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(54) **Heterociklusos aromás vegyületek, amelyek növekedési hormon szekretagógokként használhatók**

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(54) **Heterocyclic aromatic compounds useful as growth hormone secretagogues**

Heterozyklische aromatische Verbindungen, die als Wachstumshormonssekretagogene verwendbar sind

Composés hétérocycliques aromatiques utilisés comme sécrétagogues de l'hormone de croissance

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(56) References cited:
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Description

RELATED APPLICATIONS

[0001] This application claims priority benefit under Title 35 § 119(e) of United States provisional Application Nos. 60/408,099, filed September 4, 2002, and 60/491,645, filed July 31, 2003.

FIELD OF THE INVENTION

[0002] The present invention relates to novel heterocyclic aromatic compounds which stimulate endogenous production and/or release of growth hormone. Further, the present invention relates to to pharmaceutical compositions containing such compounds.

BACKGROUND OF THE INVENTION

[0003] Growth hormone is important not only for linear body growth, but is also important for the maintenance of body composition, metabolism and heart function in adult life. In fact, treatment with growth hormone is employed in both adults and children suffering from growth hormone deficiency. Treatment with growth hormone has been shown to reduce body fat, increase fat-free mass, increase muscle strength, improve bone mass and well-being. These beneficial effects associated with growth hormone treatment suggest that growth hormone treatment may further be useful for the treatment of osteoporosis, frailty in the elderly, complicated fracture, cardiomyopathy, obesity and some nitrogen-wasting conditions resulting from, for example, AIDS, chronic dialysis, catabolic disease and glucocorticoid treatment. Johan Svensson, Exp. Opin. Ther. Patents, 2000 10(7) 1071-1080; Ankersen et al., DDT, 1999, 4(11) 497-506. Moreover, growth hormone therapy is also been explored with a view towards reversing changes associated with aging.

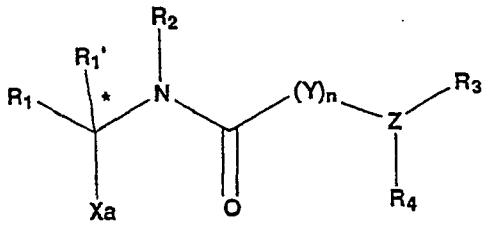
[0004] Current methods for administering growth hormone are invasive in that synthetic growth hormone must be administered by daily injection. Therefore, if an orally administered secretagogue could be introduced that is safe, efficacious, well tolerated, it would provide an attractive treatment alternative to current growth hormone treatment.

[0005] Growth hormone secretagogues are synthetically produced peptides and non-peptides that stimulate the endogenous production and/or release of growth hormone by acting on one or more specific receptors at both pituitary and hypothalamic levels. Accordingly, orally active growth hormone secretagogues could offer attractive alternatives to traditional growth hormone therapy, thus providing a more convenient means to treat a wider array of diseases or disorders associated with growth hormone levels in patient circulation.

[0006] WO 00/54729 relates to heterocyclic aromatic compounds which are useful in stimulating endogenous production or release of growth hormone and in treating obesity, osteoporosis (improving bone density) and in improving muscle mass and muscle strength.

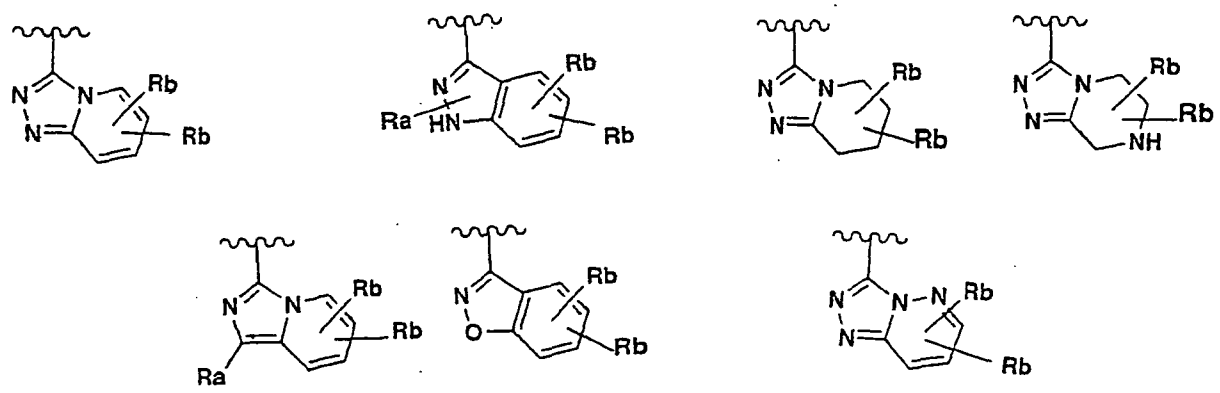
SUMMARY OF THE INVENTION

[0007] In accordance with the present invention, novel heterocyclic aromatic compounds are provided that have the general structure of formula I



I

wherein Xa has the structure



[0008] WO 00/54729 relates to heterocyclic aromatic compounds which are useful in stimulating endogenous production or release of growth hormone and in treating obesity, osteoporosis (improving bone density) and in improving muscle mass and muscle strength.

R_1 is a substituted or unsubstituted functional group selected from the group consisting of alkyl, aryl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heterocycle, alkoxyalkyl, arylalkyloxyalkyl, aryloxyalkyl, heteroaryl, cycloalkylalkoxyalkyl, heteroarylalkoxy, heteroarylalkyl and heterocycloalkyl;

R_2, R_3 and R_4 are each independently a substituted or unsubstituted functional group selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, heterocycle, alkoxyalkyl, arylalkyloxyalkyl, aryloxyalkyl, heteroaryl, cycloalkylalkoxyalkyl, heteroarylalkyl and heterocycloalkyl, or R_3 and R_4 taken together can form a 3 to 8 membered cycloalkyl or heterocyclic ring, or one or more of R_3 and R_4 can be taken together with one or more of Y and Z to form a mono- or bicyclic cycloalkyl or heterocyclic ring;

R_1' is a substituted or unsubstituted functional group selected from the group consisting of hydrogen, alkyl, cycloalkyl, heterocycle, aryl and heteroaryl;

Y is a linking group selected from the group consisting of alkylene, alkenylene, alkynylene, arylene and heteroarylene, said linking group may optionally be substituted with one or more functional groups selected from the group consisting of alkyl, aryl, cycloalkyl, heterocycle, alkoxyalkyl, heteroaryl, arylalkyl, arylalkyloxyalkyl, aryloxyalkyl, cycloalkylalkoxyalkyl, heteroarylalkyl, $-OR_5$, $-OC(O)R_5$, $-CF_3$, $-OCF_3$, $-N(R_5)C(O)R_5$' and-NR_5R_5';

R_5 and R_5' for each occurrence are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, heterocycle and aryl, wherein R_5 and R_5' for each occurrence may optionally be substituted with one or more Rb; Ra and Rb for each occurrence may be absent or are each independently selected from the group consisting of alkyl, alkenyl, alkynyl, halogen, cyano, carbonyl, -CN, aryl, arylalkyl, arylalkenyl, arylalkynyl, cycloalkyl, alkoxy, alkoxyalkyl, aryloxy, aryloxyalkyl, heterocycle, heteroaryl, heteroarylalkyl, $-OR_2$, $-NR_5R_5$', $-CF_3$, $-SO_2R_6$, $-OC(O)R_5$, $-SO_2NR_6R_6$', $-(CH_2)mR_8$ and R_9;

R_6 and R_6' for each occurrence are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkylthioalkyl, alkoxyalkyl, aryl, arylalkyl, heterocycle, heteroaryl, heteroarylalkyl, heterocycloalkyl and cycloalkyl, wherein R_6 and R_6' for each occurrence may optionally be substituted with 1 to 3 substituents selected from the group consisting of halogen, $-OR_2$, alkoxy, heterocycloalkyl, $-NR_5C(O)NR_5R_5$', $-C(O)NR_5R_5$', $-NR_5C(O)R_5$', -CN, $-NR_5SO_2R_5$',$-OC(O)R_5$, $-SO_2NR_5R_5$', $-SOR_7$, -COOH and $-C(O)OR_7$, or R_6 and R_6' taken together can be cyclized to form $-(CH_2)_qX(CH_2)_s$-;

R_7 for each occurrence is independently selected from the group consisting of C_1 to C_6 alkyl, aryl and heteroaryl, wherein R_7 may optionally be substituted with-$(CH_2)_wOH$;

R_8 is selected from the group consisting of alkoxy, alkoxycarbonyl,$-C(O)NR_6R_6$', $-NR_5R_5$', $-C(O)R_6$, $-NR_5C(O)NR_5R_5$' and -N-heteroaryl;

R_9 is selected from the group consisting of heterocycloalkyl, heteroaryl, -CN,$-(CH_2)_pN(R_6)C(O)R_6$', $-(CH_2)_pCN$, $-(CH_2)_pN(R_6)C(O)OR_6$', $-(CH_2)_pN(R_6)C(O)NR_6R_6$', $-(CH_2)pN(R_6)SO_2R_6$, $-(CH_2)_pC(O)NR_6R_6$',) $-(CH_2)_pC(O)OR_6$, $-(CH_2)_pOC(O)OR_6$,$-(CH_2)_pOC(O)R_6$, $-(CH_2)_pOC(O)NR_6R_6$', $-(CH_2)_pN(R_6)SO_2NR_6R_6$', $-(CH_2)_pOR_6$,$-(CH_2)_pOC(O)N(R_6)(CH_2)_mOH$, $-(CH_2)_pSOR_6$ and $-(CH_2)_pOCH_2C(O)N(R_6)(CH_2)_mOH$;

X is selected from the group consisting of $-CR_5R_5$'-, -O-, -S-, -SO-, $-SO_2$-, $-NC(O)OR_7$-, $-NC(O)NR_5$- and $-NR_5$-;

Z is nitrogen;

m is an integer between 1 and 6;

n is an integer from 1 to 6;

p is an integer from 0 to 5;

w is an integer between 0 and 5; and

q and s are each independently an integer between 1 and 3, with the proviso that R_5, R_5', R_6 or R_6 cannot be hydrogen when either is connected to a carbonyl group (e.g., $-C(O)R_6$) or sulfone group (e.g., $-SO_2R_6$).

[0009] The definition of formula I above is inclusive of all stereoisomers and pharmaceutically acceptable salts of formula L

[0010] Compounds of formula I demonstrate activity as growth hormone secretagogues, that is they stimulate endogenous production and/or release of growth hormone and are useful in the treatment of diseases or disorders associated with growth hormone levels, such as those diseases or disorders disclosed herein.

[0011] The present invention provides for compounds of formula I, pharmaceutical compositions employing such compounds and the use of such compounds. In particular, the present invention provides a pharmaceutical composition comprising a compound of formula I, alone or in combination with a pharmaceutically acceptable carrier.

[0012] Moreover, in accordance with the present invention, a use , is provided for increasing levels of endogenous growth hormone or increasing the endogenous production or release of growth hormone in
a mammalian, e.g., human, patient in need of treatment.

[0013] Furthermore, in accordance with the present invention, a use is provided for preventing or treating diseases or disorders associated with mammialian growth hormone levels, such as described herein, in
a mammalian, i.e., human, patient in need of treatment.

[0014] The compounds of the invention can be used alone, in combination with other compounds of the present invention, or in combination with one or more other agent(s) active in the therapeutic areas described herein.

[0015] Further, the present invention provides a use for preventing, inhibiting or treating the diseases as defined above and hereinafter, wherein a therapeutically effective amount of a combination of a compound of formula I and another compound of formula I and/or at least one other type of therapeutic agent, is administered to a mammalian, i.e., human patient in need of treatment.

[0016] Although the preferred Xa structures disclosed above illustrate one or more Ra and/or Rb substituents on any particular cycloalkyl, aryl, heteroaryl or heterocycle ring, the preferred Xa structures are not limited to the specific Ra/Rb substitution illustrated above, nor is an Ra and/or Rb group needed. Rather, the presence of the Rb and/or Ra substituents in the preferred Xa structures, the subsequent Schemes and the claims hereafter, indicate that one or more Ra/Rb group(s) may optionally be attached at any available position of attachment upon the ring to which an Ra/Rb group is associated. Therefore, even though the preferred Xa structures, Schemes and claims hereinafter may reference a particular embodiment, it should be understood that various other modifications, such as the substitution of one or more Rb and/or Ra groups, or other modifications and therapeutically equivalent compounds known to

Q_3 is a 3 to 8 membered fused or spiral cycloalkyl, heterocyclic, aryl or heteroaryl ring, wherein Q_3 may optionally be substituted with 1 to 5 substituents selected from the group consisting of Ra, Rb and Q_4; and

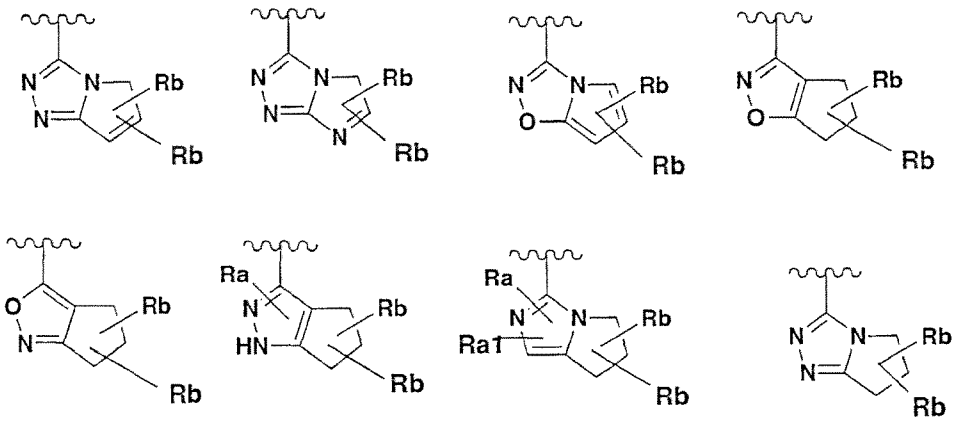
Q_4 is a 3 to 8 membered fused or spiral cycloalkyl, heterocyclic, aryl or heteroaryl ring, wherein Q_4 may optionally be substituted with 1 to 5 substituents selected from the group consisting of Ra and Rb;

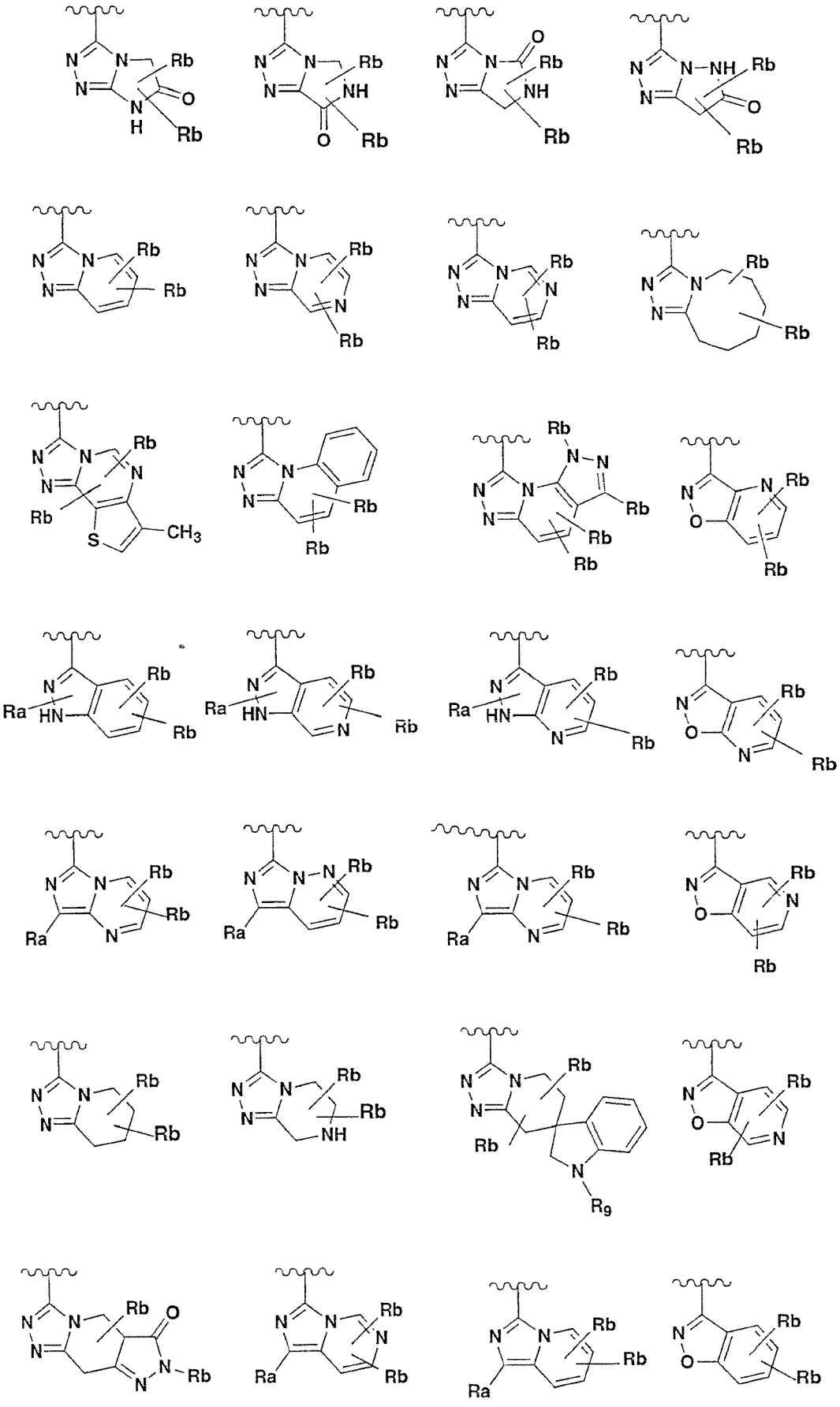
A is N or CR_{11};

