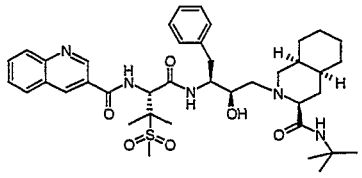
Example 157, $[M+H]^+$ 731 was prepared in a manner analogous to that described in Example 3 but starting from 4-fluorophenol in place of 3-hydroxypyridine.

In a manner analogous to that described for Examples 2 and 3, the compounds in Table 7 were prepared starting from N-tert-butyl-2-[3(S)-[[N-[(9-fluorenyl)methoxycarbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide.

Other reagents used in the synthesis of the compounds in Table 7 were obtained from commercial sources such as Aldrich, Lancaster, and Maybridge Int. or were prepared using methods described in the art or analogous to those described in the art.

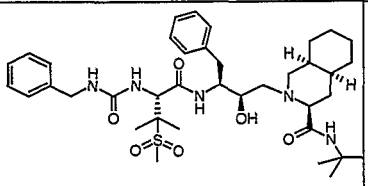
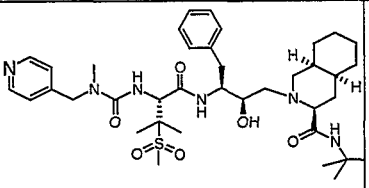
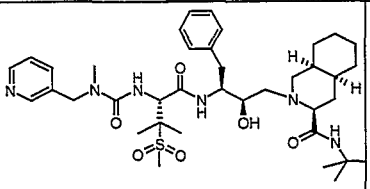
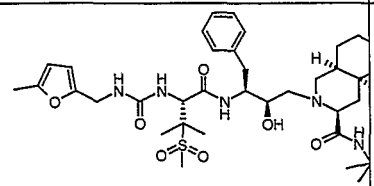
Table 7

Name	*Structure*	*[M+H]⁺*	Ex.No.
(E)-N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[3-(4-pyridyl)acroyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		710	158
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(6-quinolinyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		734	159
2-[3(S)-[[N-[(6-Benzothiazolyl)carbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		740	160
(E)-N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[3-(2-pyridyl)acroyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		710	161
(E)-N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[3-(3-pyridyl)acroyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		710	162

N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(2-quinoxalinyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		735	163
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(pyrido[4,3-b]pyridin-2-yl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		735	164
(E)-N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-[3-(3-indolyl)acroyl]-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		748	165
(E)-2-[3(S)-[[N-[3-(1,3-Benzodioxol-5-yl)acroyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		753	166
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(3-quinolyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		734	167

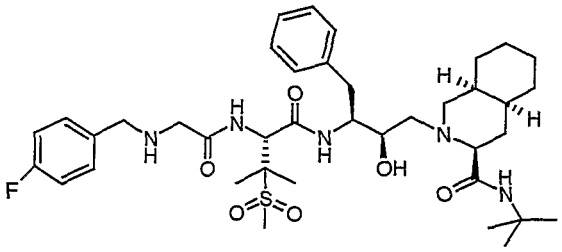
In a manner analogous to that described for Example 100, starting from N-tert-butyl-2-[3(S)-[[N-[(9-fluorenyl)methoxycarbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide the compounds shown in Table 8 were also prepared. Other reagents used in the synthesis of the compounds in Table 8 were obtained from commercial sources such as Aldrich and Lancaster or were prepared using methods described in the art or analogous to those described in the art.

Table 8

Name	*Structure*	*$[M+H]^+$*	*Ex. No.*
2-[3(S)-[[N-(Benzylcarbamoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide		712	168
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[N-methyl-N-[(4-pyridyl)methyl]carbamoyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		727	169
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[N-methyl-N-[(3-pyridyl)methyl]carbamoyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		727	170
N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(5-methyl-2-furfuryl)carbamoyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide		716	171

Example 172

N-tert-Butyl-2-[3(S)-[[N-[2-(4-fluorobenzylamino)acetyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S).5.6.7.8.8a(S)-decahydro-3(S)-isoquinolinecarboxamide

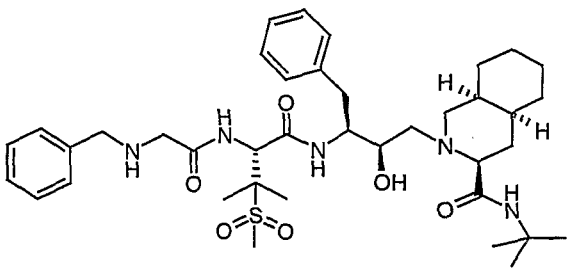


Example 172, $[M+H]^+$ 744, was prepared in a manner analogous to that described for Example 121 starting from 4-fluorobenzaldehyde and N-tert-butyl-2-[3(S)-[[N-glycyl-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide.

The starting material N-tert-butyl-2-[3(S)-[[N-glycyl-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide was prepared in a manner analogous to that described for Example 94 starting from N-(benzyloxycarbonyl)glycine

Example 173

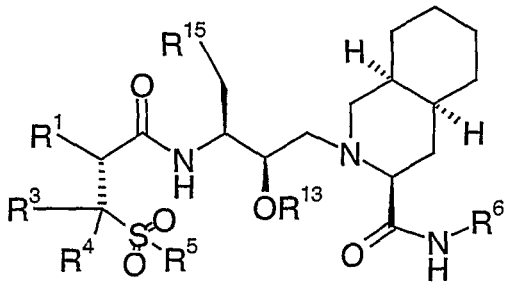
2-[3(S)-[[N-[2-(Benzylamino)acetyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S).5.6.7.8.8a(S)-decahydro-3(S)-isoquinolinecarboxamide



Example 173, [M+H]+ 726, was prepared in a manner analogous to that described for Example 172 starting with benzaldehyde in place of 4-fluorobenzaldehyde

Claims:

1. Compounds of the formula

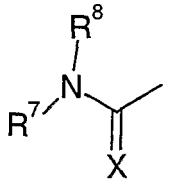


I

and pharmaceutically acceptable salts thereof

wherein R^1 is H, hydroxy or NHR^2

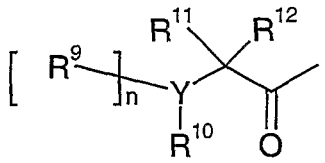
wherein R^2 is H, alkyl, alkenyl, alkynyl, arylalkyl, heterocyclylalkyl, cycloalkyl, alkyl carbonyl, cycloalkyl carbonyl, aryl carbonyl, heterocyclyl carbonyl, aryl alkyl carbonyl, heterocyclyl alkyl carbonyl, alkyl oxy carbonyl, aryl alkyl oxy carbonyl, heterocyclyl alkyl oxy carbonyl, aryl, heterocyclyl, sulfonyl, alkyl sulfonyl, aryl sulfonyl, heterocyclyl sulfonyl or a group of the formula



wherein X is O or S and

R^7 and R^8 independently are H, alkyl, aryl, heterocyclyl, aryl alkyl, heterocyclyl alkyl or R^7 and R^8 together with the nitrogen atom to which they are attached form a saturated ring optionally containing a further hetero atom

or a group



wherein when n=0, Y represents O or S

and R^{10} is H, alkyl, aryl alkyl, heterocyclyl alkyl, aryl, heterocyclyl

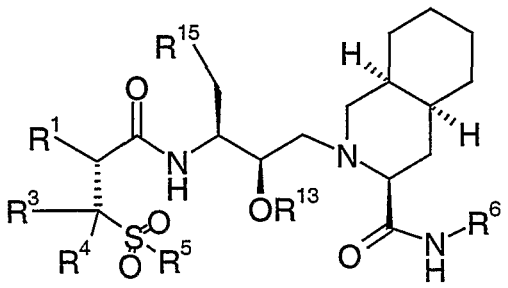
or when n=1, Y represents N, R^9 is H or alkyl and R^{10} is H, alkyl, aryl alkyl, heterocyclyl alkyl, aryl, heterocyclyl

or R^9 and R^{10} taken together with the hetero atom to which they are attached form a heterocycle,

R^{11} and R^{12} independently are H or alkyl
or R^{11} and R^{12} taken together with the carbon atom to which they are attached form a cycle,

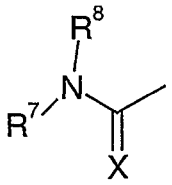
R^3, R^4 independently are alkyl or taken together with the carbon atom to which they are attached form a carbocycle,
R^5 is alkyl, aryl alkyl, heterocyclyl alkyl
or R^4 and R^5 taken together with the carbon and sulfur atom to which they are attached form a heterocycle and
R^6 is alkyl, aryl alkyl, heterocyclyl alkyl, alkyl oxy alkyl, hydroxy alkyl, amino alkyl, fluoro alkyl and
R^{13} is H or the residue of an inorganic or an organic ester and
R^{15} is aryl,
with the proviso that, if R^3, R^4 and R^5 are methyl, R^6 is tert-butyl, R^{13} is H and R^{15} is phenyl, R^2 is not benzyl oxycarbonyl and not 2-quinoline carbonyl.