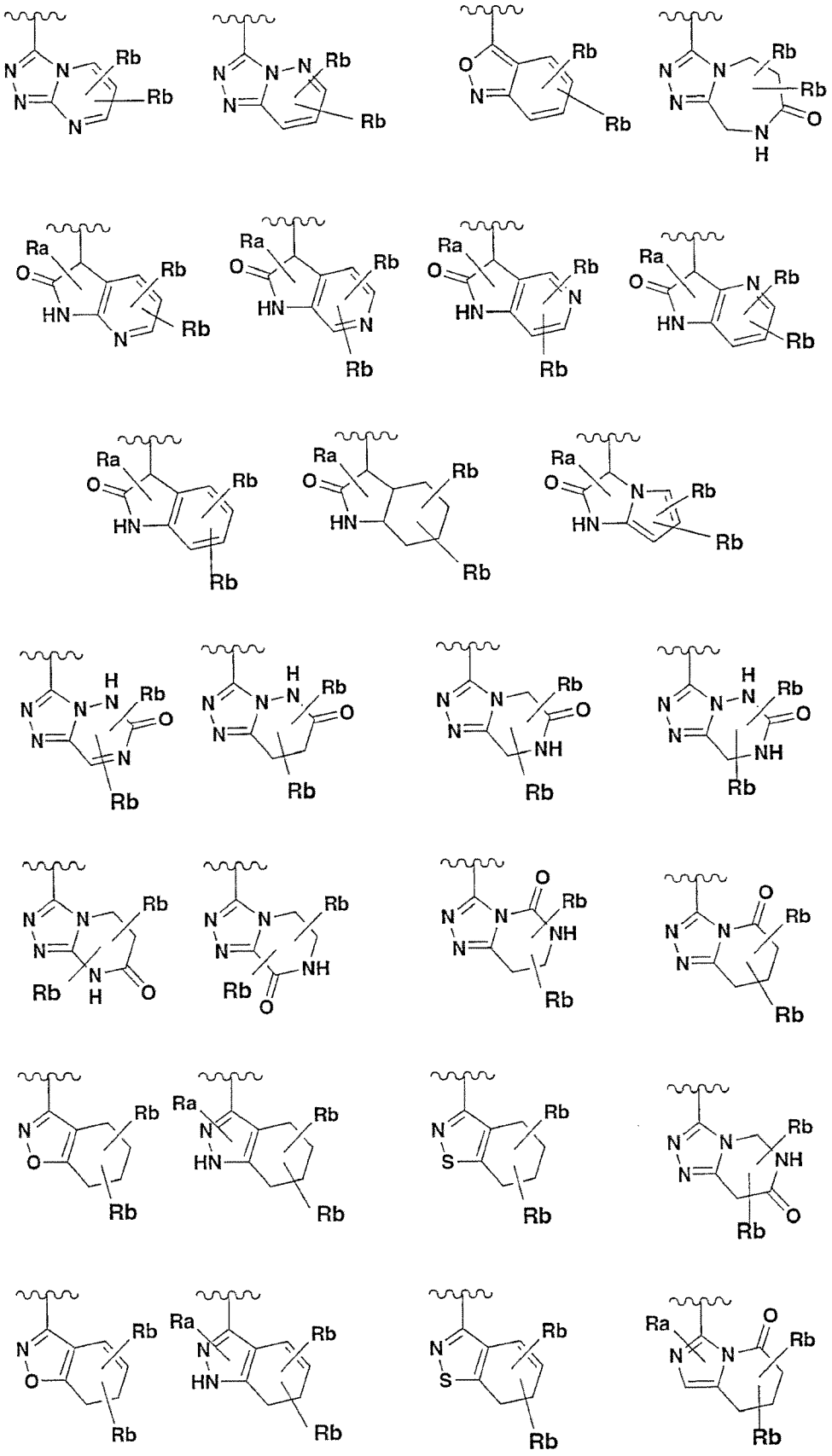
B is N or CR_{11}; and

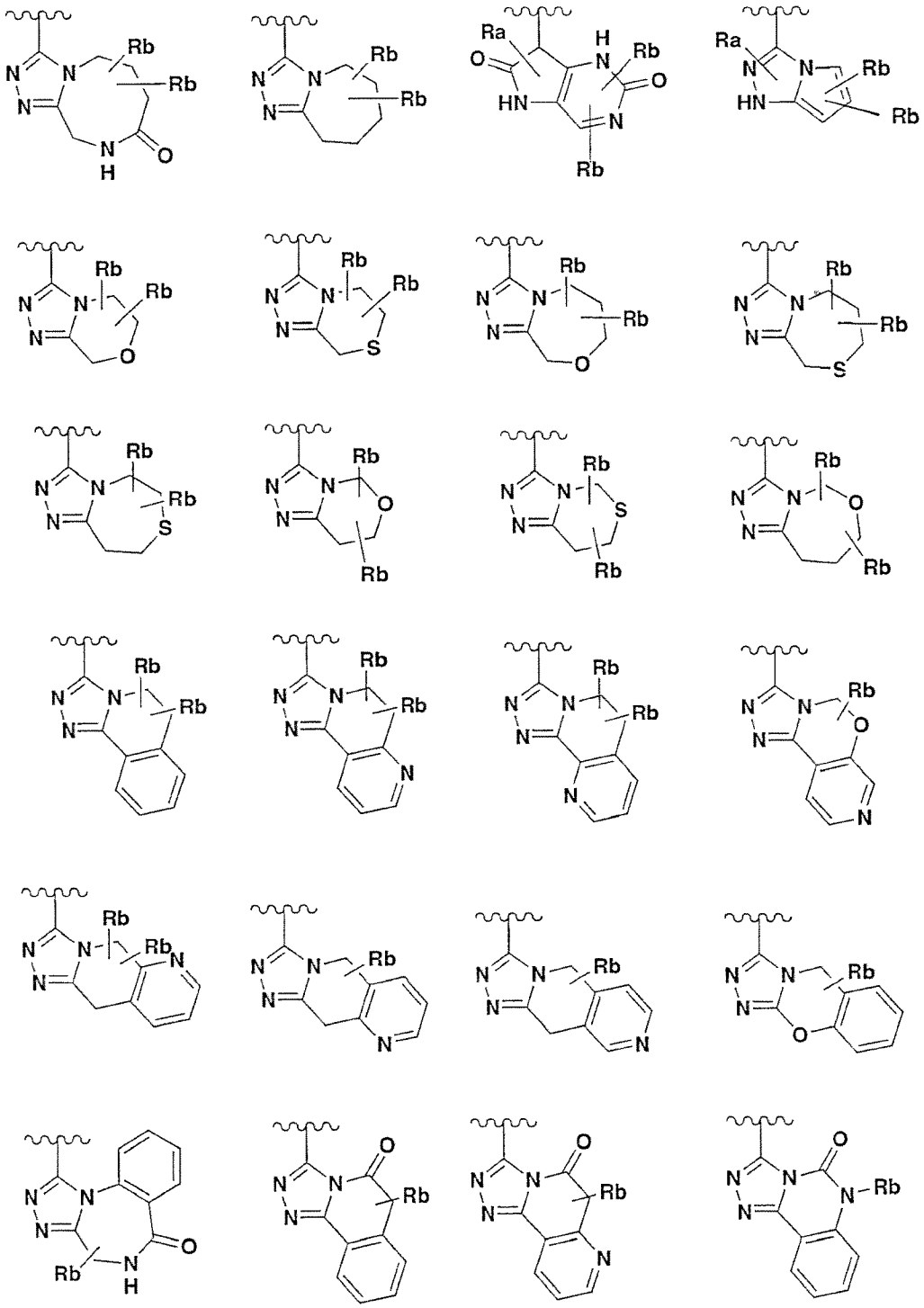
R_{11} is H or a bond.

[0017] Further embodiments include compounds of formula I wherein Xa has the structure









[0018] Although the preferred Xa structures disclosed above illustrate one or more Ra and/or Rb substituents on any particular cycloalkyl, aryl, heteroaryl or heterocycle ring, the preferred Xa structures are not limited to the specific Ra/Rb substitution illustrated above, nor is an Ra and/or Rb group needed. Rather, the presence of the Rb and/or Ra substituents in the preferred Xa structures, the subsequent Schemes and the claims hereafter, indicate that one or more Ra/Rb group(s) may optionally be attached at any available position of attachment upon the ring to which an Ra/Rb group is associated. Therefore, even though the preferred Xa structures, Schemes and claims hereinafter may reference a particular embodiment, it should be understood that various other modifications, such as the substitution of one or more Rb and/or Ra groups, or other modifications and therapeutically equivalent compounds are known to

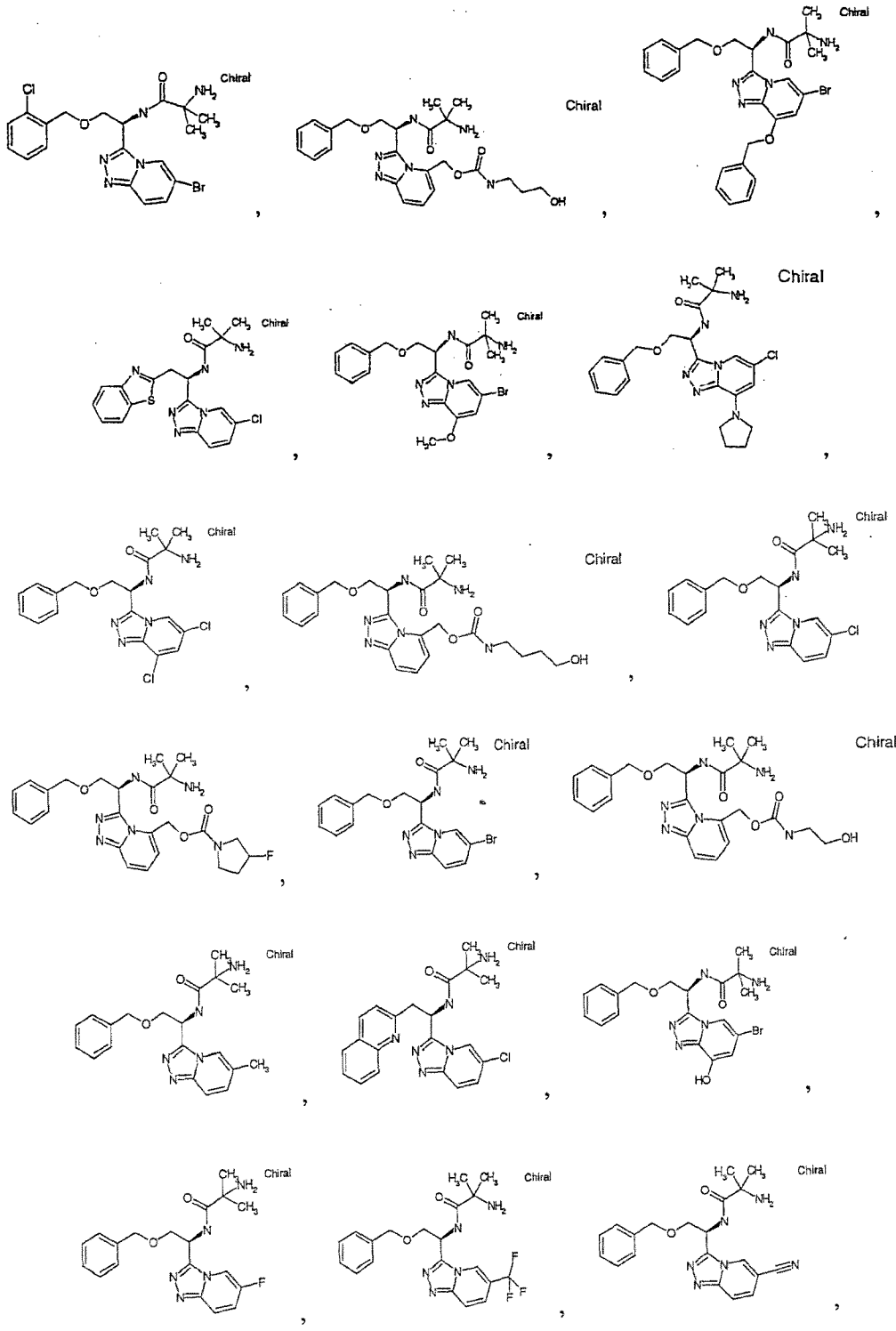
[0019] Preferred are compounds of formula I wherein when Ra or Rb are R_9, R_6 is heterocycle or alkyl, optionally substituted with hydroxyl or halogen.

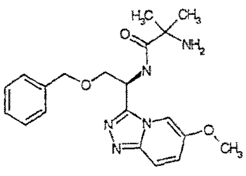
[0020] Preferred are compounds of formula I wherein when Ra or Rb are R_9, R_6 and R_6' are independently hydrogen, alkyl, or cycloalkyl, where the alkyl or cycloalkyl is optionally substituted with $-C(O)OR_7$ or $-C(O)NR_5R_5$', or R_6 and R_6' taken together can be cyclized to form $-(CH_2)_qX(CH_2)_s-$.

[0021] Also preferred are compounds of formula I wherein when Ra or Rb are R_9, R_9 is $(CH_2)_pC(O)OR_6$, $(CH_2)_pOC(O)R_6$, or $(CH_2)_pOC(O)N(R_6)(CH_2)_mOH$.

[0022] Also preferred are compounds of formula I wherein R_9 is $-(CH_2)_pN(R_6)C(O)OR_6$', $-(CH_2)_pN(R_6)C(O)NR_6R_6$', or $(CH_2)_pOC(O)N\ R_6R_6$', where R_6 and R_6' are independently hydrogen or alkyl, where the alkyl is optionally substituted with $-C(O)NR_5R_5$', where R_5 and R_5' are independently hydrogen or alkyl.

[0023] Further preferred embodiments include compounds of formula I having the structure:

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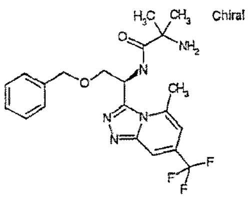
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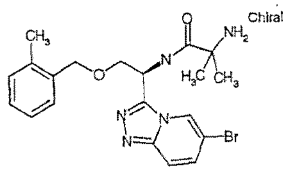
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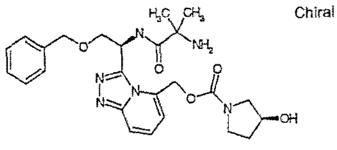
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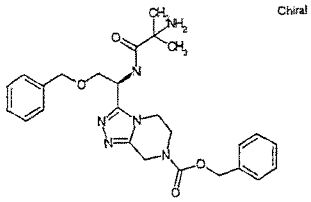
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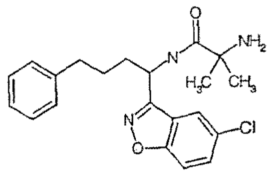
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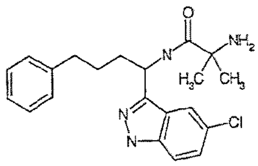
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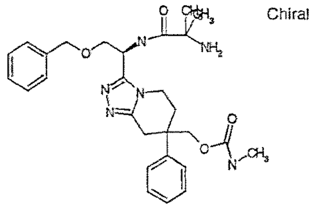
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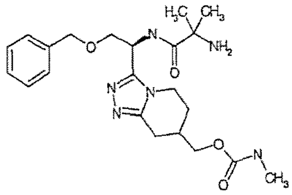
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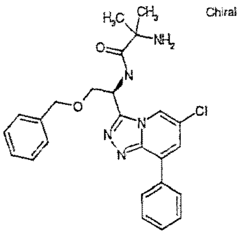
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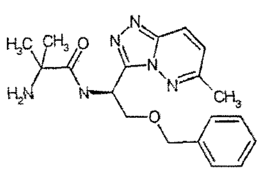
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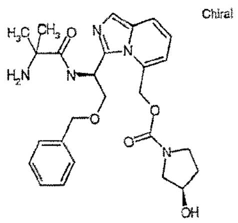
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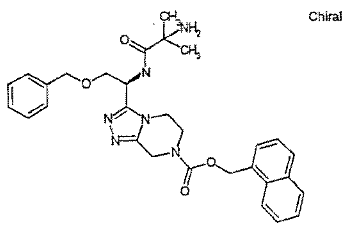
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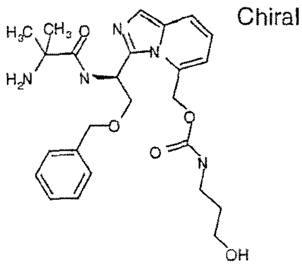
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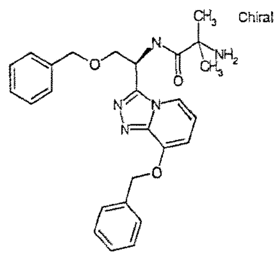
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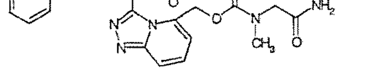
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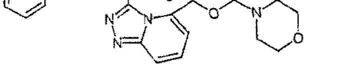
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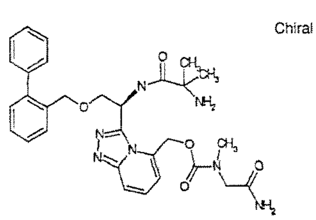
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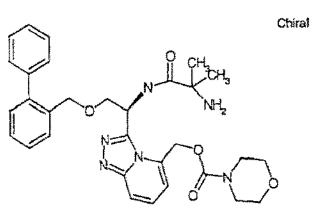
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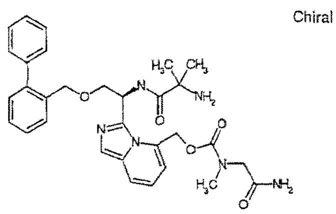
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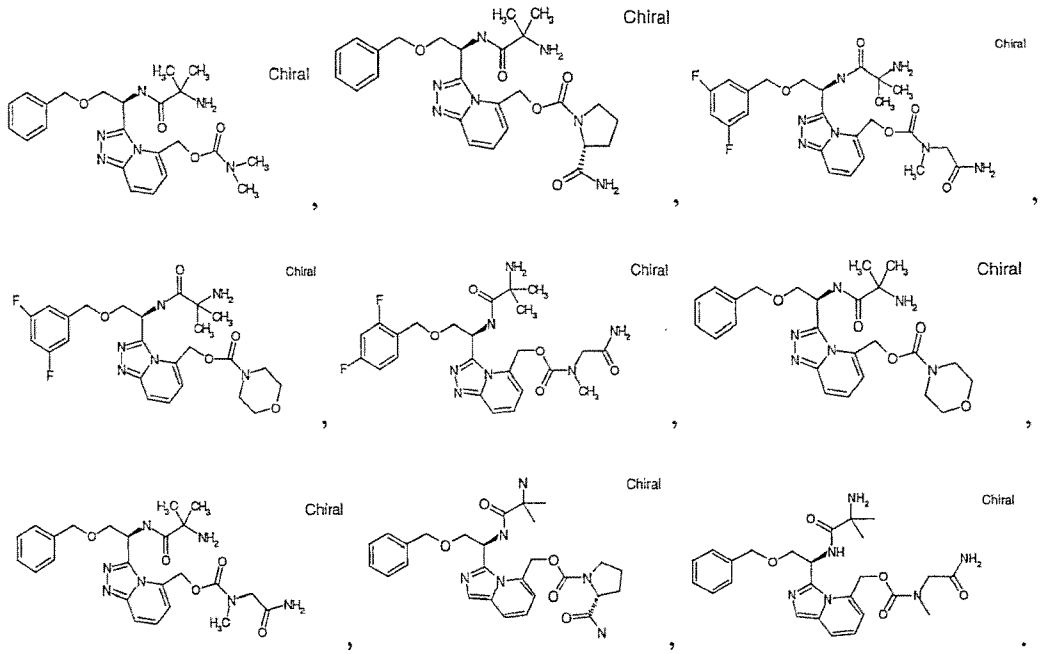
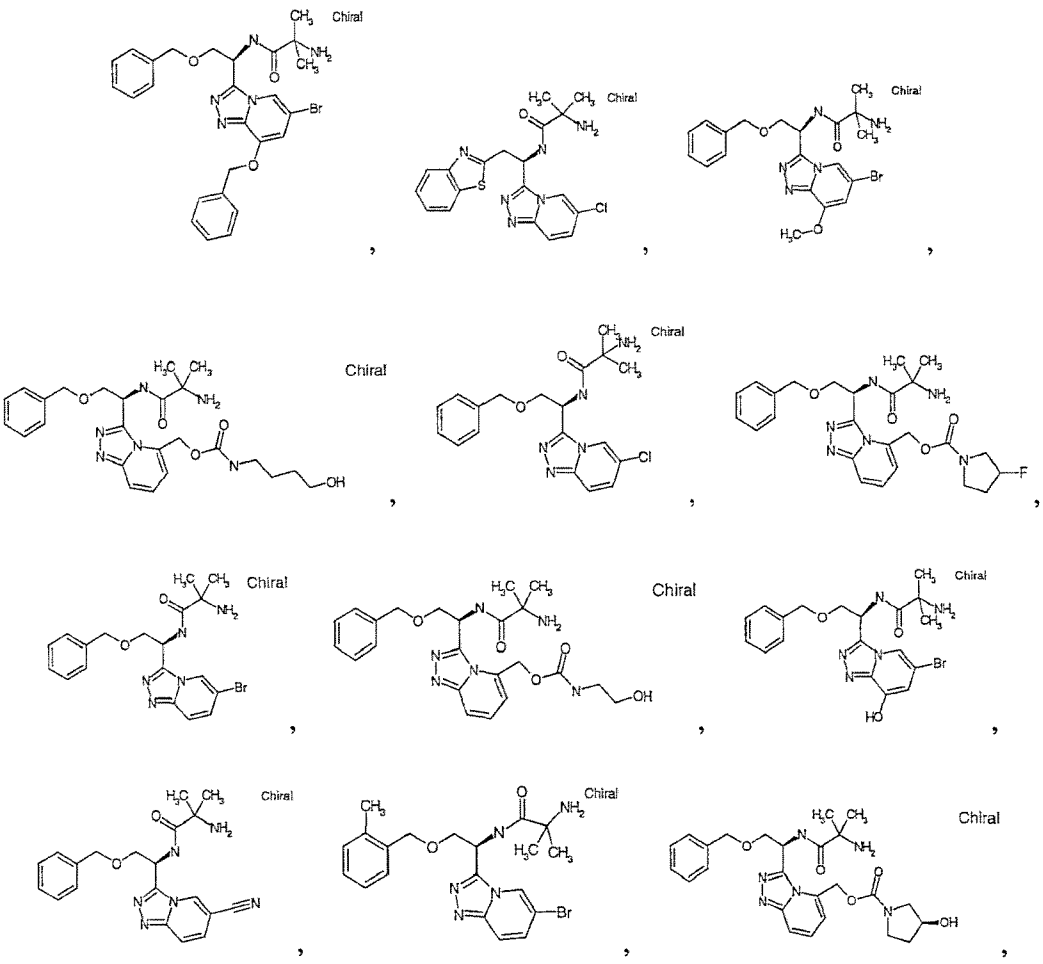
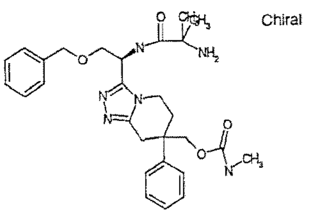


[0024] Additional preferred embodiments include compounds of formula I having the structure:

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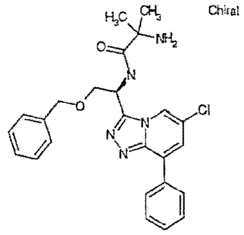
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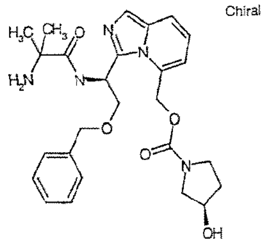
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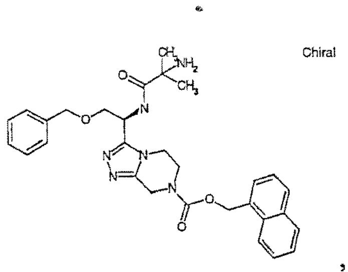
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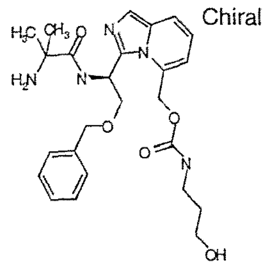
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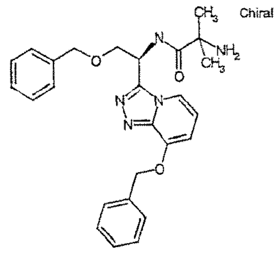
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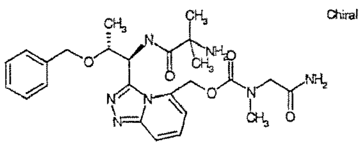
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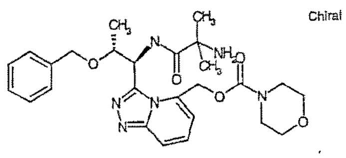
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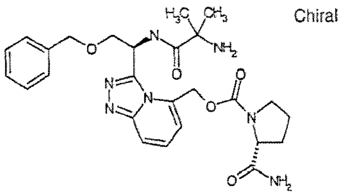
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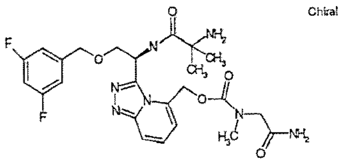
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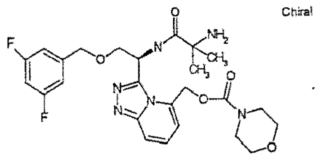
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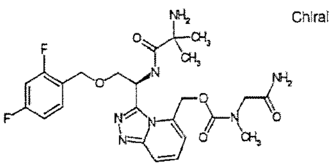
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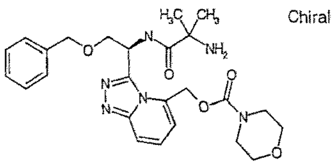
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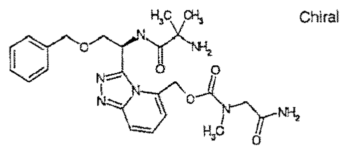
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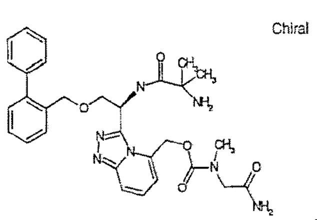
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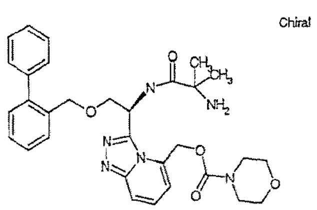
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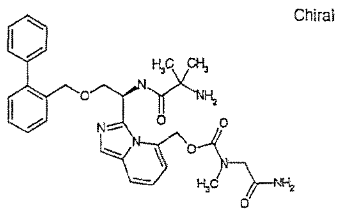
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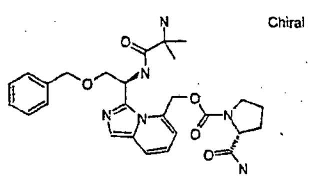
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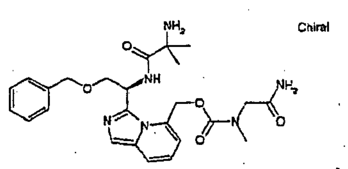
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[0025] The compounds of this invention all have at least one asymmetric center as noted by the asterisk in structural formula I. Additional asymmetric centers may be present on the molecule depending upon the nature of the various substituents on the molecule. Each such asymmetric center will produce two optical isomers.

[0026] In the case of the asymmetric center represented by the asterisk in formula I, the more active and thus more preferred configuration is R as determined by the R/S rules. Isomers may be separated by conventional methods, for example, chromatographic or fractional crystallization.

DETAILED DESCRIPTION OF THE INTENTION

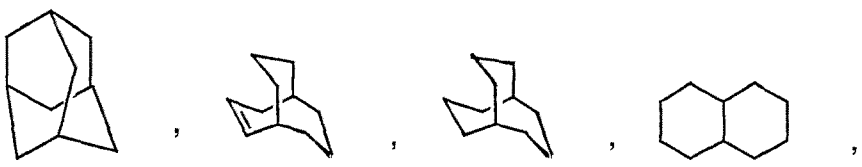
[0027] The following abbreviations are employed herein:

Boc = *tert*-butoxycarbonyl
CBZ = benzyloxycarbonyl (or carbobenzoxy)
DIBAL = diisobutylaluminum hydride
DMAP = 4-(dimethylamino)pyridine
DMF = N,N-dimethylformamide
EDAC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EtOAc = ethyl acetate
HOBT = hydroxybenztriazole
HPLC = high performance liquid chromatography
LC/MS = high performance liquid chromatography/mass spectrometry
MS or Mass Spec = mass spectrometry
Pd/C = palladium on activated charcoal
TFA = trifluoroacetic acid
YMC = trademark of YMC Co, Ltd., Kyoto, Japan
g = gram(s)
h or hr = hour(s)
min = minute(s)
ml = milliliter
mg = milligram(s)
mol = moles
mmol = millimole(s)
nM = nanomolar
r.t. = room temperature
Et = ethyl
i-Pr = isopropyl
Me = methyl

[0028] The following definitions apply to the terms as used throughout this specification, unless otherwise limited in specific instances.

[0029] Unless otherwise indicated, the term "alkyl" as employed herein alone or as part of another group includes both straight and branched chain hydrocarbons, containing 1 to 40 carbons, preferably 1 to 20 carbons, more preferably 1 to 6 carbons, in the normal chain, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl and the various branched chain isomers thereof.

[0030] Unless otherwise indicated, the term "cycloalkyl" as employed herein alone or as part of another group includes saturated or partially unsaturated (containing 1 or 2 double bonds) cyclic hydrocarbon groups containing 1 to 3 rings, including monocyclic alkyl, bicyclic alkyl and tricyclic alkyl, containing a total of 3 to 20 carbons forming the rings, preferably 4 to 10 carbons, forming the ring and which may be fused to 1 aromatic ring as described for aryl, which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl, cyclododecyl, cyclohexenyl,



any of which groups may be optionally substituted with 1 to 3 substituents as defined above for alkyl.

[0031] The term "aryl" as employed herein alone or as part of another group refers to monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or naphthyl) and may optionally include one to three additional rings fused to "aryl" (such as aryl, cycloalkyl, heteroaryl or cycloheteroalkyl rings) and may be optionally substituted through any available carbon atoms with 1 or more groups selected from hydrogen, halo, , alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, cycloalkylalkyl, fluorenyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, aryloxy, aryloxyalkyl, arylalkoxy, arylthio, arylazo, heteroarylalkyl, heteroarylalkenyl, heteroarylheteroaryl, heteroaryloxy, hydroxy, nitro, oxo, cyano, amino, substituted amino wherein the amino includes 1 or 2 substituents (which are alkyl, aryl or any of the other aryl compounds mentioned in the definitions), thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkoxyarylthio, alkylcarbonyl, arylcarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonylamino or arylsulfonaminocarbonyl, or any of alkyl substituents as set out above.

[0032] The term "arylalkyl" as used herein alone or as part of another group refers to alkyl groups as defined above having an aryl substituent, such as benzyl, phenethyl or naphthylpropyl, wherein said aryl and/or alkyl groups may optionally be substituted as defined above.

[0033] The term "alkoxy" or "aryloxy" as employed herein alone or as part of another group includes an alkyl or aryl group as defined above linked through an oxygen atom.

[0034] Unless otherwise indicated, the term "alkenyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 3 to 12 carbons, and more preferably 2 to 6 carbons in the normal chain, which include one or more double bonds in the normal chain, such as vinyl, 2-propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-nonenyl, 4-decenyl, 3-undecenyl, 4-dodecenyl, 4,8,12-tetradecatrienyl, and the like, and which may be optionally substituted with one or more functional groups as defined above for alkyl.

[0035] Unless otherwise indicated, the term "alkynyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 2 to 12 carbons and more preferably 2 to 8 carbons in the normal chain, which include one or more triple bonds in the normal chain, such as 2-propynyl, 3-butynyl, 2-butynyl, 4-pentynyl, 3-pentynyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, 3-nonynyl, 4-decynyl,3-undecynyl, 4-dodecynyl and the like, and which may be optionally substituted with one or more functional groups as defined above for alkyl.

[0036] The term "alkylene" as employed herein alone or as part of another group refers to alkyl linking groups above having single bonds for attachment to other groups at two different carbon atoms and may optionally be substituted as defined above for "alkyl".

[0037] The terms "alkenylene" and "alkynylene" as employed herein alone or as part of another group refer to alkenyl and alkynyl linking groups, having single bonds for attachment at two different carbon atoms and may optionally be substituted as defined above for "alkyl". The term "halogen" or "halo" as used herein alone or as part of another group refers to chlorine, bromine, fluorine and iodine.

[0038] The term "heteroaryl" as used herein refers to a 5-, 6- or 7-membered aromatic heterocyclic ring which contains one or more heteroatoms selected from nitrogen, sulfur, oxygen and/or a SO or SO_2 group. Such rings may be fused to another cycloalkyl, cycloheteroalkyl, aryl or heteroaryl ring and include possible N-oxides. Optionally a heteroaryl group may be substituted with one or more functional groups commonly attached to such chains, such as those described for alkyl.

[0039] The term "heterocyclo", "heterocycle" or "heterocyclic", as used herein, represents an unsubstituted or substituted stable 4-, 5-, 6- or 7-membered monocyclic ring system which may be saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from N, O, S and or a SO or SO_2 group, wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic groups include, but is not limited to, piperidinyl, piperazinyl, oxopiperazinyl, oxopiperidinyl and oxadiazolyl. Optionally a heterocyclo group may be substituted with one or more functional groups, such as those described for alkyl.

[0040] The term "heterocycloalkyl" or "heteroarylalkyl" as used herein alone or as part of another group refers to a heterocyclo or heteroaryl group respectively, linked through an alkyl group.

[0041] The term "alkoxyalkyl," or "aryloxyalkyl" as used herein alone or as part of another group refers to a alkoxy or aryloxy group respectively, linked through an alkyl group.

[0042] The term "heteroarylalkoxy" as used herein alone or as part of another group refers to a heteroaryl group linked through an alkoxy group.

[0043] As used herein alone or as part of another group, the term "cycloalkylalkoxyalkyl" and "arylalkyloxyalkyl" refers to a cycloalkyl group and an aryl group respectively, linked through an alkoxy group, that is in turn linked through an alkyl group.

[0044] The term "arylene" or "heteroarylene" as used herein alone or as part of another group, refers to a alkylene, alkenylene or alkynylene linking group as defined above, wherein said alkylene, alkenylene or alkynylene linking group contains an aryl, (Ar) or heteroaryl (Het) group in the carbon chain. Examples include, but are not limited to $-(CH_2)_2$-Ar-$(CH_2)_2$- or $-(CH_2)_2$-Het-$(CH_2)_2$-.

[0045] The term "carbonyl," as used herein, refers to a -C(O)- group or when referred to as a possible substitutent, refers to a (=O) group attached to any available carbon atom with in the functional group or linking group being substituted.

[0046] The term "phenoxy" as used herin, refers to a phenyl substituent linked through and oxygen atom. Optionally the phenyl ring porton a phenoxy group may be substituted with one or more functional groups, such as described for aryl.

[0047] An administration of a therapeutic agent of the invention includes administration of a therapeutically effective amount of the agent of the invention. The term "therapeutically effective amount" as used herein refers to an amount of a therapeutic agent to treat or prevent a condition treatable by administration of a composition of the invention. That amount is the amount sufficient to exhibit a detectable therapeutic or preventative or ameliorative effect. The effect may include, for example, treatment or prevention of the conditions listed herein. The precise effective amount for a subject will depend upon the subject's size and health, the nature and extent of the condition being treated, recommendations of the treating physician, and the therapeutics or combination of therapeutics selected for administration. Thus, it is not useful to specify an exact effective amount in advance.

[0048] Any compound that can be converted in vivo to provide the bioactive agent (i.e., the compound of formula I) is a prodrug.

[0049] The term "prodrug esters" as employed herein includes esters and carbonates formed by reacting one or more hydroxyls of compounds of formula I with alkyl, alkoxy, or aryl substituted acylating agents employing procedures known to those skilled in the art to generate acetates, pivalates, methylcarbonates, benzoates and the like.

[0050] Various forms of prodrugs are well known in the art and are described in:

a) The Practice of Medicinal Chemistry, Camille G. Wermuth et al., Ch 31, (Academic Press, 1996);
b) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985); and
c) A Textbook of Drug Design and Development, P. Krogsgaard-Larson and H. Bundgaard, eds. Ch 5, pgs 113 - 191 (Harwood Academic Publishers, 1991).

[0051] All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The compounds of the present invention can have asymmetric centers at any of the carbon atoms including any one of the R substituents. Consequently, compounds of formula I can exist in enantiomeric or diastereomeric forms or in mixtures thereof. The processes for preparation can utilize racemates, enantiomers or diastereomers as starting materials. When diastereomeric or enantiomeric products are prepared, they can be separated by conventional methods for example, chromatographic techniques or fractional crystallization.

[0052] The pharmaceutically acceptable salts of the compounds of formula I of the invention include alkali metal salts such as lithium, sodium or potassium, alkaline earth metal salts such as calcium or magnesium, as well as zinc or aluminum and other cations such as ammonium, choline, diethanolamine, ethylenediamine, t-butylamine, t-octylamine, dehydroabietylamine, as well as pharmaceutically acceptable anions such as chloride, bromide, iodide, tartrate, acetate, methanesulfonate, maleate, succinate, glutarate, stearate and salts of naturally occurring amino acids such as arginine, lysine, alanine and the like,

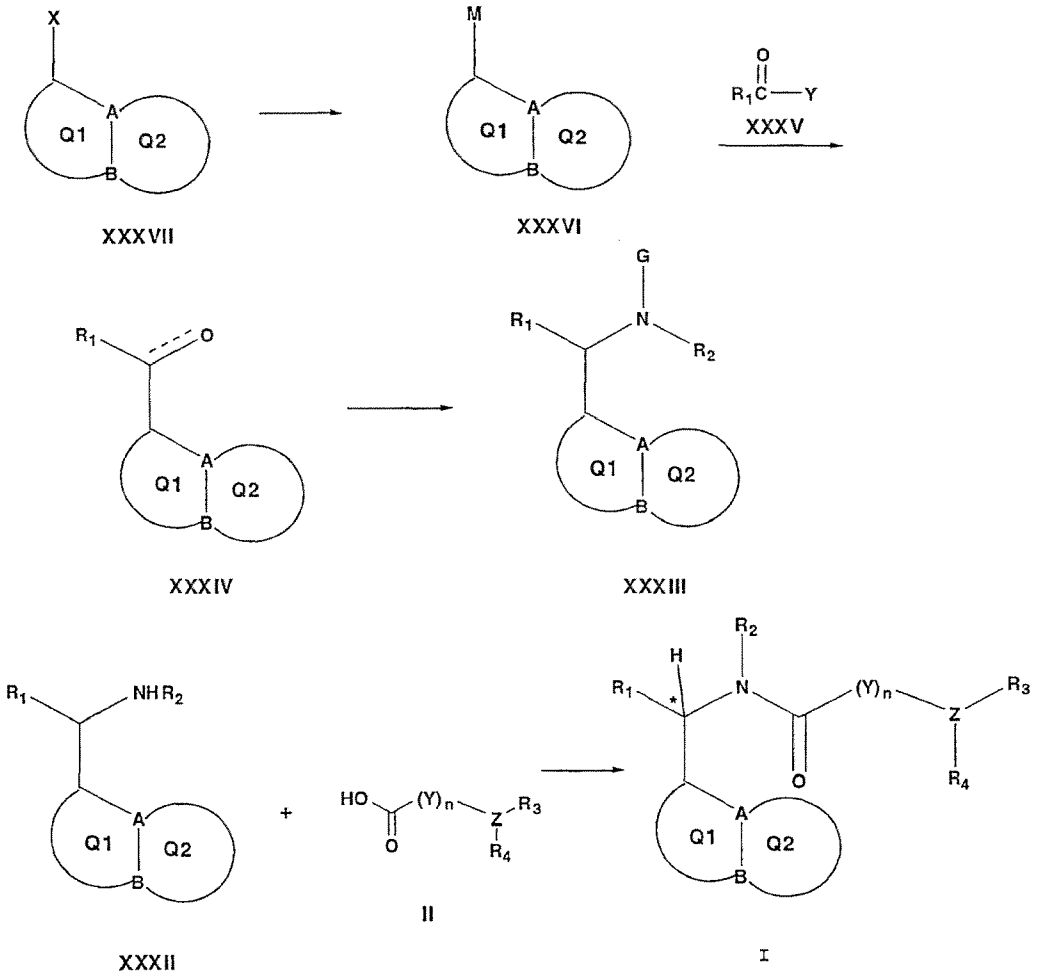
GENERAL SYNTHETIC SCHEMES

[0053] The compounds of the present invention may be prepared according to the following general synthetic reaction schemes as well as relevant published literature procedures that may be used by one skilled in the art. Exemplary reagents, procedures and conditions for these reactions appear hereinafter and in the working examples. Starting materials are commercially available or can be readily prepared by one of ordinary skill in the art using known methods. Unless otherwise specified the various substituents of the compounds are defined in the same manner as the formula I.

[0054] High Speed Analoging (HSA) may be employed in the preparation of compounds, for example, where the intermediates possess an amine position or activated aromatic position, such as the halogenated Q1 and Q2.