2. Compounds of the formula



I

and pharmaceutically acceptable salts thereof
wherein R^1 is H, hydroxy or NHR^2
wherein R^2 is H, alkyl, alkenyl, alkynyl, arylalkyl, heterocyclylalkyl
cycloalkyl,
alkyl carbonyl, cycloalkyl carbonyl, aryl carbonyl, heterocyclyl carbonyl, aryl alkyl carbonyl,
heterocyclyl alkyl carbonyl,
alkyl oxy carbonyl, aryl alkyl oxy carbonyl, heterocyclyl alkyl oxy carbonyl,
aryl,
heterocyclyl,
sulfonyl, alkyl sulfonyl, aryl sulfonyl, heterocyclyl sulfonyl or a group of the formula

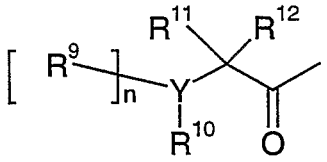


wherein X is O or S and

R^7 and R^8 independently are H, alkyl, aryl, heterocyclyl, aryl alkyl, heterocyclyl alkyl

or R^7 and R^8 together with the nitrogen atom to which they are attached form a saturated ring optionally containing a further hetero atom

or a group



wherein when n=0, Y represents O or S

and R^{10} is H, alkyl, aryl, heterocyclyl

or when n=1, Y represents N, R^9 is H or alkyl and R^{10} is H, alkyl, aryl, heterocyclyl

or R^9 and R^{10} taken together with the hetero atom to which they are attached form a heterocycle,

R^{11} and R^{12} independently are H or alkyl

or R^{11} and R^{12} taken together with the carbon atom to which they are attached form a cycle,

R^3, R^4 independently are alkyl or taken together with the carbon atom to which they are attached form a carbocycle,

R^5 is alkyl, aryl alkyl, heterocyclyl alkyl

or R^4 and R^5 taken together with the carbon and sulfur atom to which they are attached form a heterocycle and

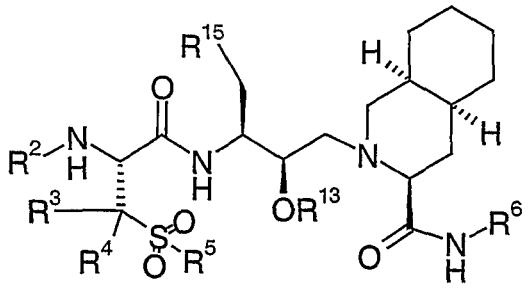
R^6 is alkyl, aryl alkyl, heterocyclyl alkyl, alkyl oxy alkyl, hydroxy alkyl, amino alkyl, fluoro alkyl and

R^{13} is H or the residue of an inorganic or an organic ester and

R^{15} is aryl,

with the proviso that, if R^3, R^4 and R^5 are methyl, R^6 is tert-butyl, R^{13} is H and R^{15} is phenyl, R^2 is not benzyl oxycarbonyl and not 2-quinoline carbonyl.

3. Compounds of claim 1 or 2 having the formula

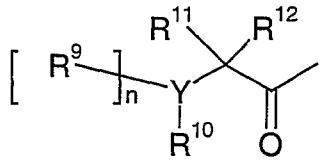


II

wherein R^2, R^3, R^4, R^5, R^6, R^{13} and R^{15} are as above.

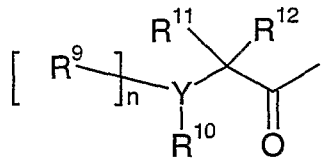
4. Compounds of claim 1 or 3 wherein R^3, R^4 and R^5 are methyl, R^6 is tert-butyl or and R^{15} is phenyl.

5. Compounds of claims 1 to 4 wherein R^2 is alkyl carbonyl, cycloalkyl carbonyl, aryl carbonyl, heterocyclyl carbonyl, heterocyclyl alkyl carbonyl or a group of the formula



wherein when n=0, Y represents O or S
and R^{10} is alkyl, aryl alkyl, heterocyclyl alkyl, aryl, heterocyclyl
or when n=1, Y represents N, R^9 is H and R^{10} is alkyl, aryl alkyl, heterocyclyl alkyl, aryl, heterocyclyl
and wherein R^{11} and R^{12} independently are H.

6. Compounds of claims 1 to 5 wherein R^3, R^4 and R^5 are methyl, R^6 is tert-butyl, R^{15} is phenyl and R^2 is alkyl carbonyl, cycloalkyl carbonyl, aryl carbonyl, heterocyclyl carbonyl, heterocyclyl alkyl carbonyl or a group of the formula

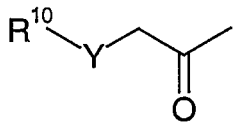


wherein when n=0, Y represents O or S
and R^{10} is alkyl, aryl alkyl, heterocyclyl alkyl, aryl, heterocyclyl
or when n=1, Y represents N, R^9 is H and R^{10} is alkyl, aryl alkyl, heterocyclyl, alkyl, aryl,

heterocyclyl

and wherein R^{11} and R^{12} independently are H.

7. Compounds of claims 1 to 6 wherein R^3, R^4 and R^5 are methyl, R^6 is tert-butyl, R^{15} is phenyl and R^2 is aryl carbonyl, heterocyclyl carbonyl, or a group of the formula



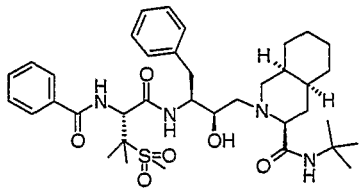
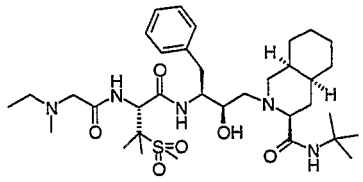
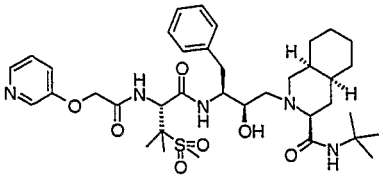
wherein Y represents O, NH, S, CH_2

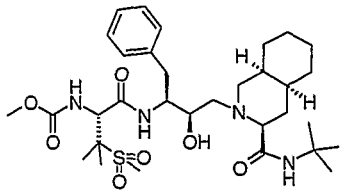
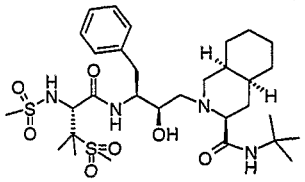
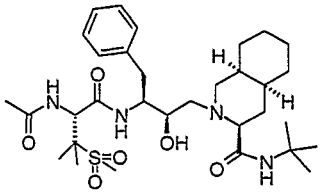
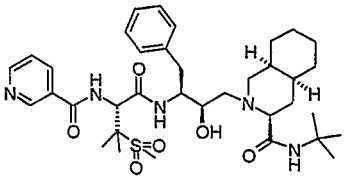
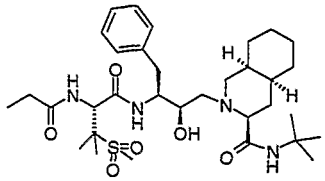
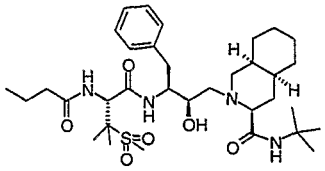
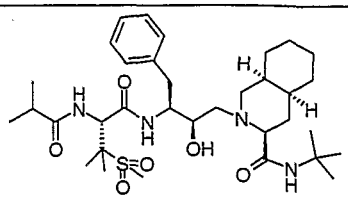
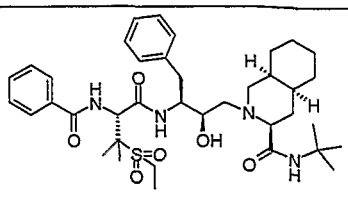
and R^{10} is aryl, heterocyclyl