SCHEME I

[0055] Scheme I describes a general synthetic sequence for the preparation of the compounds of formula I. During the preparation of compounds of formula I, one or more protecting groups might be used, reaction conditions for protection and deprotection may be found in the 'Protective Groups in Organic Synthesis" Greene et al., John Wiley and Sons Inc, 1991, or other methods used by one of ordinary skill in the art.



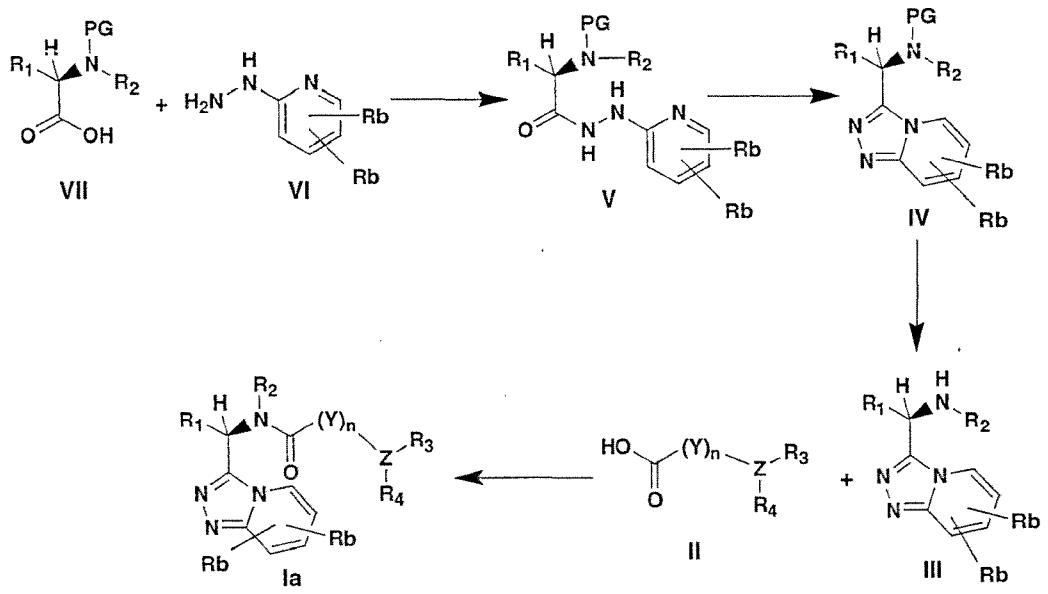
[0056] Compounds of formula I can be prepared from a compound of formula II and amine XXXII using an appropriate carboxylic acid activating reagent in an inert solvent. Exemplary carboxylic acid activating agents include isobutylchloroformate, carbonyldiimidazole, dicyclohexylcarbodiimide, pentofluorophenol trifluoroacetate, or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide. Exemplary inert solvents include ethers, dioxane, tetrahydrofuran, N,N-dimethylformamide, acetonitrile, or methylene chloride. If R_3 and/or R_4 are an amine protecting group, such as Boc-, CBZ or Trityl, they will be deprotected to afford the final products. Reaction conditions for deprotection may be founds in the 'Protective Groups in Organic Synthesis" Greene et al., John Wiley and Sons Inc, 1991, or other methods used by one of ordinary skill in the art.

[0057] Compound XXXII can be prepared by the deprotection of compound IV where PG is an appropriate amino protecting group such as Boc-, CBZ or Trityl, etc. Exemplary deprotection reagents for Boc- are hydrogen chloride in dioxane, TFA in dichloromethane, etc.; exemplary deprotection for CBZ is catalytic hydrogenation, exemplary deprotection for Trityl is hydrogen chloride in acetone or tetrahydrofuran.

[0058] Compound XXXIII can be prepared from compound XXXIV. When C---O is a hydroxyl group in compound XXXIV, it can be converted to an azide group followed by reduction to give the amino group in compound XXXIII. (for an example, see Lautens et al, J. Org. Chem. (1997) 62, 5246-5247). When C---O is a carbonyl group, it can be reduced to a hydroxyl group then converted to the amino group in compound XXXIII. Alternatively, it can be converted to an O-methyl oxime, then followed by reduction to give the amino group in compound XXXIII. Reduction of O-methyl oxime to amine can be carried out with borane tetrahydrofuran complex or other methods used by one of ordinary skill in the art.

[0059] Compound XXXIV can be prepared from reaction of compound XXXVI and compound XXXV. Compounds XXXV [Y = H, SPh, Cl, NMe(OMe)] can be prepared by one of the ordinary skill in the art. Compounds XXXVI (M = Li, MgBr, MgCl, ZnBr, ZnI) is an organometalic intermediate, which can be prepared from an appropriate precursor (X = B, I, Cl). or other methods used by one of ordinary skill in the art. Organic zinc reagents can be prepared via treatment of arylbromide or aryliodide with Rieke®zinc metal as described in J. Org. Chem. (1991), 56, 1445 or Tetrahedron (1997), 53, 1925. Alternatively, it can also be prepared via treatment of arylbromide or aryliodide with n-BuLi or tert-BuLi followed by addition of zinc bromide or zinc iodide.

SCHEME IIa



[0060] Compounds of the formula Ia can be prepared via the aminolysis of a compound of formula II using an appropriate carboxylic acid activating reagent and amine III in an inert solvent. Exemplary carboxylic acid activating agents include isobutylchloroformate, carbonyldiimidazole, dicyclohexylcarbodiimide, pentofluorophenol trifluoroacetate, or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide. Exemplary inert solvents include ethers, including tetrahydrofuran and dioxane, N, N-dimethylformamide, acetonitrile, or methylene chloride. If R_3 and/or R_4 are an amine-protecting group, such as Boc-, or CBZ, they will be deprotected to afford the final products. Deprotections are done by one of ordinary skill in the art as described in the following.

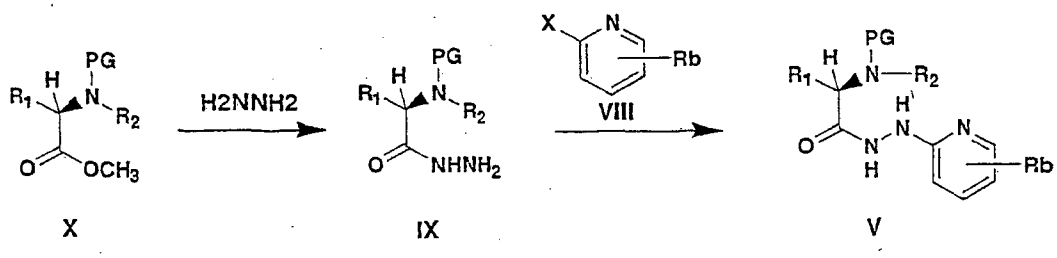
[0061] Compound III can be prepared by the deprotection of compound IV where G is an appropriate amino protecting group such as Boc-, CBZ, etc., as commonly used by one of ordinary skill in the art. Exemplary deprotection reagents for Boc- are hydrogen chloride in dioxane, TFA, etc; exemplary deprotection for CBZ is catalytic hydrogenation.

[0062] Compound IV can be prepared from compound V via a dehydrating process. Exemplary dehydrating agents include $POCl_3$, $SOCl_2$, HCl, HOAc and Mitsunobu reactions.

[0063] Compound V can be prepared from compounds VII via aminolysis using an appropriate carboxylic acid activating reagent and amine VI in an inert solvent. Exemplary carboxylic acid activating agents include isobutylchloroformate, carbonyldiimidazole, dicyclohexylcarbodiimide, pentofluorophenol trifluoroacetate, or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide. Exemplary inert solvents include ethers, including tetrahydrofuran and dioxane, N,N-dimethylformamide, acetonitrile, or methylene chloride.

[0064] Although compound VI discloses two Rb substituents on the pyridine ring, the schemes are not limited to a single Rb group, nor is an Rb group needed. Rather, the presence of the Rb substituents in Scheme IIa and the subsequent Schemes hereafter, indicate that one or more Rb groups may optionally be attached at any available position of attachment upon the ring to which the Rb group is associated. Therefore, even though Scheme IIa and the Schemes hereinafter may reference a particular embodiment, it should be understood that various other modifications, such as the substitution of one or more Rb groups, or other modifications are known to those skilled in the art.

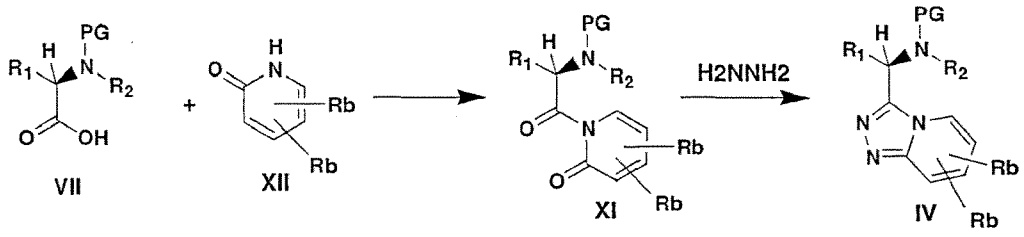
SCHEME IIb



[0065] Alternately, compound V can be prepared by the condensation of IX and VIII (where X is a leaving group such as a halogen) in an inert solvent at elevated temperatures. Exemplary inert solvents include DMF, THF, dioxane, acetonitrile, pyridine, and inert alcohol such as ethanol. Exemplary temperatures can range from 40 to 150 °C.

[0066] Compound IX can be prepared by the hydrazinolysis of X via procedures used by one of ordinary skill in the art.

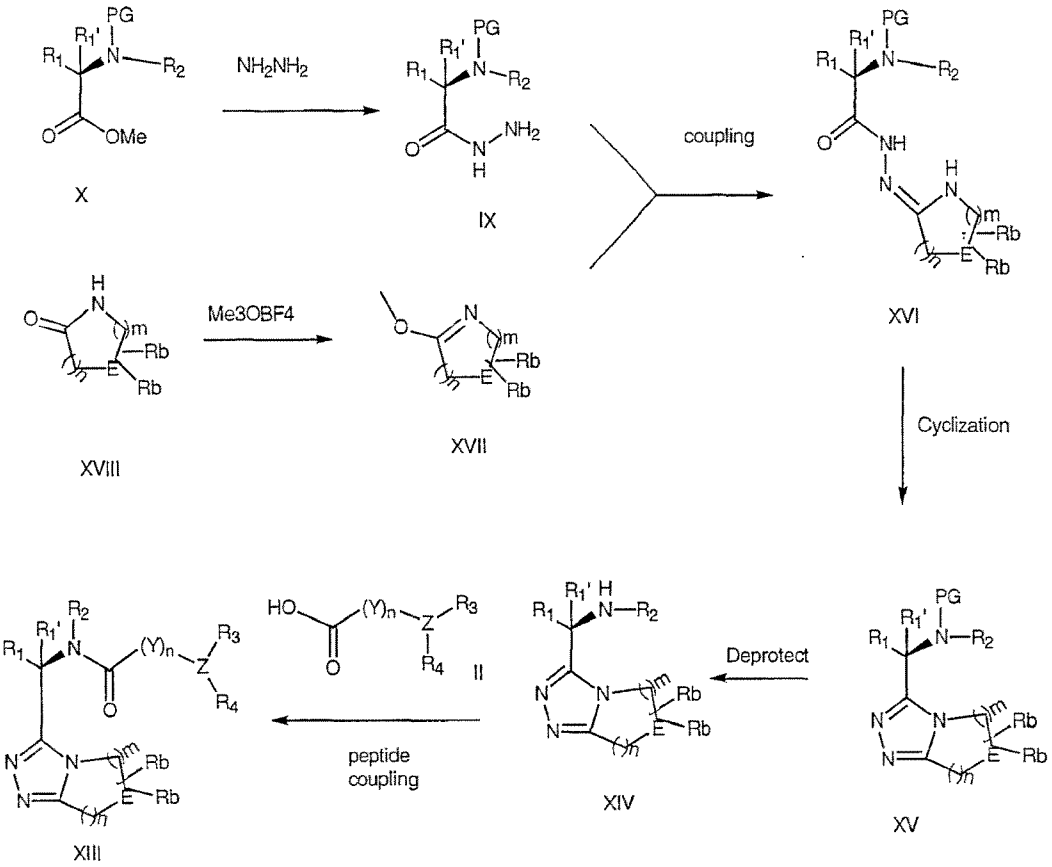
SCHEME IIc



[0067] Alternately, compound IV can be prepared by the hydrazinolysis of compound XI in an inert solvent at elevated temperature. Exemplary inert solvents include hydrazine, HOAc, THF, dioxane, pyridine and inert alcohol such as ethanol. Exemplary temperatures can range from 40 to 150 °C.

[0068] Compound XI can be prepared by the condensation of XII and VII via an appropriate carboxylic acid activating agent in an inert solvent. Exemplary carboxylic acid activating agents include isobutylchloroformate, carbonyldiimidazole, dicyclohexylcarbodiimide, pentofluorophenol trifluoroacetate, or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide. Exemplary inert solvents include ethers, including tetrahydrofuran and dioxane, N,N-dimethylformamide, acetonitrile, or methylene chloride.

SCHEME IIIa



[0069] Scheme IIIa describes a general synthetic sequence for the preparation of the compounds of formula XIII (where E can be CH_2, CRaRb, NRa , O, S, SO_2, SO, CO, C(O)O, C(O)NRa, and m and n can independently be an integer from 0 to 6, with the caveat that m and n together form a 5-12 membered ring structure.

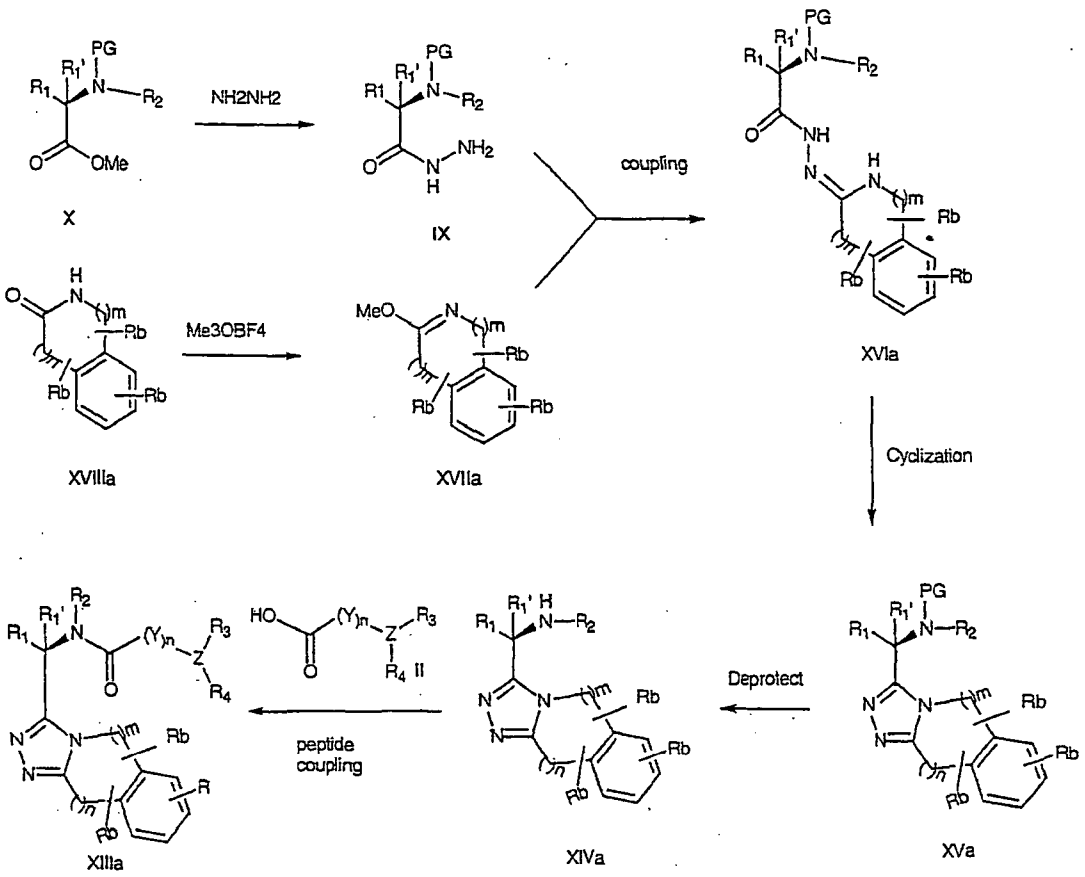
[0070] Compounds of formula XIII can be prepared via the aminolysis of a compound of formula II using an appropriate carboxylic acid activating reagent and amine XIV in an inert solvent. Exemplary carboxylic acid activating agents include isobutylchloroformate, carbonyldiimidazole, dicyclohexylcarbodiimide, pentofluorophenol trifluoroacetate, or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide. Exemplary inert solvents include ethers, including tetrahydrofuran and dioxane, N, N-dimethylformamide, acetonitrile, or methylene chloride. If R_3 and/or R_4 are an amine-protecting group, such as Boc-, or CBZ, they will be deprotected to afford the final products. Deprotections are done by one of ordinary skill in the art as described in the following.

[0071] Compound XIV can be prepared by the deprotection of compound XV where PG is an appropriate amino protecting group such as Boc-, CBZ, etc. used by one of ordinary skill in the art. Exemplary deprotection reagents for Boc- are hydrogen chloride in dioxane, TFA, etc; exemplary deprotection for CBZ is catalytic hydrogenation.

[0072] Compound XVI can be prepared from compound X via a dehydrating conditions in protonic and aprotic solvents. Dehydrating conditions can be exemplified by using protonic solvent along or by using combinations with dehydrating agents include HOAc, PPTS or by using Mitsunobu reactions in the inert solvents.

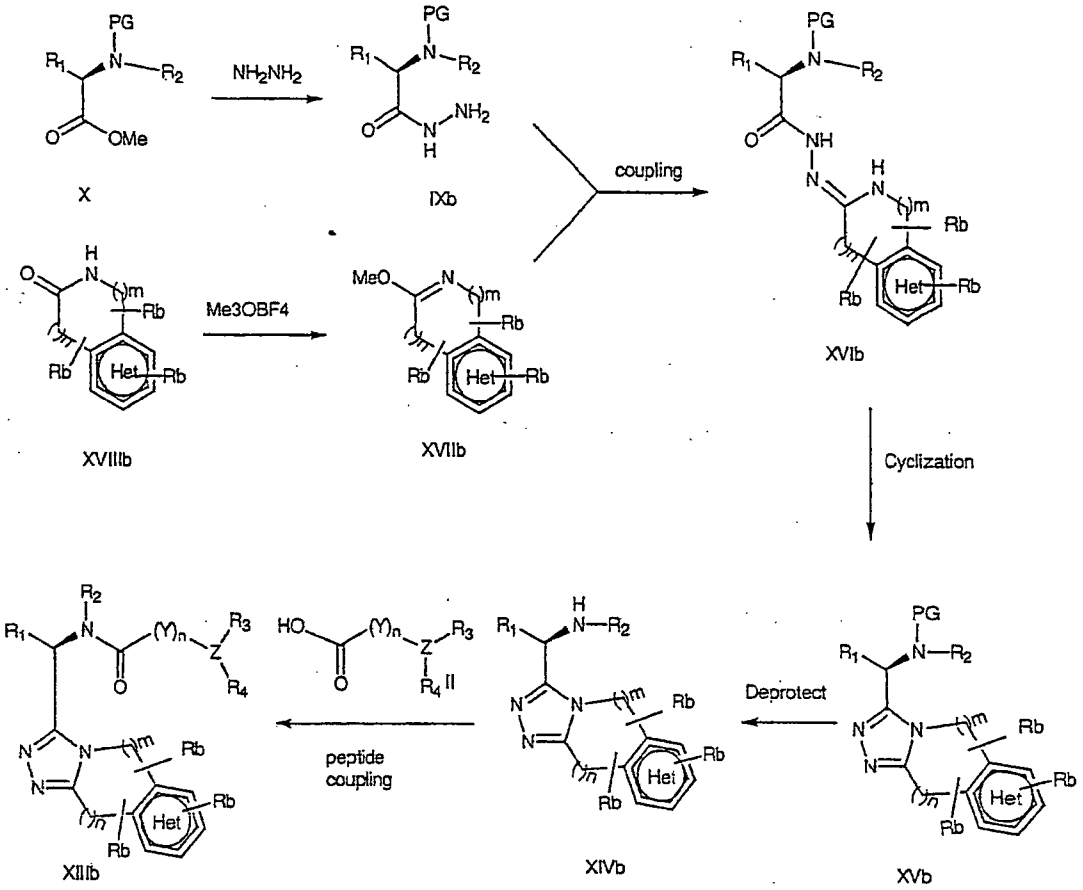
[0073] Compound XVI can be prepared from coupling compounds IX and compound XVII in inert solvent.

Ref. SCHEME IVa

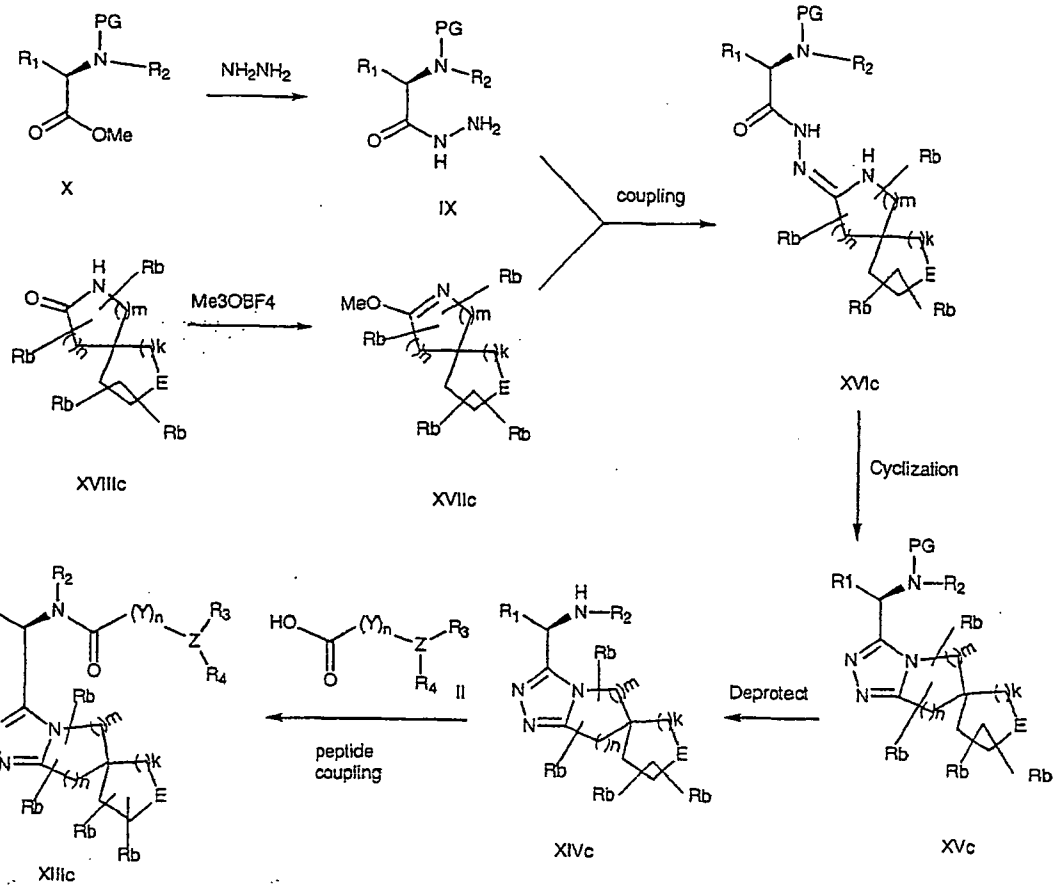


[0074] Schemes IVa - IVc can be carried out using similar general procedures as described for Scheme IIIa, where intermediates XVIIIa, XVIIIb and XVIIIc are utilized in place of intermediate XVIII. m and n can independently be an integer from 0 to 5, with the caveat that m and n together form a 6 - 12 membered ring structure.

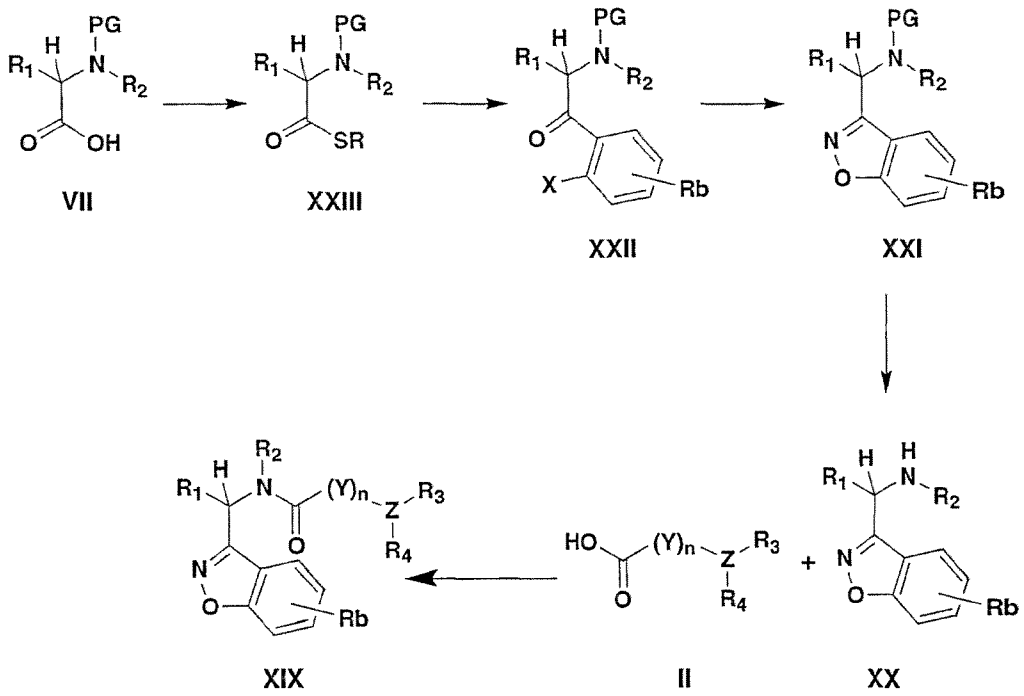
Ref. SCHEME IVb



Ref. SCHEME IVc



SCHEME V



[0075] Compounds of formula XIX can be prepared from a compound of formula II and amine XX using an appropriate carboxylic acid activating reagent in an inert solvent. Exemplary carboxylic acid activating agents include isobutylchloroformate, carbonyldiimidazole, dicyclohexylcarbodiimide, pentofluorophenol trifluoroacetate or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide. Exemplary inert solvents include ethers, dioxane, tetrahydrofuran, N,N-dimethylformamide, acetonitrile or methylene chloride. If R_3 and/or R_4 are an amine-protecting group, such as Boc-, CBZ or Trityl, they will be deprotected to afford the final products. Reaction conditions for deprotection may be founds in the 'Protective Groups in Organic Synthesis" Greene et al., John Wiley and Sons Inc, 1991, or other methods used by one of ordinary skill in the art.

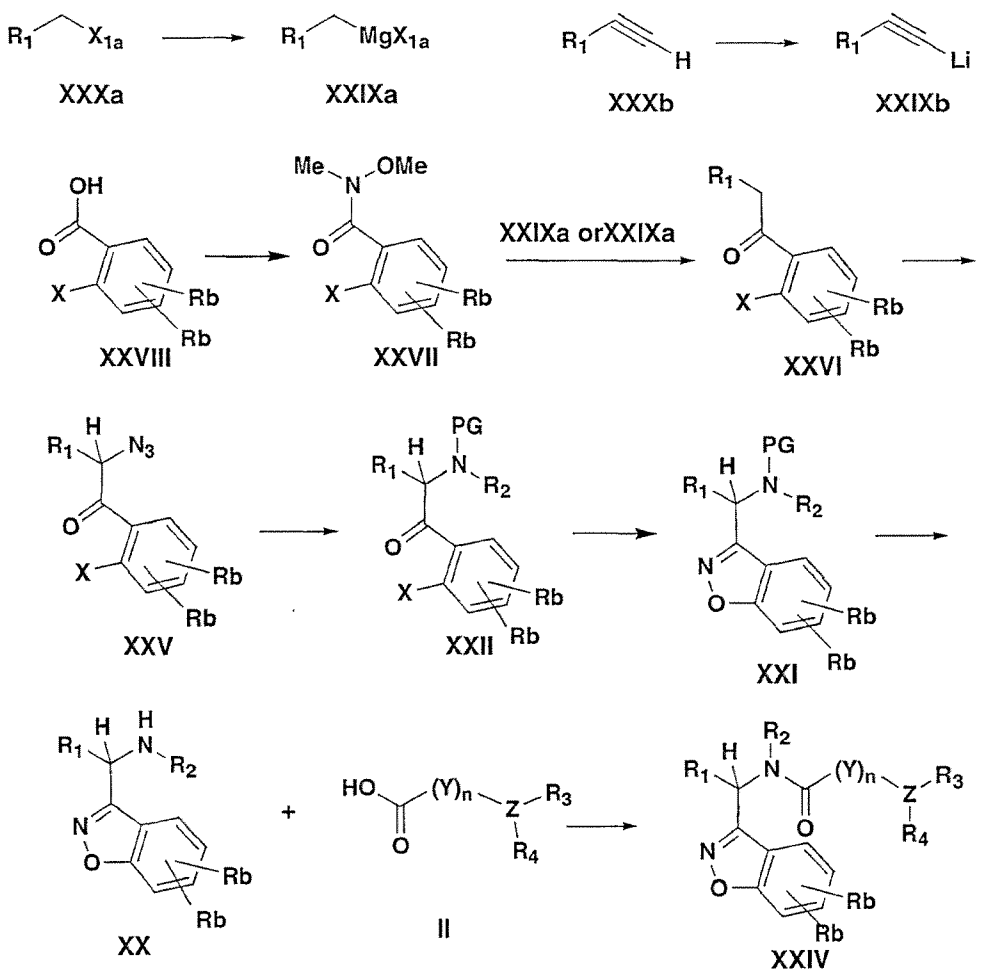
[0076] Compound XX can be prepared by the deprotection of compound XXI where PG is an appropriate amino protecting group such as Boc-, CBZ or Trityl, etc. Reaction conditions for deprotection may be founds in the 'Protective Groups in Organic Synthesis" Greene et al., John Wiley and Sons Inc, 1991, or other methods used by one of ordinary skill in the art. Exemplary deprotection reagents for Boc- are hydrogen chloride in dioxane, TFA in dichloromethane, etc.; exemplary deprotection for CBZ is catalytic hydrogenation, exemplary deprotection for Trityl is hydrogen chloride in acetone or tetrahydrofuran.

[0077] Compound XXI can be prepared from compound XXII (X = Cl or F). Compound XXII first react with hydroxyamine to give an oxime intermediate, then followed by cyclization under basic condition or other methods used by one of ordinary skill in the art.

[0078] Compound XXII can be prepared from compound XXIII via treatment of appropriate organic zinc reagents in an inert solvent such as ethers, tetrahydrofuran or toluene. Organic zinc reagents can be prepared via treatment of arylbromide or aryliodide with Rieke®zinc metal as described in J. Org. Chem. (1991), 56, 1445 or Tetrahedron (1997), 53, 1925. Alternatively, it can also be prepared via treatment of arylbromide or aryliodide with n-BuLi or tert-BuLi followed by addition of zinc bromide or zinc iodide.

[0079] Compounds XXIII can be prepared from a compound of formula VII and a mercapto compound such as thiophenol using an appropriate carboxylic acid activating reagent in an inert solvent. Exemplary carboxylic acid activating agents include isobutylchloroformate, carbonyldiimidazole, dicyclohexylcarbodiimide, pentofluorophenol trifluoroacetate, or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide. Exemplary inert solvents include ethers, dioxane, tetrahydrofuran, N, N-dimethylformamide, acetonitrile, or methylene chloride.

SCHEME VI



[0080] XXIV can be prepared from a compound of formula II and amine XX using an appropriate carboxylic acid activating reagent in an inert solvent. Exemplary carboxylic acid activating agents include isobutylchloroformate, carbonyldiimidazole, dicyclohexylcarbodiimide, pentofluorophenol trifluoroacetate, or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide. Exemplary inert solvents include ethers, dioxane, tetrahydrofuran, N, N-dimethylformamide, acetonitrile, or methylene chloride. If R3 and/or R4 are an amine-protecting group, such as Boc-, CBZ or Trityl, they will be deprotected to afford the final products. Reaction conditions for deprotection may be founds in the 'Protective Groups in Organic Synthesis" Greene et al., John Wiley and Sons Inc, 1991, or other known methods used by one of ordinary skill in the art.

[0081] Compound XX can be prepared by the deprotection of compound XXI where PG is an appropriate amino protecting group such as Boc-, CBZ or Trityl, etc. Reaction conditions for deprotection may be founds in the 'Protective Groups in Organic Synthesis" Greene et al., John Wiley and Sons Inc, 1991, or other known methods used by one of ordinary skill in the art. Exemplary deprotection reagents for Boc- are hydrogen chloride in dioxane, TFA in dichloromethane, etc.; exemplary deprotection for CBZ is catalytic hydrogenation, exemplary deprotection for Trityl is hydrogen chloride in acetone or tetrahydrofuran.

[0082] Compound XXI can be prepared from compound XXII (X = Cl or F). Compound XXII first react with hydroxyamine to give an oxime intermediate, then followed by cyclization under basic condition or other methods used by one of ordinary skill in the art.

[0083] Compound XXII can be prepared by reduction of azido compound XXV followed by protection of the resulting amine intermediate by an amine protecting group such as Boc, CBz or Trityl, etc. Exemplary reduction reaction include hydrogenation or with triphenylphosphine in aqueous tetrahydrofuran. Reaction conditions for protection of the resulting amine intermediate may be founds in the 'Protective Groups in Organic Synthesis" Greene et al., John Wiley and Sons Inc, 1991, or other methods used by one of ordinary skill in the art.

[0084] Compounds XXV can be prepared from a compound of formula XXVI in a two step sequence or other known

methods in the art. Treatment of compound XXVI with bromine resulted in a α-bromoketone intermediate, which was followed by treatment with azide ion such as sodium azide.

[0085] Compounds XXVI can be prepared from a compound of formula XXVII with an organic metal reagent XXIXa or XXIXb.

[0086] Compound XXVII can be prepared from an acid XXVIII and N, O-dimethyl-amine hydrochloride using an appropriate carboxylic acid activating reagent and base in an inert solvent. Exemplary carboxylic acid activating agents include isobutylchloroformate, carbonyldiimidazole, dicyclohexylcarbodiimide, pentofluorophenol trifluoroacetate, or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide. Exemplary inert solvents include ethers, dioxane, tetrahydrofuran, N, N-dimethylformamide, acetonitrile, or methylene chloride. Alternatively, acid XXVIII can be converted to the corresponding acid chloride using oxalyl chloride, thionyl chloride or other known methods in the art. The resulting acid chloride can then reacted with N, O-dimethyl-amine hydrochloride in the presence of a base such as trimethylamine in an inert solvent.

[0087] Compound XXIXa is commonly known as Grignard reagents, and can be prepared by known methods used by one of ordinary skill in the art.

[0088] Compound XXIXb can be prepared by treatment of compound XXXb with MeLi or n-BuLi or by known methods used by one of ordinary skill in the art.

UTILITIES AND COMBINATIONS

Utilities

[0089] The growth hormone releasing compounds of formula I can be administered to animals, including man, to release growth hormone in vivo. For example, the compounds can be administered to commercially important animals such as swine, cattle, sheep and the like to accelerate and increase their rate and extent of growth, and to increase milk production in such animals.

[0090] The present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of formula I in association with a pharmaceutical carrier or diluent. Optionally, the active ingredient of the pharmaceutical compositions can comprise a growth promoting agent in addition to at least one of the compounds of formula I or another composition which exhibits a different activity, e.g., an antibiotic or other pharmaceutically active material.

[0091] Growth promoting agents include, but are not limited to, TRH, diethylstilbesterol, theophylline, enkephalins, E series prostaglandins, compounds disclosed in U.S. Patent No. 3,239,345, e.g., zeranol, and compounds disclosed in U.S. Patent No. 4,036,979, e.g., sulbenox or peptides disclosed in U.S. Patent No. 4,411,890.

[0092] A still further use of the disclosed compounds of formula I of the invention is in combination with other growth hormone secretagogues such as GHRP-6, GHRP-1 as described in U.S. Patent No. 4,411,890; and publications WO 89/07110 and WO 89/07111 and B-HT920 or growth hormone releasing factor and its analogs or growth hormone and its analogs or somatomedins including IGF-1 and IGF-2. A still further use of the disclosed compounds of formula I of the invention is in combination with parathyroid hormone or bisphosphonates, such as MK-217 (alendronate), in the treatment of osteoporosis.

[0093] A still further use of the disclosed compounds of formula I is in combination with estrogen, testosterone, a selective estrogen receptor modulator, such as tamoxifen or raloxifene, or a selective androgen receptor modulator, such as disclosed in Edwards, J. P. et al., Bio. Med. Chem. Let., 9, 1003-1008 (1999) and Hamann, L. G. et al., J. Med. Chem., 42, 210-212 (1999), for the treatment of aspects of Metabolic Syndrome, maintenance of muscle strength and function in elderly humans, reversal or prevention of frailty in elderly humans, stimulation and increase in muscle mass and muscle strength, attenuation of protein catabolic response after a major operation or trauma; reducing cachexia and protein loss due to chronic illness such as cancer or AIDS; improvement in muscle mobility, and maintenance of skin thickness.

[0094] A further use of the compounds of this invention is in combination with progestin receptor agonists ("PRA").

[0095] As is well known to those skilled in the art, the known and potential uses of growth hormone are varied and multitudinous. Thus, the administration of the compounds of this invention for purposes of stimulating the release of endogenous growth hormone can have the same effects or uses as growth hormone itself.