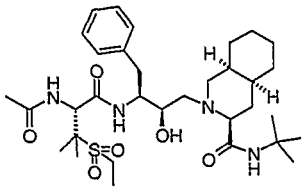
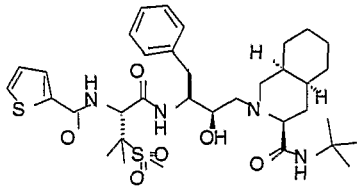
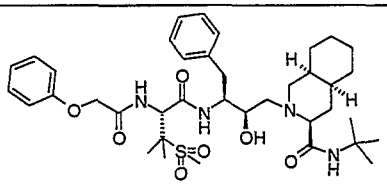
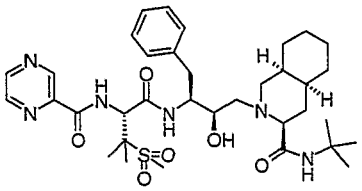
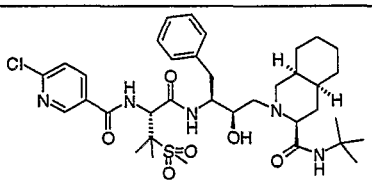
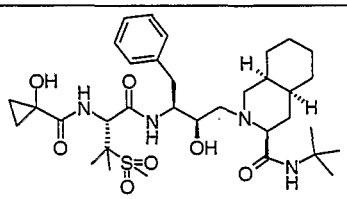
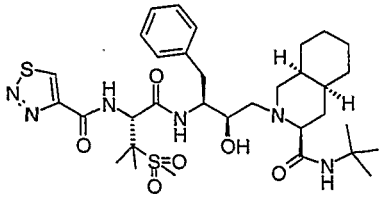
8. Compounds of claims 1 to 7 wherein R^{13} is H

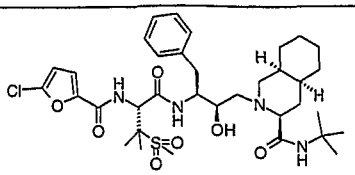
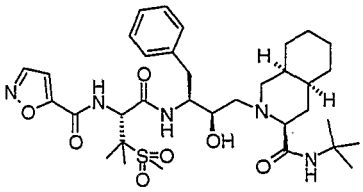
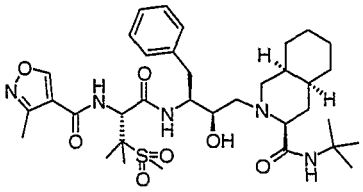
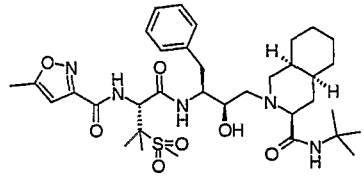
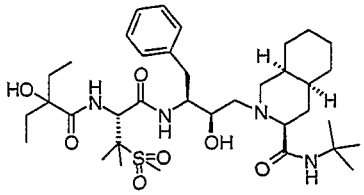
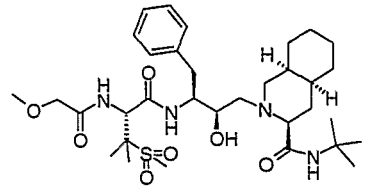
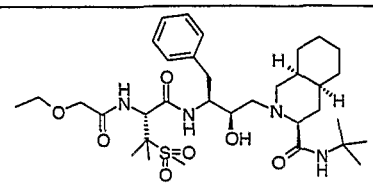
9. Compounds of claim 1 to 8 selected from

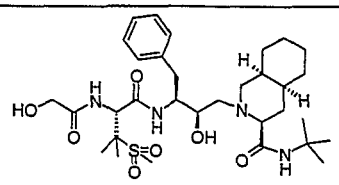
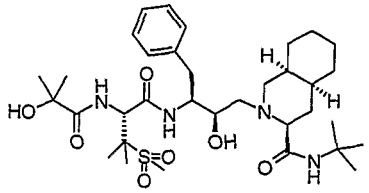
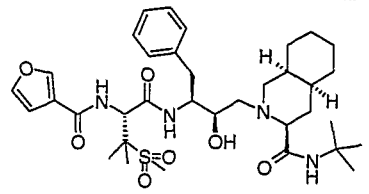
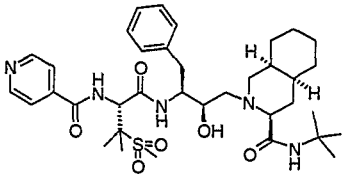
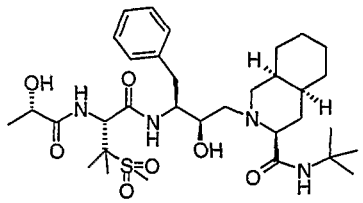
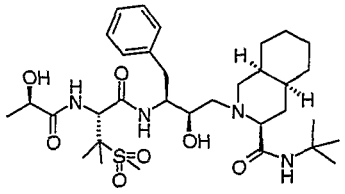
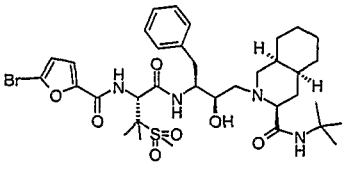
Table A

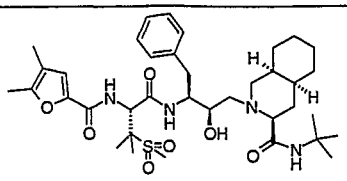
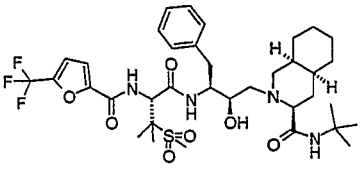
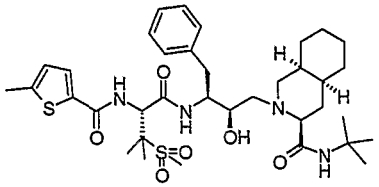
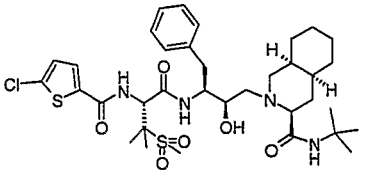
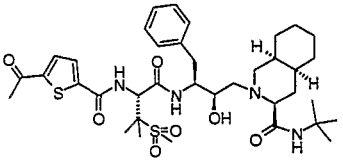
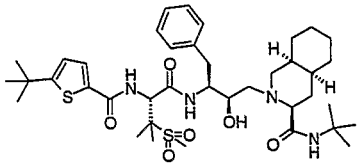
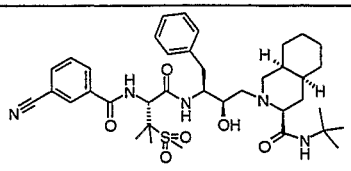
Ex	Name	Structures
1	2-[3(S)-[[N-Benzoyl-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-benzyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
2	N-tert-Butyl-2-[3(S)-[[N-[(9-fluorenyl)methoxycarbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
3	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[2-(3-pyridyloxy)acetyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	

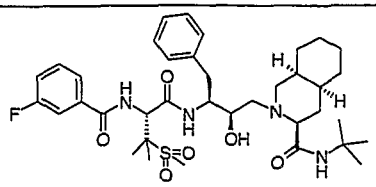
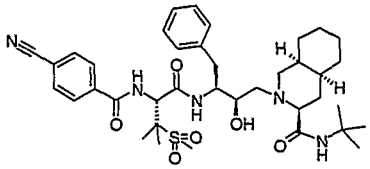
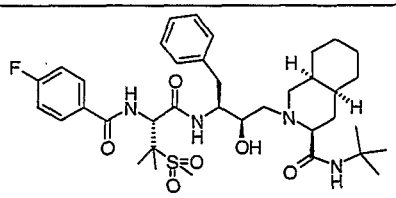
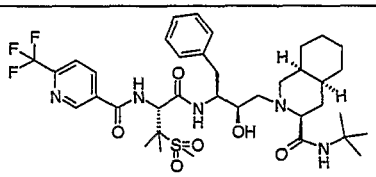
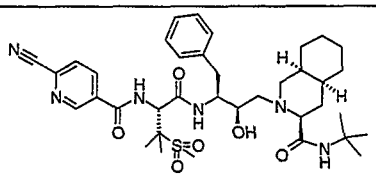
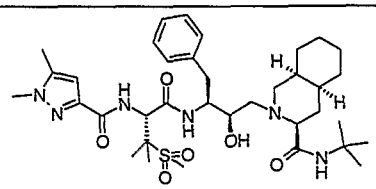
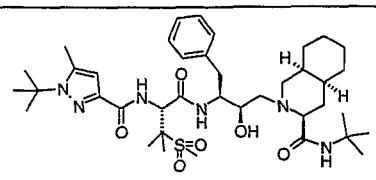
4	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(methoxycarbonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinlinecarboxamide	
5	2-[3(S)-[[N,3-Bis(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
6	2-[3(S)-[[N-Acetyl-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
7	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(3-pyridyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
8	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-propionyl-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
9	2-[3(S)-[[N-Butyryl-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
10	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-isobutyryl-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
11	2-[3(S)-[[N-Benzoyl-3-(ethanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	