[0096] To those skilled in the art, it is well known that the current and potential uses of growth hormone are varied and multitudinous. Thus, compounds of formula I can be administered for purposes stimulating release of endogenous growth hormone and would thus have similar effects or uses as growth hormone itself. Compounds of formula I are useful for stimulation of growth hormone release (e.g., in the elderly); maintenance of muscle strength and function (e.g., in the elderly); reversal or prevention of frailty or age-related functional decline ("ARFD") in the elderly; prevention of catabolic side effects of glucocorticoids; prevention and treatment of osteoporosis; treatment of chronic fatigue syndrome (CFS); treatment of acute fatigue syndrome and muscle loss following election surgery; stimulation of the immune system,

including improvement of immune response to vaccination; acceleration of wound healing; accelerating bone fracture repair (such as accelerating the recovery of hip fracture patients); accelerating healing of complicated fractures, e.g. disctraction osteogenesis; acceleration of tooth repair or growth; maintenance of sensory function (e.g., hearing, sight, olefaction and taste); treatment of wasting secondary to fractures; treatment of growth retardation; treatment of growth retardation resulting from renal failure or insufficiency; treatment of cardiomyopathy; treatment of wasting in connection with chronic liver disease; treatment of thrombocytopenia; treatment of growth retardation in connection with Crohn's disease; treatment of short bowel syndrome; treatment of irritable bowel syndrome; treatment of inflammatory bowel disease; treatment of Crohn's disease and ulcerative colits; treatment of wasting in connection with chronic obstructive pulmonary disease (COPD); treatment of complications associated with transplantation; treatment of physiological short stature including growth hormone deficient children and short stature associated with chronic illness; treatment of obesity and growth retardation associated with obesity; treatment of anorexia (e.g., associated with cachexia or aging); treatment of growth retardation associated with the Prader-Willi syndrome and Turner's syndrome; increasing the growth rate of a patient having partial growth hormone insensitive syndrome; accelerating the recovery and reducing hospitalization of burn patients; treatment of intrauterine growth retardation, skeletal dysplasia, hypercortisolism and Cushing's syndrome; induction of pulsatile growth hormone release; replacement of growth hormone in stressed patients; treatment of osteochondrodysplasias; treatment of Noonan's syndrome; treatment of schizophrenia; treatment of depression; improvement of cognitive function (e.g., treatment of dementia; treatment of Alzheimer's disease; treatment of delayed wound healing and psychosocial deprivation; treatment of catabolism in connection with pulmonary dysfunction and ventilator dependency; treatment of cardiac dysfunction (e.g. associated with valvular disease, myocarial infarction, cardiac hypertrophy or congestive heart failure); lowering blood pressure; protection against ventricular dysfunction or prevention of reperfusion events; treatment of adults in chronic dialysis; reversal or slowing of the catabolic state of aging; attenuation or reversal of protein catabolic responses following trauma (e.g., reversal of the catabolic state associated with surgery, congestive heart failure, cardiac myopathy, burns, cancer, COPD etc.); reducing cachexia and protein loss due to chronic illness such as cancer or AIDS; treatment of hyperinsulinemia including nesidioblastosis; adjuvant treatment for ovulation induction; stimulation of thymic development and prevention of the age-related decline of thymic function; treatment of immunosuppressed patients; treatment of sarcopenia; treatment of wasting in connection with AIDS; treatment of wasting in connection with multiple sclerosis or other neurodegenerative disorders; improvement in muscle strength, mobility, maintenance of skin thickness; hair/nail growth; treatment of metabolic homeostasis and renal homeostasis (e.g., in the frail elderly); stimulation of osteoblasts, bone remodelling and cartilage growth; regulation of food intake; stimulation of the immune system in companion animals and treatment of disorders of aging in companion animals; promoting growth in livestock; stimulation of wool growth in sheep; increasing milk production in livestock; treatment of insulin resistance including NIDDM, in mammals (e.g. humans); treatment of insulin resistance in the heart; improvement of sleep quality and correction of the relative hyposomatotropism of senescence due to high increase in REM sleep and a decrease in REM latency; treatment of hypothermia; treatment of frailty such as that associated with aging; treatment of congestive heart failure; treatment of hip fractures; treatment of immune deficiency in individuals with a depressed T4/T8 cell ratio; treatment of lipodystrophy (e.g., in patients taking HIV or AIDS therapies such as protease inhibitors); treatment of muscular atrophy (e.g., due to physical inactivity, bed rest or reduced weight-bearing conditions); treatment of musculoskeletal impairment (e.g., in elderly); enhancing the activity of protein kinase B (PKB); improvement of the overall pulmonary function; treatment of sleep disorders; and the treatment of the catabolic state of prolonged critical illness. The term treatment is also intended to include prophylactic treatment.

[0097] In addition, the conditions, diseases, and maladies collectively referenced to as "Syndrome X" or Metabolic Syndrome as detailed in Johannsson J. Clin. Endocrinol. Metab., 82, 727-34 (1997), may be treated employing the compounds of the invention.

Combinations

[0098] The compounds of the present invention may be employed alone or in combination with each other and/or other growth hormone secretagogues or other suitable therapeutic agents useful in the treatment of the aforementioned disorders including: anti-diabetic agents; anti-osteoporosous agents; anti-obesity agents; anti-inflammatory agents; anti-anxiety agents; anti-depressants; anti-hypertensive agents; anti-platelet agents; anti-thrombotic and thrombolytic agents; cardiac glycosides; cholesterol/lipid lowering agents; mineralocorticoid receptor antagonists; phospodiesterase inhibitors; protein tyrosine kinase inhibitors; thyroid mimetics (including thyroid receptor antagonists); anabolic agents; HIV or AIDS therapies; therapies useful in the treatment of Alzheimer's disease and other cognitive disorders; therapies useful in the treatment of sleeping disorders; anti-proliferative agents; anti-tumor agents; and/or anti-ulcer and gastro-esopheageal reflux disease agents.

[0099] Examples of suitable anti-diabetic agents for use in combination with the compounds of the present invention include biguanides (e.g. metformin), glucosidase inhibitors (e.g. acarbose), insulins (including insulin secretagogues or insulin sensitizers), meglitinides (e.g. repaglinide), sulfonylureas (e.g., glimepiride, glyburide and glipizide), biguanide/gly-

buride combinations (e.g., glucovance), thiozolidinediones (e.g. troglitazone, rosiglitazone and pioglitazone), PPAR-alpha agonists, PPAR-gamma agonists, PPAR alpha/gamma dual agonists, SGLT2 inhibitors, inhibitors of fatty acid binding protein (aP2) such as those disclosed in U.S. Serial No. 09/519,079 filed March 6, 2000 (attorney docket LA27), glucagon-like peptide-1 (GLP-1), and dipeptidyl peptidase IV (DP4) inhibitors.

[0100] Examples of suitable anti-osteoporosous agents for use in combination with the compounds of the present invention include alendronate, risedronate, raloxifene, calcitonin, non-steroidal progestin receptor agonists, RANK ligand agonists, calcium sensing receptor antagonists, TRAP inhibitors, selective estrogen receptor modulators (SERM), estrogen and AP-1 inhibitors;

Examples of suitable anti-obesity agents for use in combination with the compounds of the present invention include aP2 inhibitors such as those disclosed in U.S. Serial No. 09/519,079 filed March 6, 2000 (attorney docket LA27), PPAR gamma antagonists, PPAR delta agonists, and orlistat.

[0101] Examples of suitable antinflammatory agents for use in combination with the compounds of the present invention include prednisone, dexamethasone, Enbrel, cyclooxygenase inhibitors (i.e., COX-1 and/or COX-2 inhibitors such as NSAIDs, aspirin, indomethacin, ibuprofen, piroxicam, Naproxen, Celebrex, Vioxx), CTLA4-Ig agonists/antagonists, CD40 ligand antagonists, integrin antagonists, alpha4 beta7 integrin antagonists, cell adhesion inhibitors, interferon gamma antagonists, ICAM-1, tumor necrosis factor (TNF) antagonists (e.g., infliximab, OR1384), prostaglandin synthesis inhibitors, budesonide, clofazimine, CNI-1493, CD4 antagonists (e.g., priliximab), p38 mitogen-activated protein kinase inhibitors, protein tyrosine kinase (PTK) inhibitors, IKK inhibitors, and therapies for the treatment of irritable bowel syndrome (e.g., zelmac and Maxi-K openers such as those disclosed in U.S. Patent No. 6,184,231 B1).

[0102] Example of suitable anti-anxiety agents for use in combination with the compounds of the present invention include diazepam, lorazepam, buspirone, oxazepam, and hydroxyzine pamoate.

[0103] Examples of suitable anti-depressants for use in combination with the compounds of the present invention include citalopram, fluoxetine, nefazodone, sertraline, and paroxetine.

[0104] Examples of suitable anti-hypertensive agents for use in combination with the compounds of the present invention include beta adrenergic blockers, calcium channel blockers (L-type and T-type; e.g. diltiazem, verapamil, nifedipine, amlodipine and mybefradil), diruetics (e.g., chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid tricrynafen, chlorthalidone, furosemide, musolimine, bumetanide, triamtrenene, amiloride, spironolactone), renin inhibitors, ACE inhibitors (e.g., captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril), AT-1 receptor antagonists (e.g., losartan, irbesartan, valsartan), ET receptor antagonists (e.g., sitaxsentan, atrsentan and compounds disclosed in U.S. Patent Nos. 5,612,359 and 6,043,265), Dual ET/AII antagonist (e.g., compounds disclosed in WO 00/01389), neutral endopeptidase (NEP) inhibitors, vasopepsidase inhibitors (dual NEP-ACE inhibitors) (e.g., omapatrilat and gemopatrilat), and nitrates.

[0105] Examples of suitable anti-platelet agents for use in combination with the compounds of the present invention include GPIIb/IIIa blockers (e.g., abciximab, eptifibatide, tirofiban), P2Y12 antagonists (e.g., clopidogrel, ticlopidine, CS-747), thromboxane receptor antagonists (e.g., ifetroban), aspirin, and PDE-III inhibitors (e.g., dipyridamole) with or without aspirin.

[0106] Examples of suitable cardiac glycosides for use in combination with the compounds of the present invention include digitalis and ouabain.

[0107] Examples of suitable cholesterol/lipid lowering agents for use in combination with the compounds of the present invention include HMG-CoA reductase inhibitors (e.g., pravastatin lovastatin, atorvastatin, simvastatin, NK-104 (a.k.a. itavastatin, or nisvastatin or nisbastatin) and ZD-4522 (a.k.a. rosuvastatin, or atavastatin or visastatin)), squalene synthetase inhibitors, fibrates, bile acid sequestrants, ACAT inhibitors, MTP inhibitors, lipooxygenase inhibitors, choesterol absorption inhibitors, and cholesterol ester transfer protein inhibitors (e.g., CP-529414).

[0108] Examples of suitable mineralocorticoid receptor antagonists for use in combination with the compounds of the present invention include spironolactone and eplerinone.

[0109] Examples of suitable phospodiesterase inhibitiors for use in combination with the compounds of the present invention include PDEIII inhibitors such as cilostazol, and PDE V inhibitors such as sildenafil.

[0110] Examples of suitable thyroid mimetics for use in combination with the compounds of the present invention include thyrotropin, polythyroid, KB-130015, and dronedarone.

[0111] Examples of suitable anabolic agents for use in combination with the compounds of the present invention include testosterone and SARMs.

[0112] Examples of suitable HIV or AIDS therapies for use in combination with the compounds of the present invention include indinavir sulfate, saquinavir, saquinavir mesylate, amprenavir, ritonavir, lopinavir, ritonavir/lopinavir combinations, lamivudine, zidovudine, lamivudine/zidovudine combinations, zalcitabine, didanosine, stavudine, and megestrol acetate.

[0113] Examples of suitable therapies for treatment of Alzheimer's disease and cognitive disorders for use in combination with the compounds of the present invention include donepezil, tacrine, revastigmine, 5HT6, gamma secretase inhibitors, beta secretase inhibitors, SK channel blockers, Maxi-K blockers, and KCNQs blockers.

[0114] Examples of suitable therapies for treatment of sleeping disorders for use in combination with the compounds of the present invention include melatonin analogs, melatonin receptor antagonists, ML1B agonists, and GABA/NMDA receptor antagonists.

[0115] Examples of suitable anti-proliferative agents for use in combination with the compounds of the present invention include cyclosporin A, taxol, FK 506, and adriamycin.

[0116] Examples of suitable anti-tumor agents for use in combination with the compounds of the present invention include taxol, adriamycin, epothilones, cisplatin and carboplatin.

[0117] Compounds of the present invention may further be used in combination with nutritional supplements such as those described in U.S. 5,179,080, especially in combination with whey protein or casin, amino acids (such as leucine, branched amino acids and hydroxymethylbutyrate), triglycerides, vitamins (e.g., A, B6, B12, folate, C, D and E), minerals (e.g., selenium, magnesium, zinc, chromium, calcium and potassium), carnitine, lipoic acid, creatine, and coenzyme Q-10.

[0118] The above other therapeutic agents, when employed in combination with the compounds of the present invention, may be used, for example, in those amounts indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

[0119] The compounds of the present invention are agents that are growth hormone secretagogues and can be administered to various mammalian species, such as monkeys, dogs, cats, rats, humans, etc., in need of treatment. These agents can be administered systemically, such as orally or parenterally.

[0120] The compounds of the invention can be incorporated in a conventional systemic dosage form, such as a tablet, capsule, elixir or injectable formulation. The above dosage forms will also include the necessary physiologically acceptable carrier material, excipient, lubricant, buffer, antibacterial, bulking agent (such as mannitol), anti-oxidants (ascorbic acid or sodium bisulfite) or the like. Oral dosage forms are preferred, although parenteral, intranasal or aerosol forms are quite satisfactory as well.

[0121] The dose administered must be carefully adjusted according to the age, weight, and condition of the patient, as well as the route of administration, dosage form and regimen, and the desired result. In general, the dosage forms described above may be administered in amounts from about 0.0001 to about 100 mg/kg or body weight or in an amount within the range from about 1 to about 1000 mg per day, preferably, from about 5 to about 500 mg per day in single or divided doses of one to four times daily.

[0122] In summary, the invention is defined as in the claims.

[0123] arylalkyloxyalkyl, aryloxyalkyl, cycloalkylalkoxyalkyl, heteroarylalkyl, $-OR_5$, $-OC(O)R_5$, $-CF_3$, $-OCF_3$, $-N(R_5)C(O)R_5$'and $-NR_5R_5$';

R_5 and R_5' for each occurrence are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, heterocycle and aryl, wherein R_5 and R_5' for each occurrence may optionally be substituted with one or more Rb;

Ra and Rb for each occurrence are each independently selected from the group consisting of alkyl, alkenyl, alkynyl, halogen, cyano, carbonyl, -CN, aryl, arylalkyl, arylalkenyl, arylalkynyl, cycloalkyl, alkoxy, alkoxyalkyl, aryloxy, aryloxyalkyl, heterocycle, heteroaryl, heteroarylalkyl, $-OR_2$, $-NR_5R_5$', $-CF_3$, $-SO_2R_6$, $-OC(O)R_5$-$SO_2NR_6R_6$', $-(CH_2)_mR_8$ and R_9;

R_6 and R_6' for each occurrence are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkylthioalkyl, alkoxyalkyl, aryl, arylalkyl, heterocycle, heteroaryl, heteroarylalkyl, heterocycloalkyl and cycloalkyl, wherein R_6 and R_6' for each occurance may optionally be substituted with 1 to 3 substituents selected from the group consisting of halogen, OR_2, alkoxy, heterocycloalkyl, $-NR_5C(O)NR_5R_5$', $-C(O)NR_5R_5$', $-NR_5C(O)R_5$', -CN, $-NR_5SO_2R_5$',$-OC(O)R_5$, $-SO_2NR_5R_5$', $-SOR_7$, -COOH and $-C(O)OR_7$, or R_6 and R_6' taken together can be cyclized to form $-(CH_2)_qX(CH_2)_s-$;

R_7 for each occurrence is independently selected from the group consisting of C_1 to C_6 alkyl, aryl and heteroaryl, wherein R_7 may optionally be substituted with-$(CH_2)_wOH$;

R_8 is selected from the group consisting of alkoxy, alkoxycarbonyl,$-C(O)NR_6R_6$', $-NR_5R_5$', $-C(O)R_6$, $-NR_5C(O)NR_5R_5$' and -N-heteroaryl;

R_9 is selected from the group consisting of heterocycloalkyl, heteroaryl, -CN, $-(CH_2)_pN(R_6)C(O)R_6$', $-(CH_2)_pCN$, $-(CH_2)_pN(R_6)C(O)OR_6$', $-(CH_2)_pN(R_6)C(O)NR_6R_6$', $-(CH_2)pN(R_6)SO_2R_6$, $-(CH_2)_pC(O)NR_6R_6$', $-(CH_2)_pC(O)OR_6$, $-(CH_2)_pOC(O)OR_6$, $-(CH_2)_pOC(O)R_6$, $-(CH_2)_pOC(O)NR_6R_6$', $-(CH_2)_pN(R_6)SO_2NR_6R_6$', $-(CH_2)_pOR_6$, $-(CH_2)_pOC(O)N(R_6)(CH_2)_mOH$, $-(CH_2)_pSOR_6$ and $-(CH_2)_pOCH_2C(O)N(R_6)(CH_2)_mOH$;

X is selected from the group consisting of $-CR_5R_5$'-, -O-, -S-, -SO-, $-SO_2$-,$-NC(O)OR_7$-, $-NC(O)NR_5$- and $-NR_5$-;

Z is nitrogen;

m is an integer between 1 and 6;

n is an integer from 1 to 6;

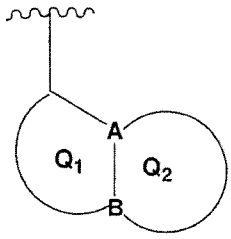
p is an integer from 0 to 5;

w is an integer between 0 and 5; and

q and s are each independently an integer between 1 and 3,

with the proviso that R_5, R_5', R_6 or R_6' cannot be hydrogen when either is connected to a carbonyl group or sulfone group.

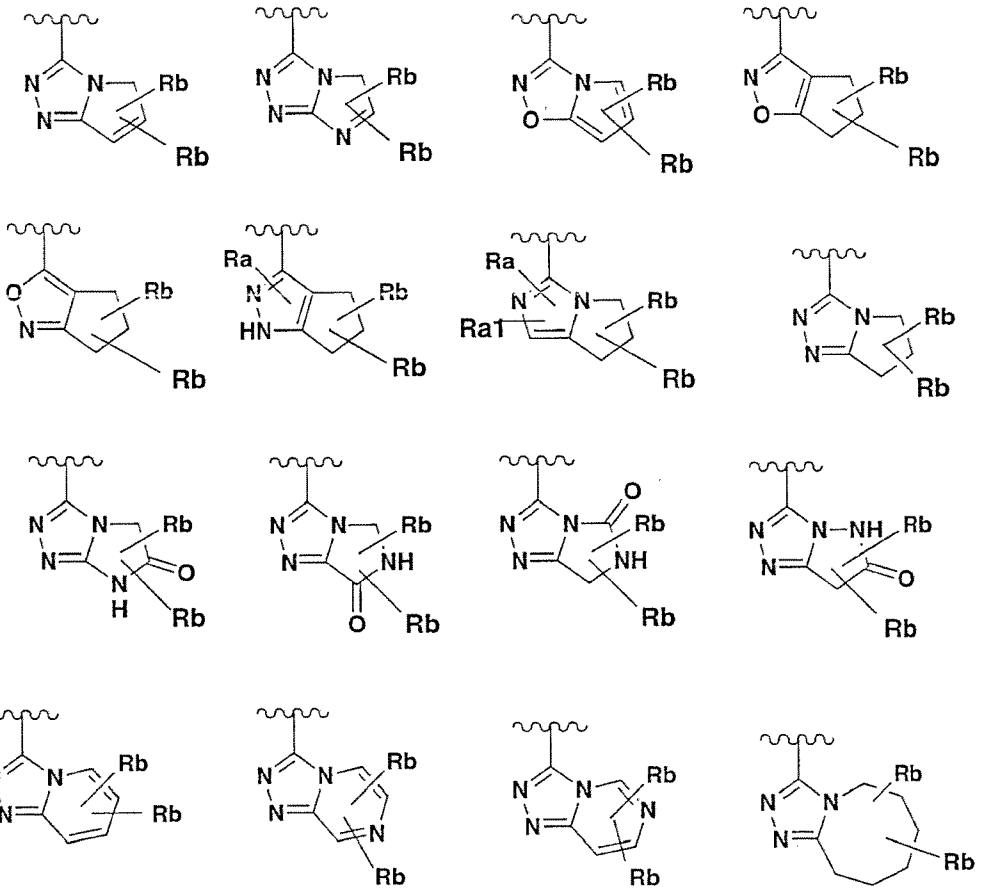
2. The compound as defined in item 1 wherein
Xa is