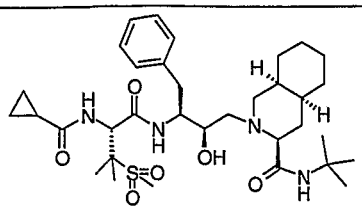
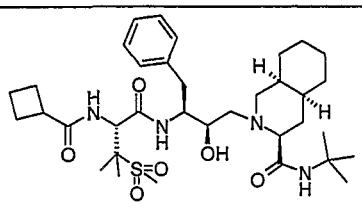
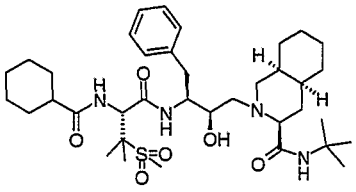
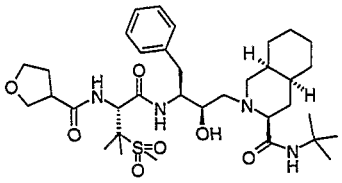
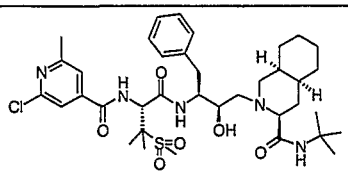
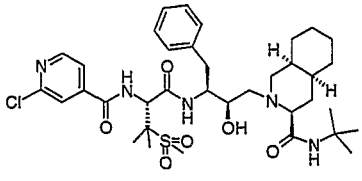
12	2-[3(S)-[[N-Acetyl-3-(ethanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
13	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(2-thenoyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
14	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(2-phenoxyacetyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
15	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(2-pyrazinyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
16	N-tert-Butyl-2-[3(S)-[[N-[(6-chloro-3-pyridyl)carbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
17	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-[(1-hydroxy-1-cyclopropyl)carbonyl]-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
18	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(1,2,3-thiadiazol-4-yl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	

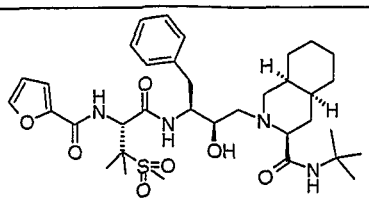
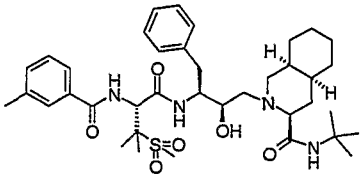
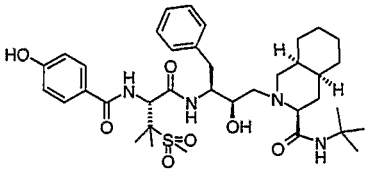
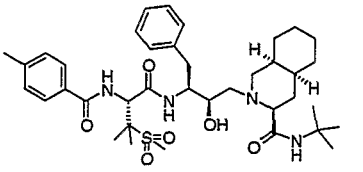
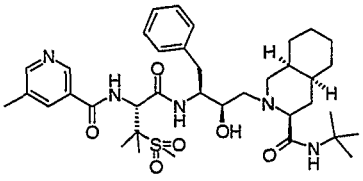
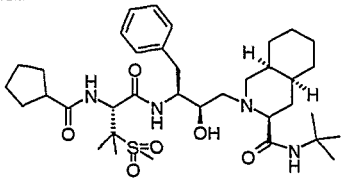
19	N-tert-Butyl-2-[3(S)-[[N-(5-chloro-2-furoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
20	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(5-isoxazolyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
21	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(3-methyl-4-isoxazolyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
22	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(5-methyl-3-isoxazolyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
23	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-(2-hydroxy-2-ethylbutyryl)-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
24	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(2-methoxyacetyl))-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
25	N-tert-Butyl-2-[3(S)-[[N-(2-ethoxyacetyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	

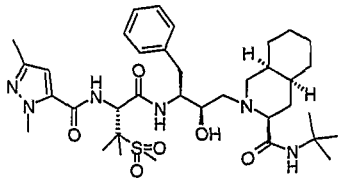
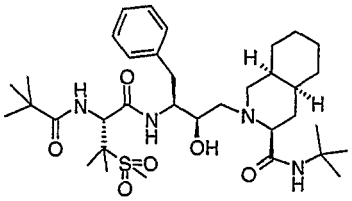
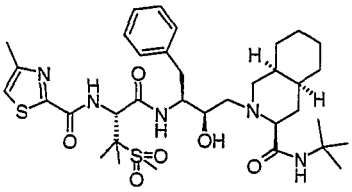
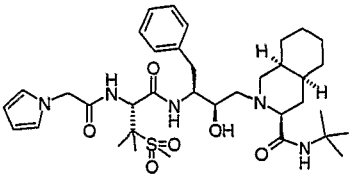
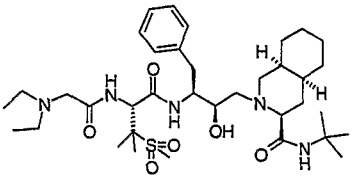
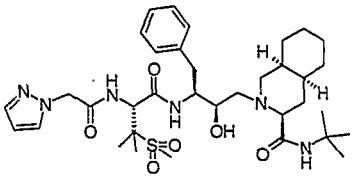
26	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-(2-hydroxyacetyl)-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
27	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-(2-hydroxy-2-methylpropionyl)-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
28	N-tert-Butyl-2-[3(S)-[[N-(3-furoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
29	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(4-pyridyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
30	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-(2(S)-hydroxypropionyl)-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
31	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-(2(R)-hydroxypropionyl)-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
32	2-[3(S)-[[N-(5-Bromo-2-furoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	

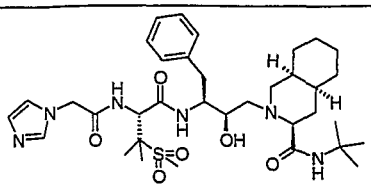
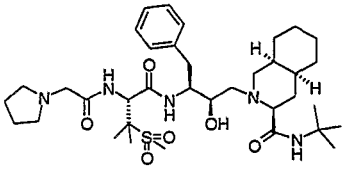
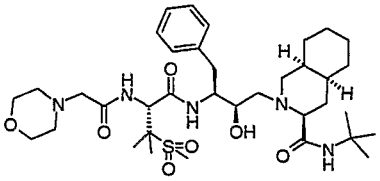
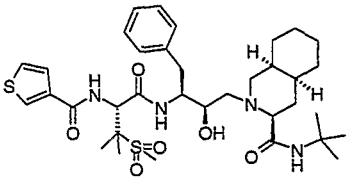
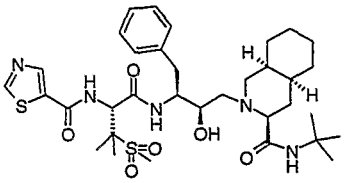
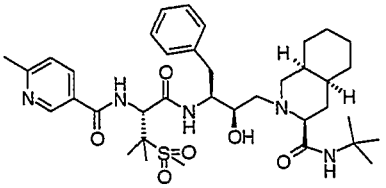
33	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(4,5-dimethyl-2-furoyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
34	N-tert-Butyl-2-[3(S)-[[N-[5-(trifluoromethyl)-2-furoyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
35	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(5-methyl-2-thenoyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
36	N-tert-Butyl-2-[3(S)-[[N-(5-chloro-2-thenoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
37	2-[3(S)-[[N-(5-Acetyl-2-thenoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
38	N-tert-Butyl-2-[3(S)-[[N-(5-tert-butyl-2-thenoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
39	N-tert-Butyl-2-[3(S)-[[N-(3-cyanobenzoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	

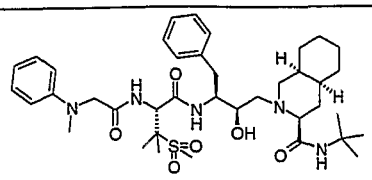
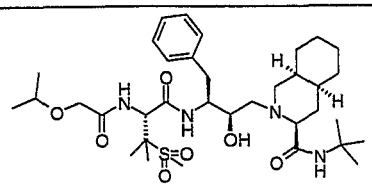
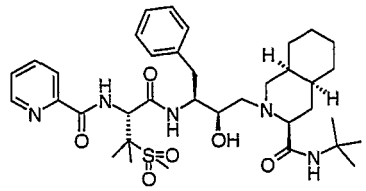
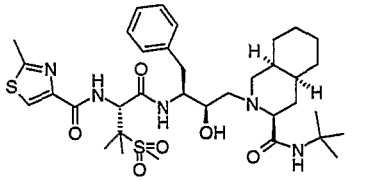
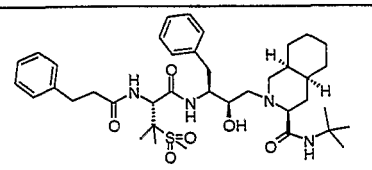
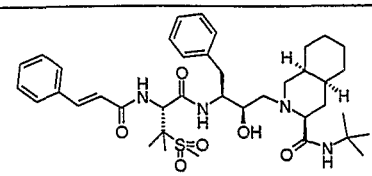
40	N-tert-Butyl-2-[3(S)-[[N-(3-fluorobenzoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
41	N-tert-Butyl-2-[3(S)-[[N-(4-cyanobenzoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
42	N-tert-Butyl-2-[3(S)-[[N-(4-fluorobenzyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
43	N-tert-Butyl-2-[3(S)-[[N-[[6-(trifluoromethyl)-3-pyridyl]carbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
44	N-tert-Butyl-2-[3(S)-[[N-[(6-cyano-3-pyridyl)carbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
45	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(1,5-dimethyl-3-pyrazolyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
46	N-tert-Butyl-2-[3(S)-[[N-[(1-tert-butyl-5-methyl-3-pyrazolyl)carbonyl]3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	

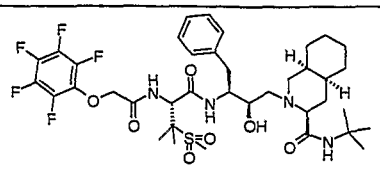
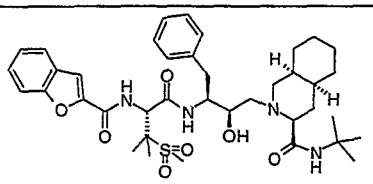
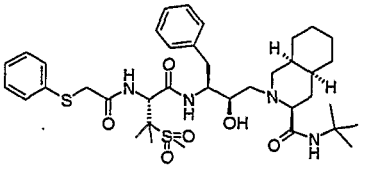
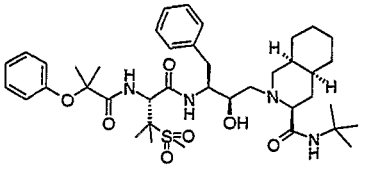
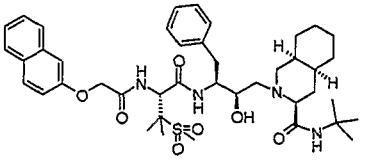
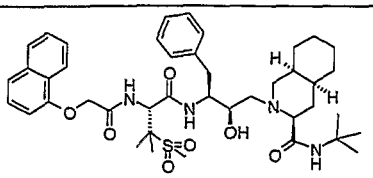
47	N-tert-Butyl-2-[3(S)-[[N-(cyclopropylcarbonyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
48	N-tert-Butyl-2-[3(S)-[[N-(cyclobutylcarbonyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
49	N-tert-Butyl-2-[3(S)-[[N-(cyclohexylcarbonyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
50	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[3(S)-[[N-(tetrahydro-3(RS)-furoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-3(S)-isoquinolinecarboxamide (1:1 mixture of diastereoisomers)	
51	N-tert-Butyl-2-[N-[(2-chloro-6-methyl-4-pyridyl)carbonyl]-3(S)-[[3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
52	N-tert-Butyl-2-[3(S)-[[N-[(2-chloro-4-pyridyl)carbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	

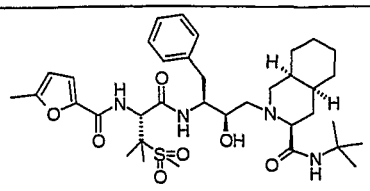
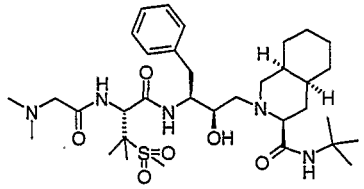
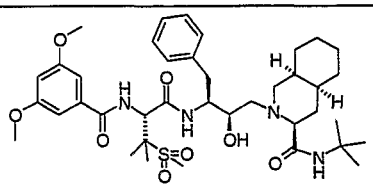
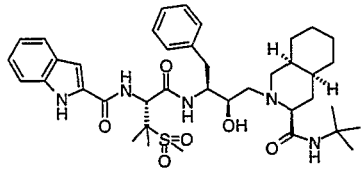
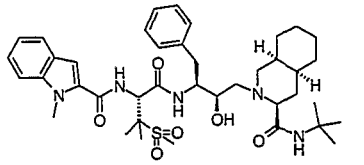
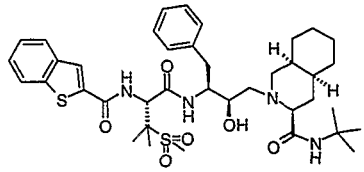
53	N-tert-Butyl-2-[N-(2-furoyl)-3(S)-[[3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
54	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(3-methylbenzoyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
55	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(4-methoxybenzoyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
56	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(4-methylbenzoyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
57	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(5-methyl-3-pyridyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
58	N-tert-Butyl-2-[3(S)-[[N-(cyclopentylcarbonyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	

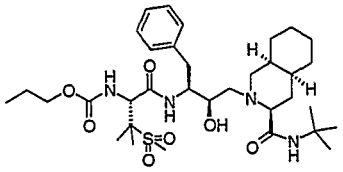
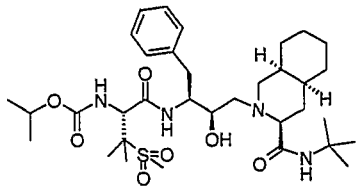
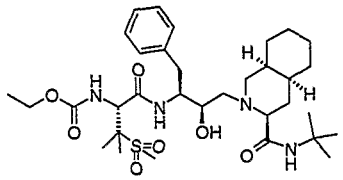
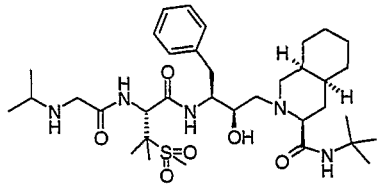
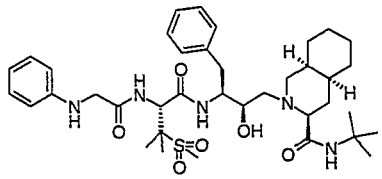
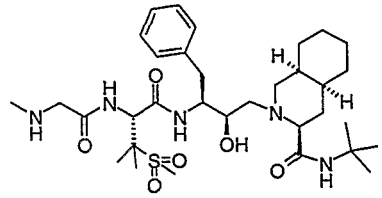
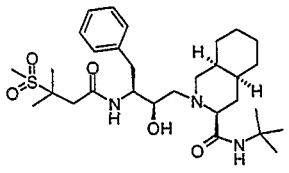
59	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(2,5-dimethyl-3-pyrazolyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
60	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-pivaloyl-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
61	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(4-methyl-2-thiazolyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
62	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-3-methyl-N-[2-(1-pyrrolyl)acetyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
63	N-tert-Butyl-2-[3(S)-[[N-[2-(diethylamino)acetyl]-3-(methanesulfonyl)-3-methyl-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro3(S)-isoquinolinecarboxamide	
64	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-3-methyl-N-[2-(1-pyrazolyl)acetyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	

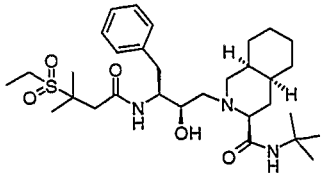
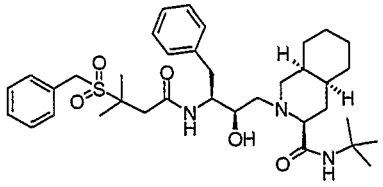
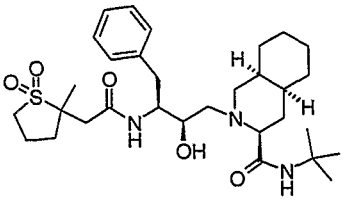
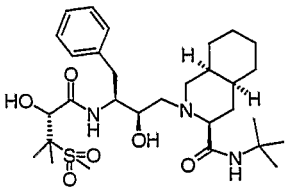
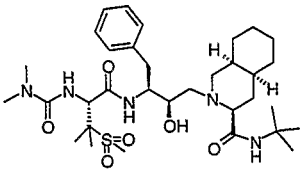
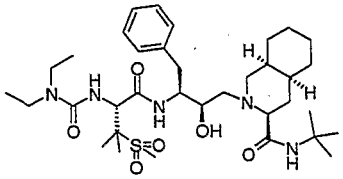
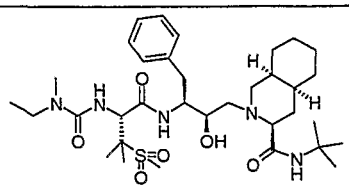
65	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-[2-(1-imidazolyl)acetyl]-3-(methanesulfonyl)-3-methyl-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
66	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[2-(1-pyrrolidinyl)acetyl]-L-valyl]amino]-4-phenylbutyl-3(S)-isoquinolinecarboxamide	
67	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(2-morpholinoacetyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
68	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(3-thenoyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
69	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(5-thiazolyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
70	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(6-methyl-3-pyridyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	