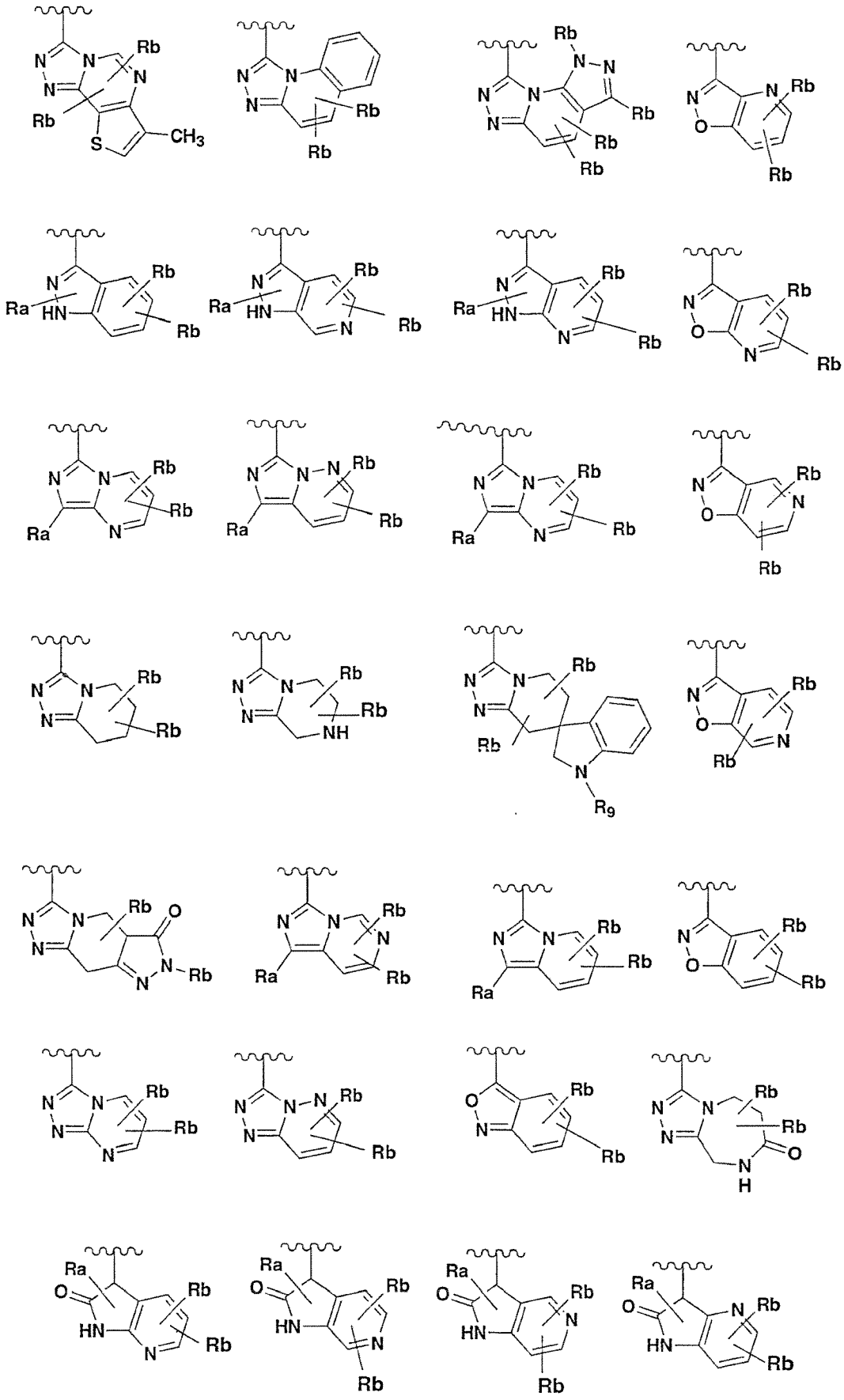


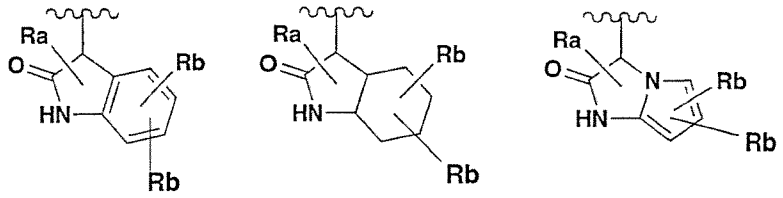
wherein

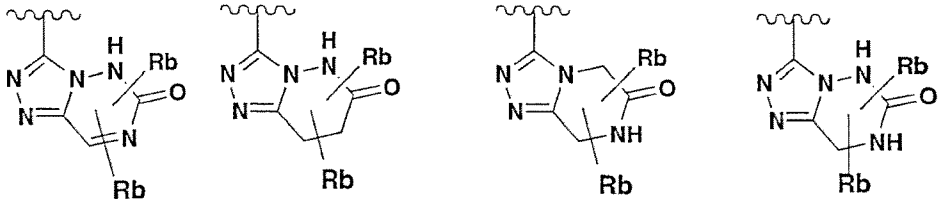
Q_1 and Q_2 are each independently a cycloalkyl, heterocyclic, aryl or heteroaryl ring, wherein Q_1 may be substituted with 1 to four substituents selected from the group consisting of Ra and Rb, and Q_2 may be substituted with 1 to four substituents selected from the group consisting of Ra, Rb and Q_3;
Q_3 is a 3 to 8 membered fused or spiral cycloalkyl, heterocyclic, aryl or heteroaryl ring, wherein Q_3 may optionally be substituted with 1 to 5 substituents selected from the group consisting of Ra, Rb and Q_4; and
Q_4 is a 3 to 8 membered fused or spiral cycloalkyl, heterocyclic, aryl or heteroaryl ring, wherein Q_4 may optionally be substituted with 1 to 5 substituents selected from the group consisting of Ra and Rb;
A is N or CR_{11};
B is N or CR_{11}; and
R_{11} is H or a bond.

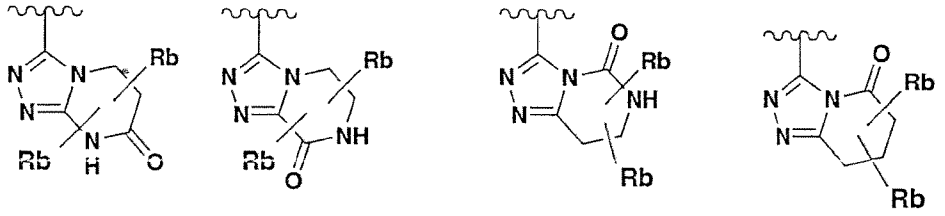
3. The compound as defined in item 1 wherein Xa has the structure

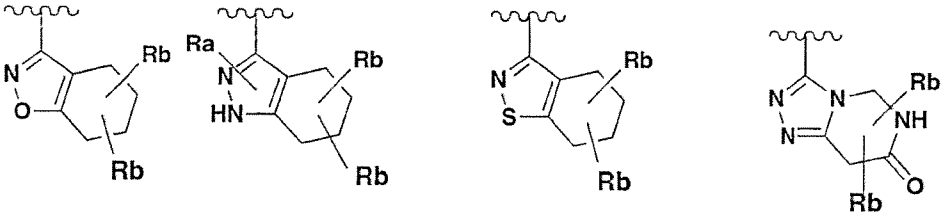


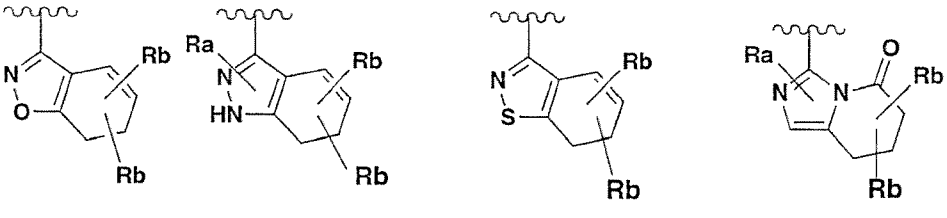


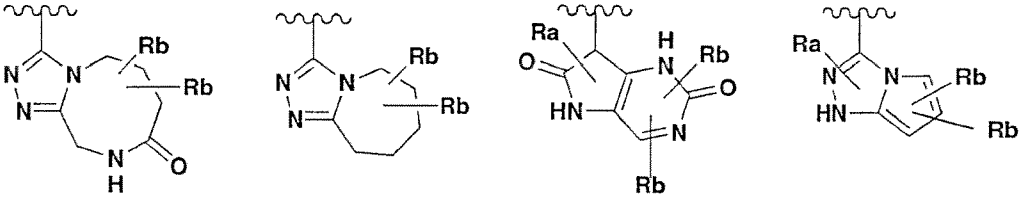


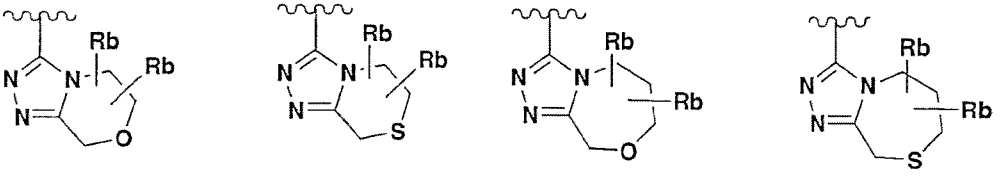


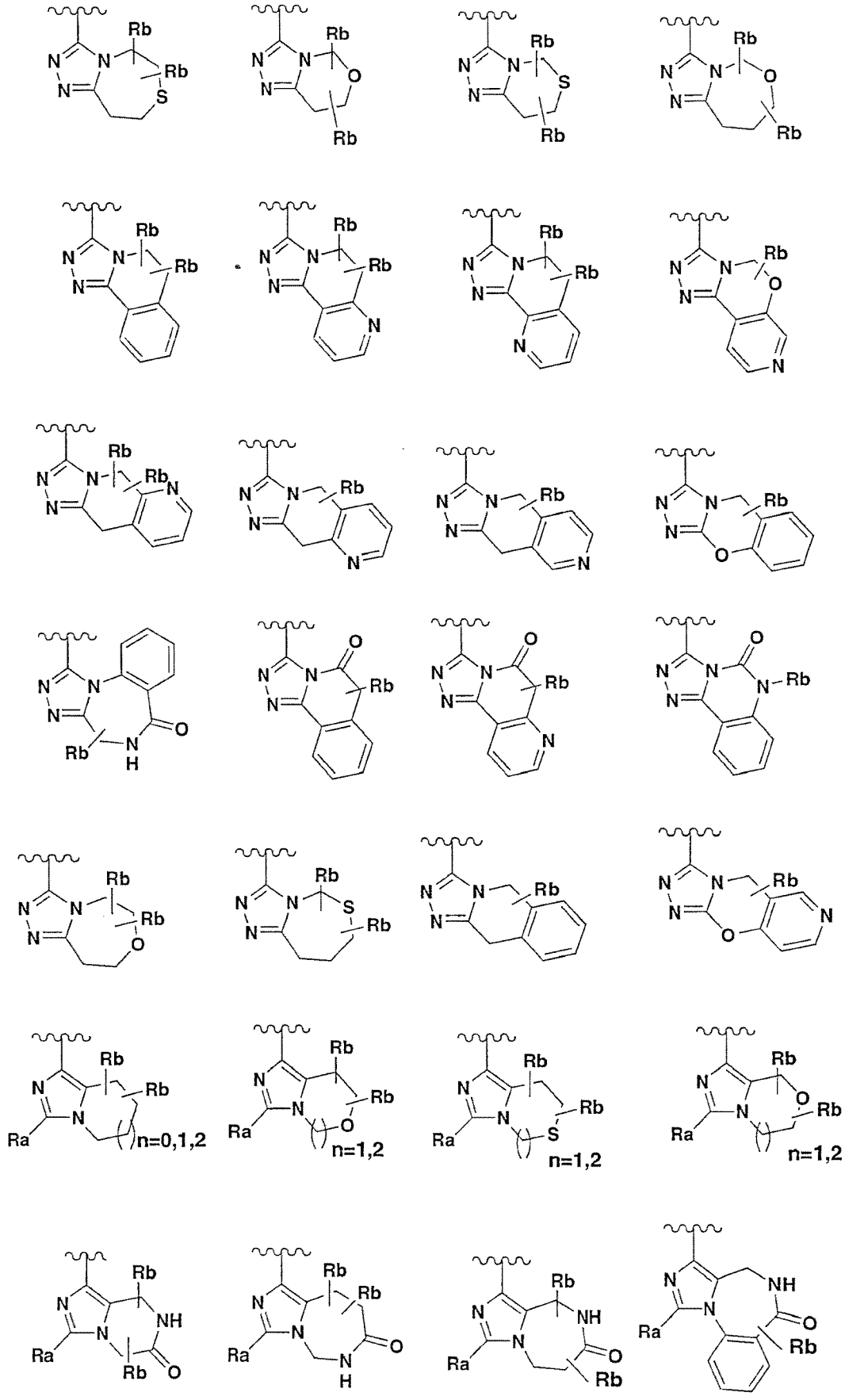








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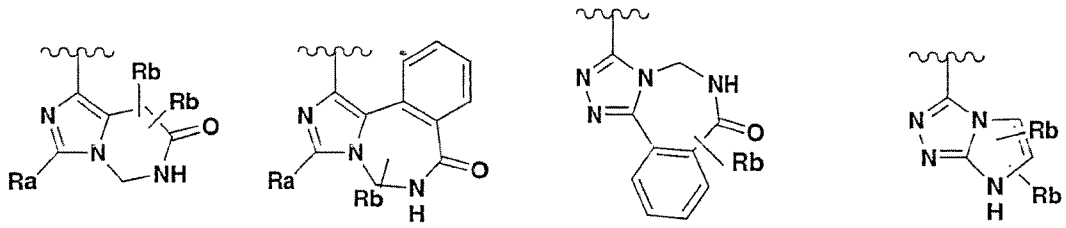
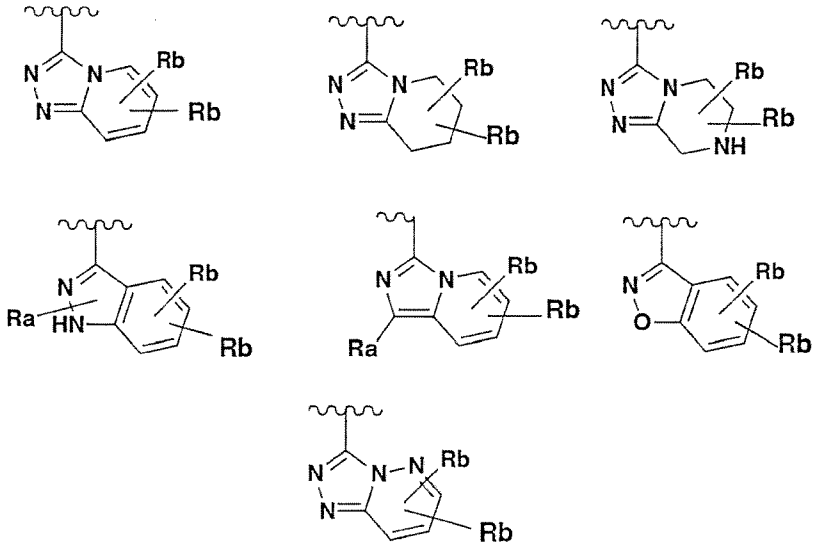


4. The compound as defined in item 1 wherein Xa has the structure



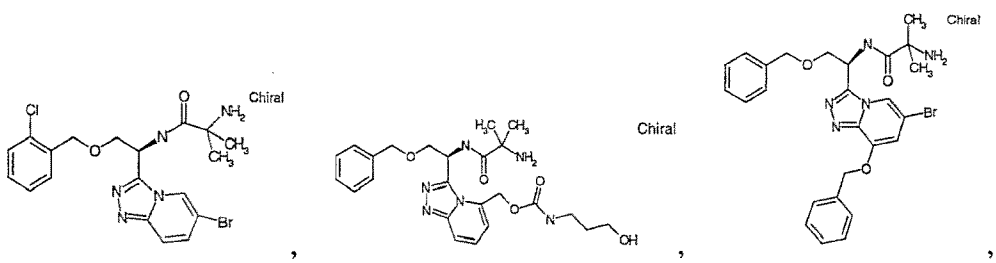
5. The compound as defined in item 2 wherein when Ra or Rb are R_9, R_6 is heterocycle or alkyl, optionally substituted with hydroxyl or halogen.

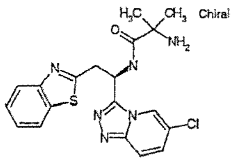
6. The compound as defined in item 5 wherein R_9 is $(CH_2)_pC(O)OR_6$, $(CH_2)_pOC(O)R_6$, or $(CH_2)_pOC(O)N(R_6)(CH_2)_mOH$.

7. The compound as defined in item 2 wherein when Ra or Rb are R_9, R_6 and R_6' are independently hydrogen, alkyl, or cycloalkyl, where the alkyl or cycloalkyl is optionally substituted with $-C(O)OR_7$ or $-C(O)NR_5R_5$', or R_6 and R_6' taken together can be cyclized to form $-(CH_2)_qX(CH_2)_s-$.

8. The compound as defined in item 7 wherein R_9 is $-(CH_2)_pN(R_6)C(O)OR_6$', $-(CH_2)_pN(R_6)C(O)NR_6R_6$', or $(CH_2)_pOC(O)NR_6R_6$', where R_6 and R_6' are independently hydrogen or alkyl, where the alkyl is optionally substituted with $-C(O)NR_5R_5$', where R_5 and R_5' are independently hydrogen or alkyl.