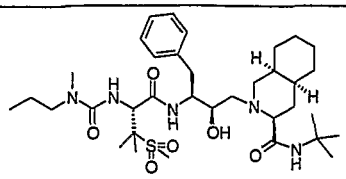
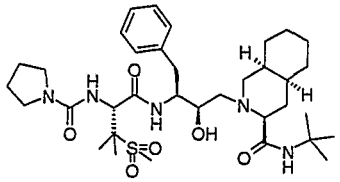
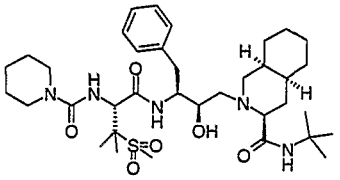
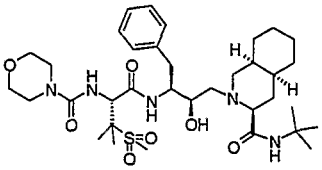
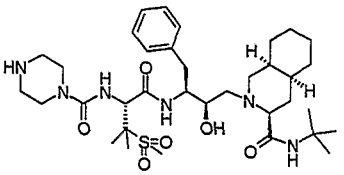
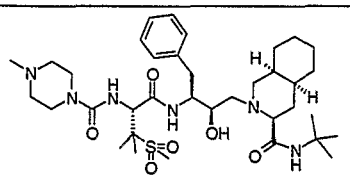
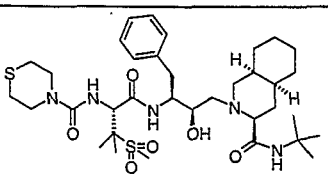
71	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[N-methyl-N-phenylglycyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
72	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-(2-isopropoxyacetyl)-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
73	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(2-pyridyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
74	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(2-methyl-4-thiazolyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
75	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(3-phenylpropionyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
76	(E)-N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(3-phenylacryloyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	

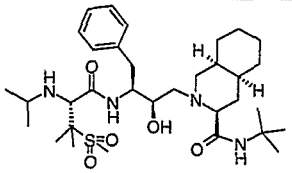
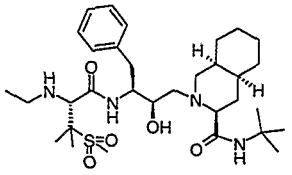
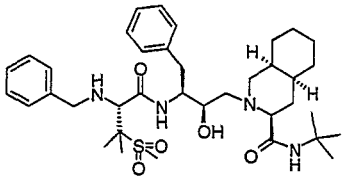
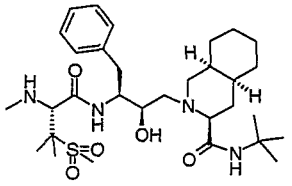
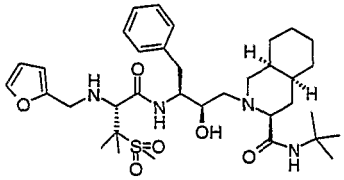
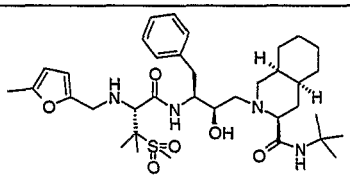
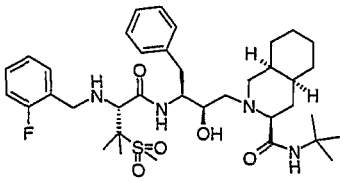
77	N-tert-Butyl-2-[3(S)-[[N-[2-(pentafluorophenoxy)acetyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
78	2-[3(S)-[[N-[[(2-Benzofuryl)carbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
79	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[2-(phenylthio)acetyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
80	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(2-methyl-2-phenoxypropionyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
81	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[2-(2-naphthyloxy)acetyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
82	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[2-(1-naphthyloxy)acetylamino]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	

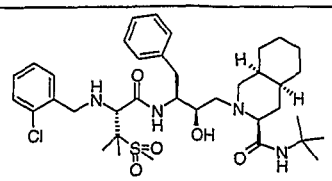
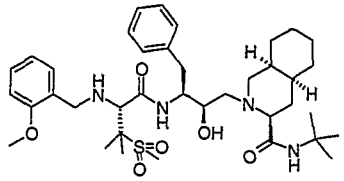
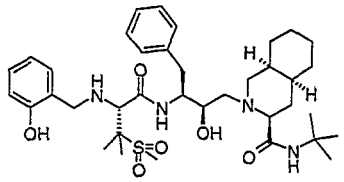
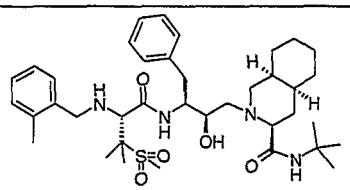
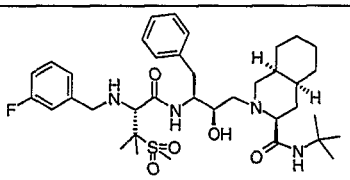
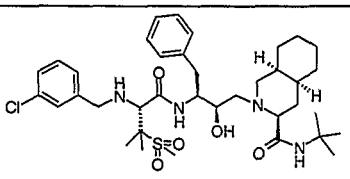
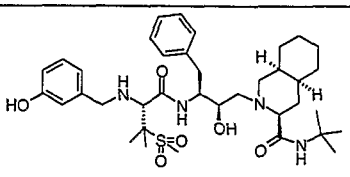
83	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(5-methyl-2-furoyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
84	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[2-[2-(dimethylamino)acetyl]-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
85	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(3,5-dimethoxybenzoyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
86	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-N-[(2-indolyl)carbonyl]-3(S)-[[3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
87	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[-3-(methanesulfonyl)-N-[1-methyl-2-indolyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
88	2-[3(S)-[[N-[(1-Benzothiophen-2-yl)carbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	

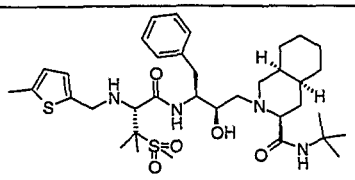
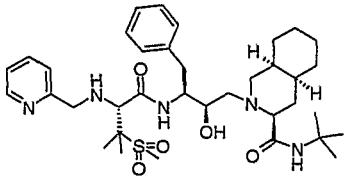
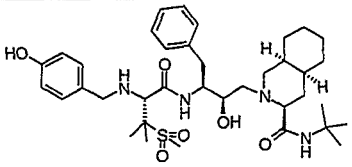
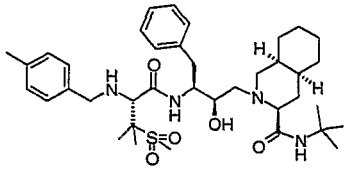
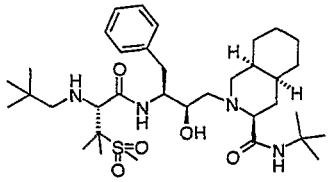
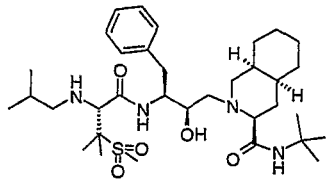
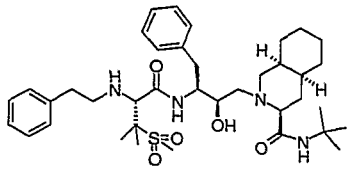
89	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(propoxycarbonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
90	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-(isopropoxycarbonyl)-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
91	N-tert-Butyl-2-[3(S)-[[N-(ethoxycarbonyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
92	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-[2-(isopropylamino)acetyl]-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]--3(S)-isoquinolinecarboxamide	
93	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(N-phenylglycyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
94	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(N-methylglycyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
95	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-1-[2(R)-hydroxy-3(S)-[3-(methanesulfonyl)butyramido]-4-phenylbutyl]-2(S)-piperazinecarboxamide	

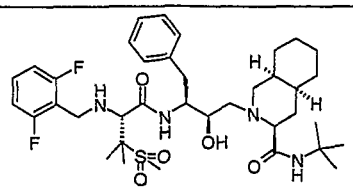
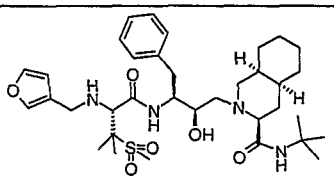
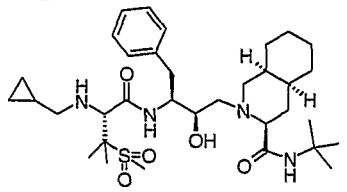
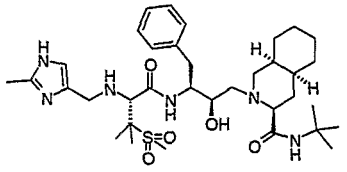
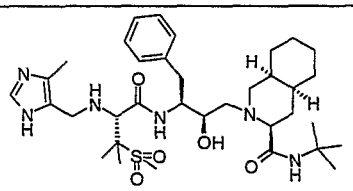
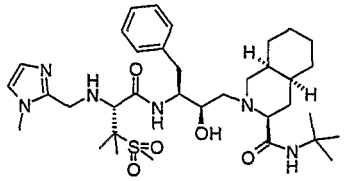
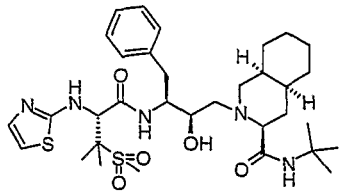
96	2-[3(S)-[3-(Ethanesulfonyl)-3-methylbutyramido]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
97	2-[3(S)-[3-(Benzenesulfonyl)-3-methylbutyramido]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
98	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[3(S)-[[N-[2-(tetrahydro-2(RS)-methyl-1,1-dioxo-2-thienyl)acetyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-3(S)-isoquinolinecarboxamide (mixture of diastereoisomers)	
99	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[2(R)-hydroxy-3-(methanesulfonyl)-3-methylbutyramido]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
100	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-(dimethylcarbamoyl-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
101	N-tert-Butyl-2-[3(S)-[[N-(diethylcarbamoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
102	N-tert-Butyl-2-[3(S)-[[N-(N-ethyl-N-methylcarbamoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	

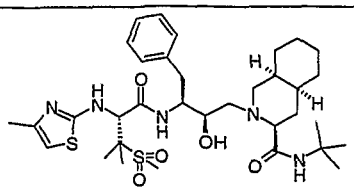
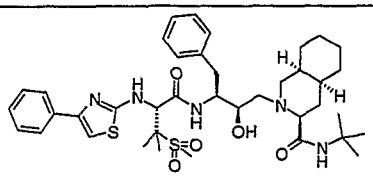
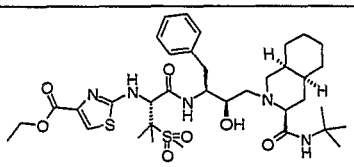
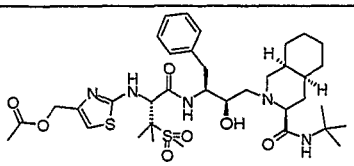
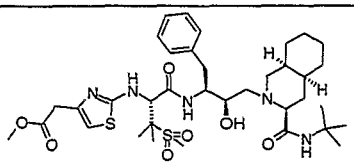
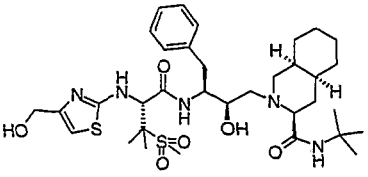
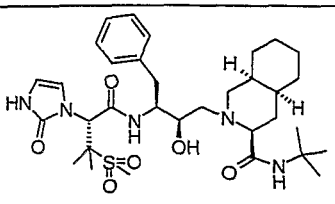
103	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(N-methyl-N-propylcarbamoyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
104	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(1-pyrrolidinyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
105	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(piperidinocarbonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
106	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(morpholinocarbonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
107	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(1-piperazinyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
108	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(4-methyl-1-piperazinyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
109	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[3(S)-[[N-[(tetrahydro-1,4-thiazin-4-yl)carbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	

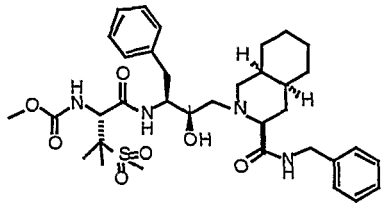
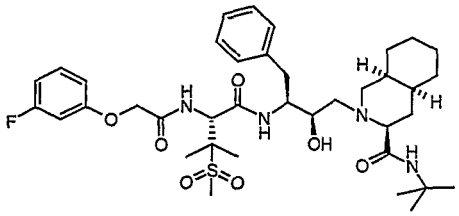
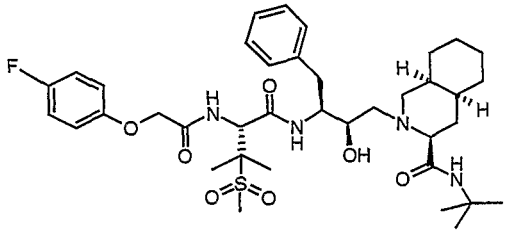
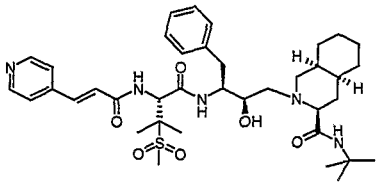
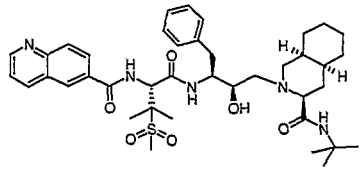
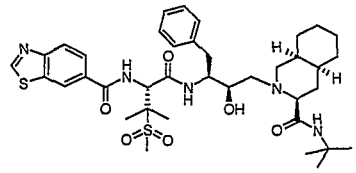
110	N-tert-Butyl-1,2,3,4,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-isopropyl-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
111	N-tert-Butyl-2-[3(S)-[[N-ethyl-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
112	2-[3(S)-[[N-Benzyl-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
113	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-methyl-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
114	N-tert-Butyl-2-[3(S)-[[N-(2-furfuryl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
115	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(5-methyl-2-furfuryl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
116	N-tert-Butyl-2-[3(S)-[[N-(2-fluorobenzyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	

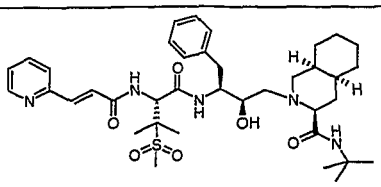
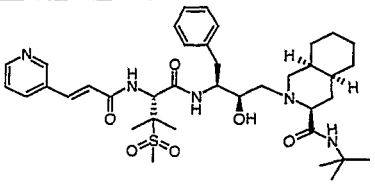
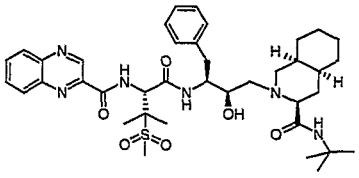
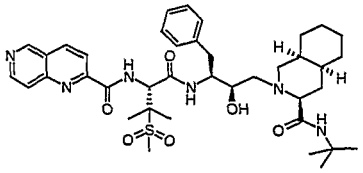
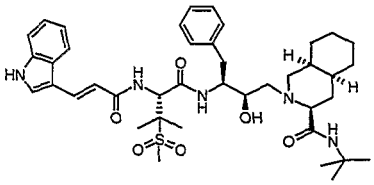
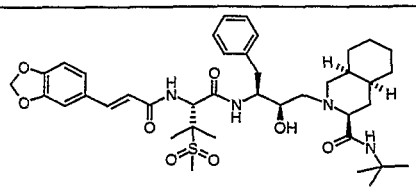
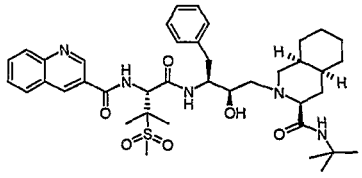
117	N-tert-Butyl-2-[3(S)-[[N-(2-chlorobenzyl)-3-(methanesulfonyl)-L-valyl]amino]-3(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
118	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(2-methoxybenzyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
119	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-(2-hydroxybenzyl)-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
120	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(2-methylbenzyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
121	N-tert-Butyl-2-[3(S)-[[N-(3-fluorobenzyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
122	N-tert-Butyl-2-[3(S)-[[N-(3-chlorobenzyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
123	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-(3-hydroxybenzyl)-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	

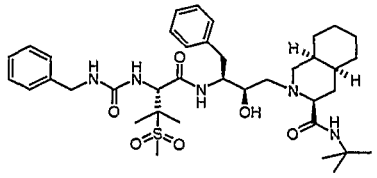
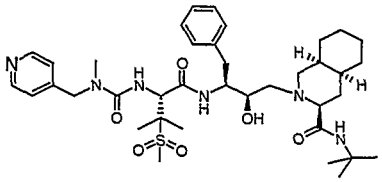
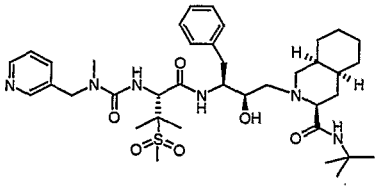
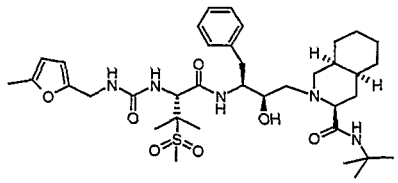
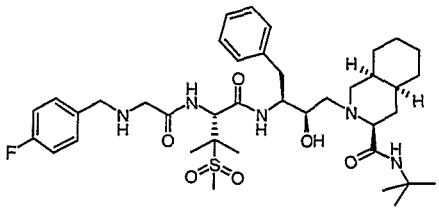
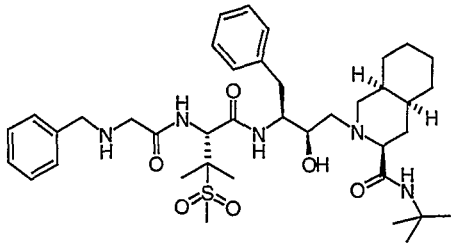
124	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(5-methyl-2-thenyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
125	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(2-pyridyl)methyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
126	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-(4-hydroxybenzyl)-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
127	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(4-methylbenzyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
128	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(2,2-dimethylpropyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
129	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-isobutyl-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
130	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(2-phenylethylyl))-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	

131	N-tert-Butyl-2-[3(S)-[[N-(2,6-difluorobenzyl)-3-(methanesulfonyl)-N-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
132	N-tert-Butyl-2-[3(S)-[[N-(3-furfuryl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
133	N-tert-Butyl-2-[3(S)-[[N-(cyclopropylmethyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
134	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(2-methyl-4-imidazolyl)methyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
135	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(5-methyl-4-imidazolyl)methyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
136	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(1-methyl-2-imidazolyl)methyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
137	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(2-thiazolyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	

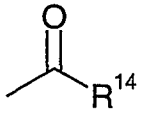
138	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(4-methyl-2-thiazolyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
139	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(4-phenyl-2-thiazolyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
140	N-tert-Butyl-2-[3(S)-[[N-[4-(ethoxycarbonyl)-2-thiazolyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro3(S)-isoquinolinecarboxamide	
141	2-[3(S)-[[N-[4-(Acetoxymethyl)-2-thiazolyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
142	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[4-[(methoxycarbonyl)methyl]-2-thiazolyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
143	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-[4-(hydroxymethyl)-2-thiazolyl]-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
144	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[3(S)-[2(R)-(2,3-dihydro-2-oxo-1H-imidazol-2-yl)-3-(methanesulfonyl)-3-methylbutyramido]-2(R)-hydroxy-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	

145	N-Benzyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-(methoxycarbonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
156	N-tert-Butyl-2-[3(S)-[[N-[2-(3-fluorophenoxy)acetyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
157	N-tert-Butyl-2-[3(S)-[[N-[2-(4-Fluorophenoxy)-acetyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
158	(E)-N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[3-(4-pyridyl)acroyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
159	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(6-quinolinyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
160	2-[3(S)-[[N-[(6-Benzothiazolyl)carbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	

161	(E)-N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[3-(2-pyridyl)acroyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
162	(E)-N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[3-(3-pyridyl)acroyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
163	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(2-quinoxalinyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
164	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(pyrido[4,3-b]pyridin-2-yl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
165	(E)-N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[N-[3-(3-indolyl)acroyl]-3-(methanesulfonyl)-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
166	(E)-2-[3(S)-[[N-[3-(1,3-Benzodioxol-5-yl)acroyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
167	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(3-quinolyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	

168	2-[3(S)-[[N-(Benzylcarbamoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
169	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[N-methyl-N-[(4-pyridyl)methyl]carbamoyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
170	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[N-methyl-N-[(3-pyridyl)methyl]carbamoyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
171	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-(methanesulfonyl)-N-[(5-methyl-2-furfuryl)carbamoyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
172	N-tert-Butyl-2-[3(S)-[[N-[2-(4-fluorobenzylamino)acetyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-1,2,3,4,4a(S).5.6.7.8.8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
173	2-[3(S)-[[N-[2-(Benzylamino)acetyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-1,2,3,4,4a(S).5.6.7.8.8a(S)-decahydro-3(S)-isoquinolinecarboxamide	

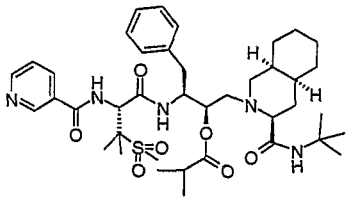
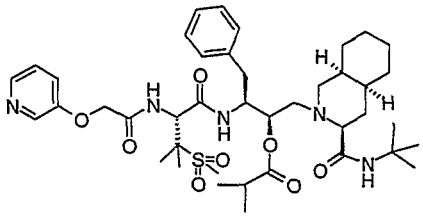
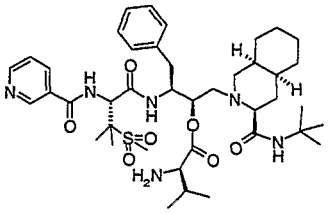
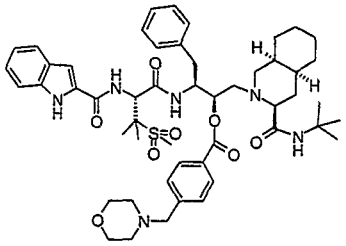
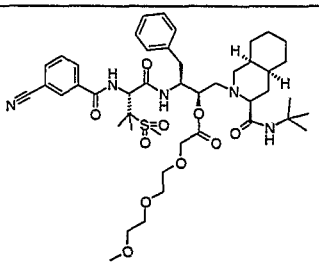
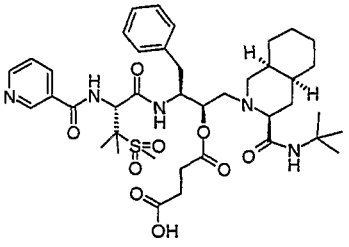
10. Compounds of claims 1 to 7 wherein R^{13} is $-SO_2OH$, $-PO(OH)_2$ or a group



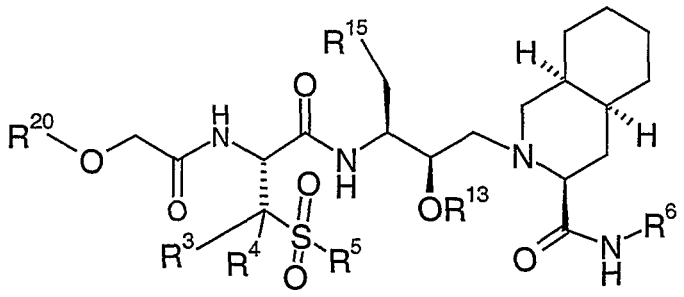
wherein R^{14} is alkyl, alkenyl, cycloalkyl, aryl, aryl alkyl, heterocyclyl or a group $-CH_2(CH_2CH_2O)_mCH_3$, wherein m is an integer from 0 to 10 or a carbonyl group-linked radical of an amino acid.

11. Compounds of claim 10 selected from

Table B

Ex	Name	Structures
146	N-tert-Butyl-1,2,3,4,4s(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-(isobutyryloxy)-3(S)-[[3-(methanesulfonyl)-N-[(3-pyridyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
147	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[2(R)-(isobutyryloxy)-3(S)-[[3-(methanesulfonyl)-N-[2-(3-pyridyloxy)acetyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
148	N-tert-Butyl-1,2,3,4,4a(S),4,5,6,8,8(a)-decahydro-2-[3(S)-[[3-(methanesulfonyl)-N-[(3-pyridyl)carbonyl]-L-valyl]amino]-4-phenyl-2(R)-(L-valyloxy)butyl]-3(S)-isoquinolinecarboxamide	
149	N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-2-[3(S)-[[N-[(2-indolyl)carbonyl]-3-(methanesulfonyl)-L-valyl]amino]-2(R)-[4-(morpholinomethyl)benzoyloxy]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide	
150	N-tert-Butyl-2-[3(S)-[[N-(3-cyanobenzoyl)-3-(methanesulfonyl)-L-valyl]amino]-2(R)-[2-[2-(2-methoxyethoxy)ethoxy]acetoxy]-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)-decahydro-3(S)-isoquinolinecarboxamide	
151	N-tert-Butyl-2-[2(R)-(3-carboxypropionyloxy)-3(S)-[[3-(methanesulfonyl)-N-[(3-pyridyl)carbonyl]-L-valyl]amino]-4-phenylbutyl]-1,2,3,4,4a(S),5,6,7,8,8a(S)decahydro-3(S)-isoquinolinecarboxamide	

12. Compounds of claim 1 of the formula



X

wherein R^3, R^4, R^5, R^6, R^{13} and R^{15} are as above and R^{20} is heterocyclyl.

13. Compounds of claim 12 wherein wherein R^3, R^4 and R^5 are methyl, R^6 is tert-butyl , R^{13} is H and R^{15} is phenyl.

14. N-tert-Butyl-1,2,3,4,4a(S),5,6,7,8a(S)-decahydro-2-[2(R)-hydroxy-3(S)-[[3-methanesulfonyl)-N-[2-(3-pyridyloxy)acetyl]-L-valyl]amino]-4-phenylbutyl]-3(S)-isoquinolinecarboxamide and pharmaceutically acceptable salts and esters thereof

15. Compounds of claims 1 to 14 for use as therapeutically active substances.

16. Compounds of claim 1 to 14 for use in the treatment of HIV mediated diseases.

17. Medicament containing a compound of claims 1 to 14 together with a therapeutically inert carrier for use in the treatment of HIV mediated diseases.

18. Use of the compounds of claims 1 to 14 for the treatment or prevention of HIV mediated diseases.

19. Use of the compounds of claims 1 to 14 for the preparation of a medicament containing a compound of claim 1 to 14 for the treatment of HIV mediated diseases.

20. The invention as hereinbefore described.