9. The compound as defined in item 1 wherein the compound has the structure:

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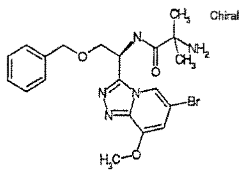
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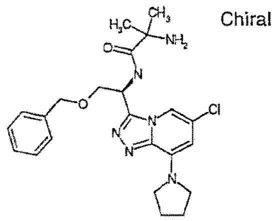
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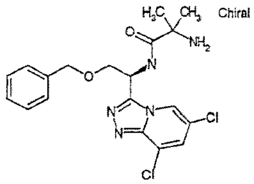
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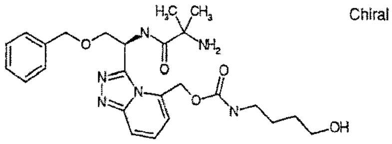
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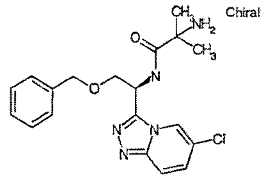
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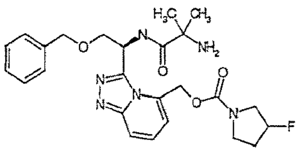
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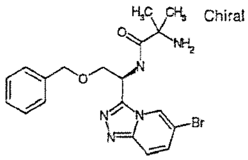
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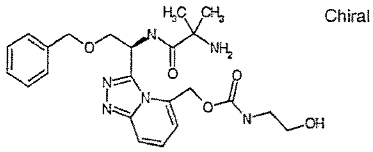
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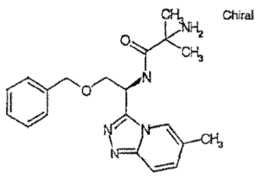
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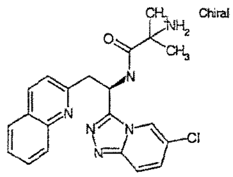
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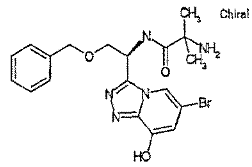
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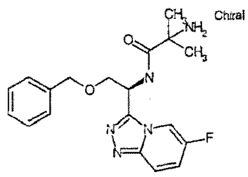
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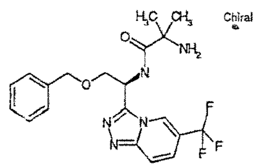
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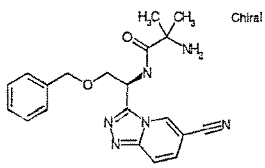
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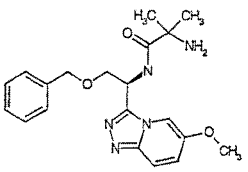
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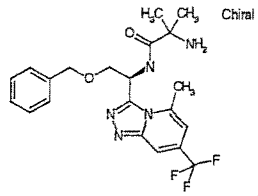
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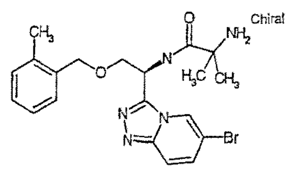
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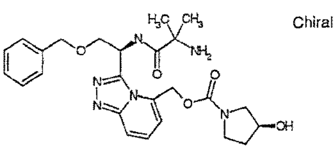
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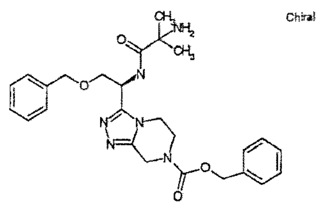
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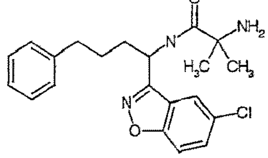
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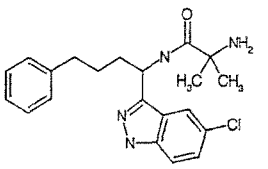
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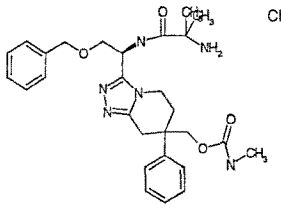
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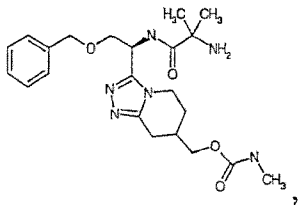
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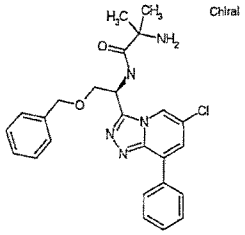
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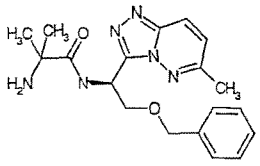
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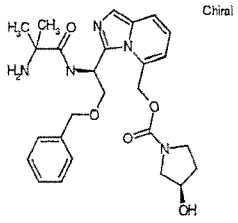
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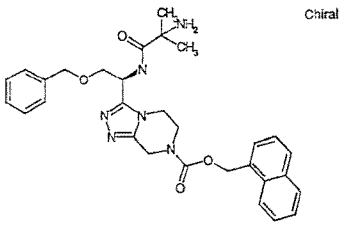
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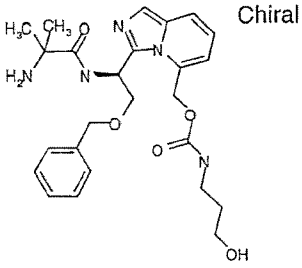
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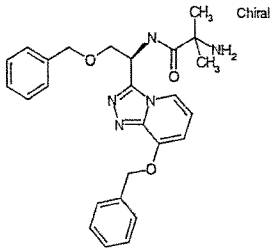
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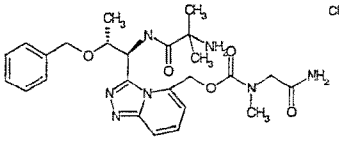
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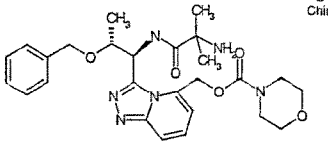
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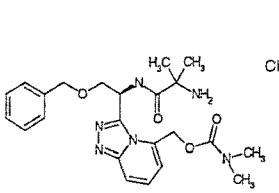
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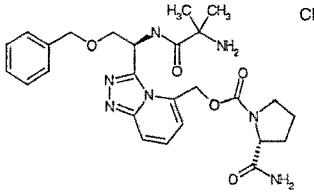
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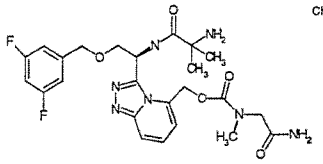
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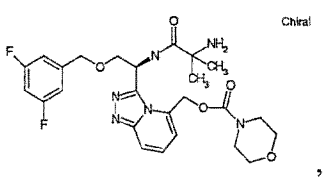
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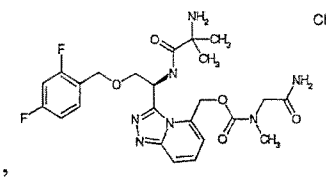
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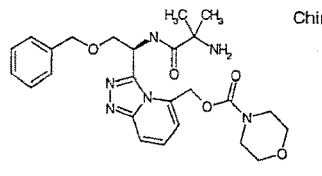
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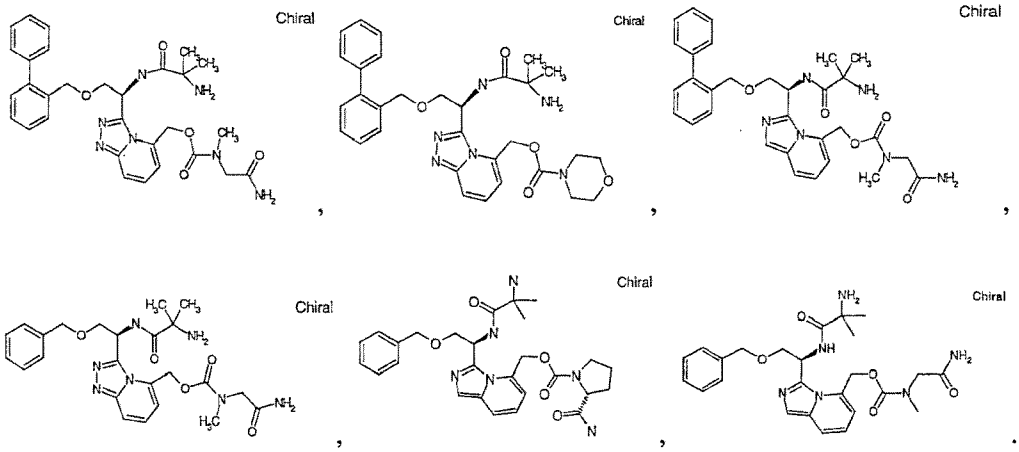
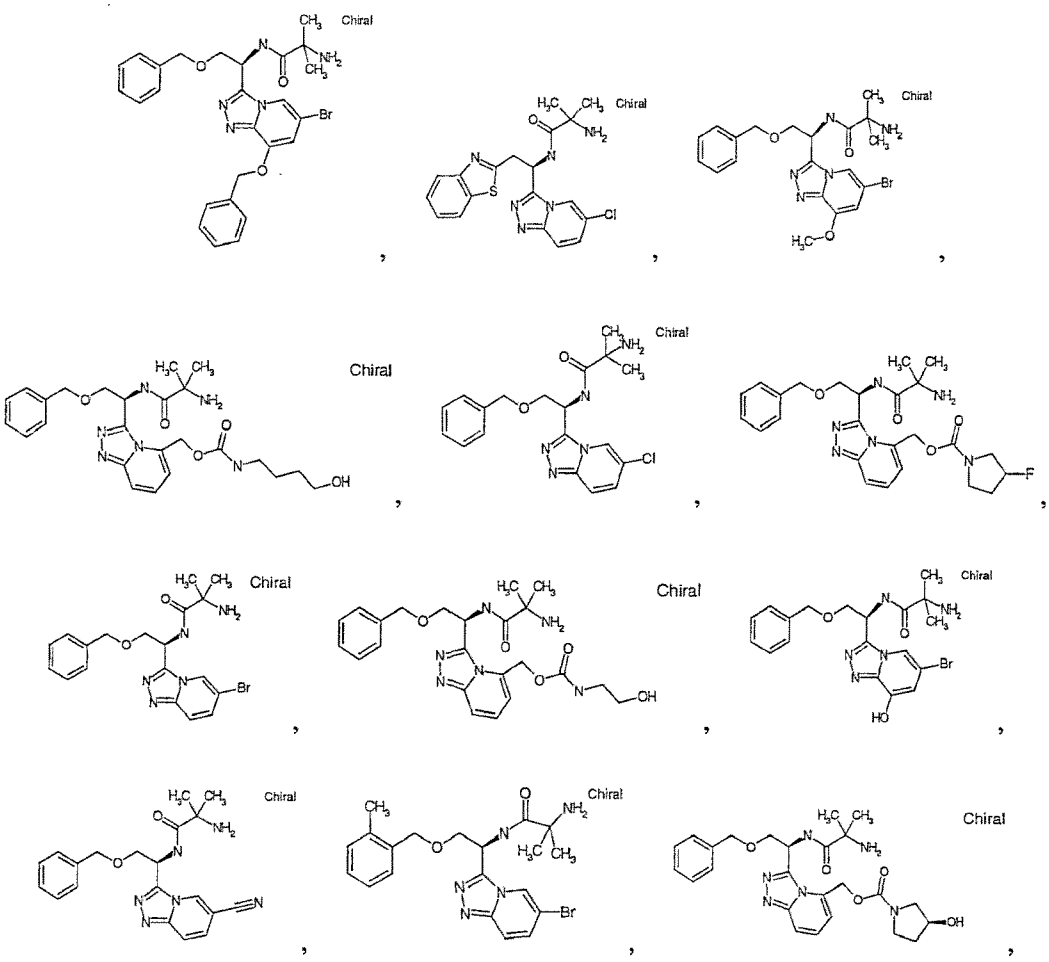
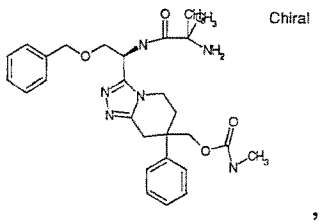


10. The compound as defined in item 1 wherein the compound has the structure:

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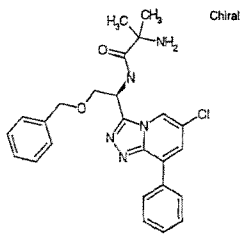
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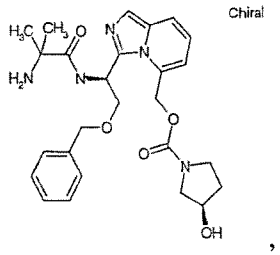
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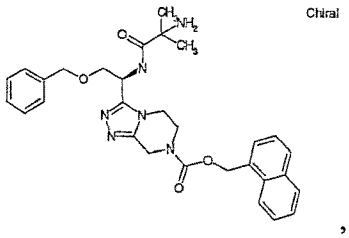
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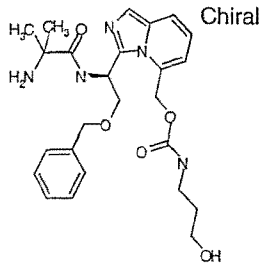
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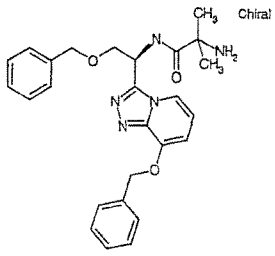
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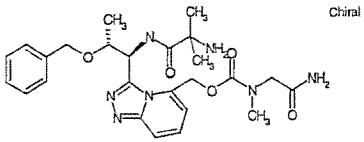
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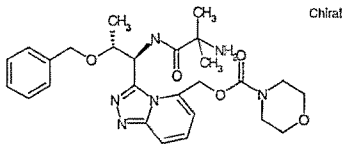
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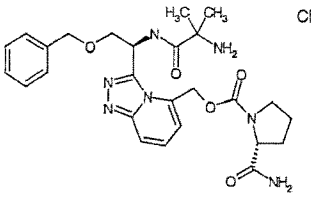
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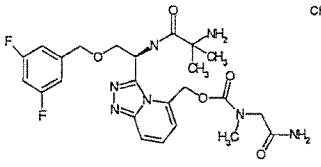
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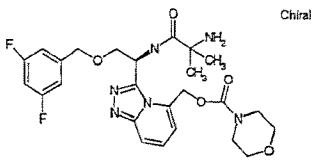
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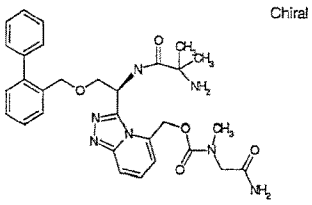
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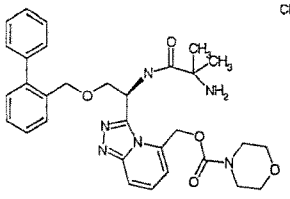
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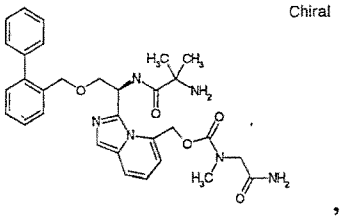
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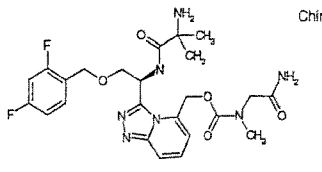
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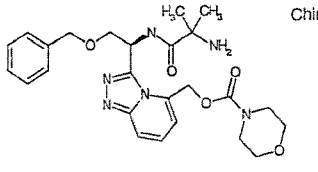
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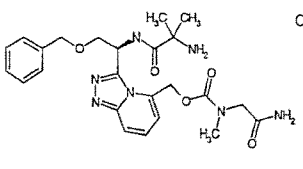
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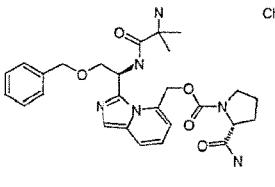
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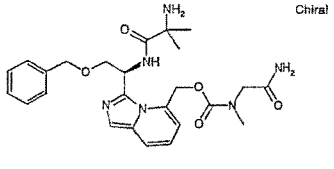
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11. A pharmaceutical composition comprising a compound as defined in item 1 and a pharmaceutically acceptable carrier therefor.

12. The pharmaceutical composition of item 9 further comprising at least one additional therapeutic agent selected from the group consisting of other compounds of formula I, parathyroid hormone, bisphosphonates, estrogen, testosterone, selective estrogen receptor modulators, selective androgen receptor modulators, progestin receptor agonists, anti-diabetic agents, anti-hypertensive agents, anti-inflammatory agents, anti-osteoporosis agents, anti-obesity agents, cardiac glycosides, cholesterol lowering agents and thyroid mimetics.

13. A method for increasing levels of endogenous growth hormone, which comprises administering a therapeutically effective amount of a compound as defined in item 1 to a patient in need thereof.

14. A method for treating or delaying the progression or onset of HIV wasting syndrome, muscular atrophy, lipodistrophy, long term critical illness, osteoporosis, sarcopenia, fraility or ARFD in the elderly, obesity, renal disease, anorexia, sleep disorders, depression, Syndrome X, diabetes, congestive heart failure, cardiac myopathy, cardiac dysfunction associated with valvular disease and cachexia which comprises administering to a mammalian patient in need of treatment a therapeutically effective amount of a compound as defined in item 1.

15. The method according to item 12 further comprising administering, concurrently or sequentially, a therapeutically effective amount of at least one additional therapeutic agent selected from the group consisting of other compounds of formula I, parathyroid hormone, bisphosphonates, estrogen, testosterone, selective estrogen receptor modulators, selective androgen receptor modulators, progestin receptor agonists, anti-diabetic agents, anti-hypertensive agents, anti-inflammatory agents, anti-osteoporosis agents, anti-obesity agents, cardiac glycosides, cholesterol lowering agents and thyroid mimetics.

16. A method for stimulating wound healing and/or the immune system which comprises administering a therapeutically effective amount of a compound as defined in item 1 to a patient in need thereof.

17. A method for increasing muscle mass and/or strength or maintaining muscle strength and function in the elderly which comprises administering a therapeutically effective amount of a compound as defined in item 1 to a patient in need thereof.

18. A method of increasing lean body mass which comprises administering a therapeutically effective amount of a compound as defined in item 1 to a patient in need thereof.

19. A method for improving cognitive function which comprises administering a therapeutically effective amount of a compound as defined in item 1 to a patient in need thereof.

20. A method for improving the immune response to vaccination which comprises administering a therapeutically effective amount of a compound as defined in item 1 to a patient in need thereof.

21. A method for accelerating the recovery of hip fracture which comprises administering a therapeutically effective amount of a compound as defined in item 1 to a patient in need thereof.

22. The pharmaceutical composition of item 9 further comprising at least one nutritional supplement.

EXAMPLES

[0124] The following Examples represent preferred embodiments of the invention. All temperatures are in °C unless indicated otherwise.

GENERAL EXPERIMENTAL

[0125] Method A: The term HPLC refers to a Shimadzu high performance liquid chromatography using a 4 minute gradient of 0-100% solvent B [MeOH:H2O:0.2% H3PO4] with a 1 min. hold, an ultra violet (uv) detector set at 220nM and using a column (4.6 X 50mm) packed with YMC C18 5 micron resin.

[0126] A mixture of solvent A (10% MeOH/90%H2O/0.2% TFA) and solvent B (90% MeOH/10% H2O/ 0.2% TFA) are used for preparative reverse phase HPLC in an automated Shimadzu system. The preparative columns are packed with

YMC ODS C18 5 micron resin.

[0127] Method B: The term HPLC refers to a Shimadzu high performance liquid chromatography using an 8 minute gradient of 0-100% solvent B [acetonitrile:H2O:0.1% TFA] with a 3 min. hold, an ultra violet (uv) detector set at 220 nM, and using a column (4.6 X 75 mm) packed with Zorbax C18 5 micron resin. A mixture of solvent A (10% acetonitrile/90%H2O/0.1% TFA) and solvent B (90% acetonitrile/10% H2O/ 0.1% TFA) are used for preparative reverse phase HPLC in an automated Shimadzu system. The preparative columns are packed with YMC ODS C18 5 micron resin.

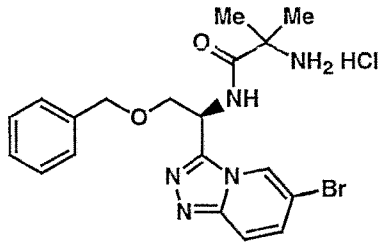
[0128] Method C: The term HPLC refers to a Shimadzu high performance liquid chromatography using an 8 minute gradient of 0-100% solvent B [MeOH:H2O:0.2% H3PO4] with a 2 min. hold, an ultra violet (uv) detector set at 220 nM, and using a column (4.6 X 75 mm) packed with Zorbax C18 5 micron resin.

[0129] The preparative column for the chiral preparative HPLC was packed with Chiralpak AD 2μM (5 X 50cm) using Isopropyl alcohol and hexane as the solvents.

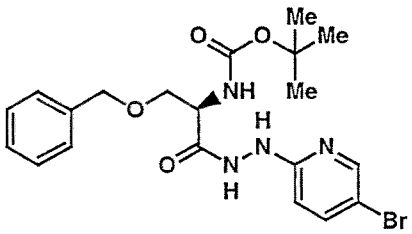
EXAMPLE 1

2-Amino-N-[1-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)-3-phenyl-propyl]-2-methyl-propionamide

[0130]

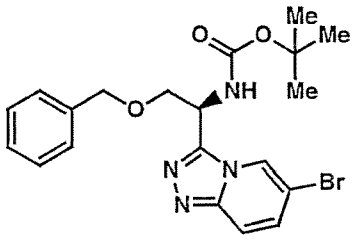


1A



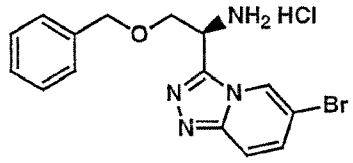
[0131] To a THF (100ml) solution of 3-benzyloxy-2-tert-butoxycarbonylamino-propionic acid (20.0 g, 67.8mmol) was added N-methyl morpholine (11.2ml, 101.7mmol), followed by the addition of iso-butyl chloroformate (11.1ml, 74.mmol) dropwise. A White suspension was formed. This suspension was stirred at r.t. For 10min and then 5-bromo-pyridin-2-yl hydrazine (14.1g, 74.6mmol) was added in three portions. The resulting suspension was stirred at r.t. for 1h and then the solvent was removed under reduced pressure until a thick slurry was formed. Water was added and the suspension was stirred to ensure the solid was finely dispersed. The off-white solid was filtered and washed with NaOH (1N, 100ml), water (100ml) and HCl(1N, 100ml) and then water (200ml) dried to give **1A** (31.5g, 100%).

1B



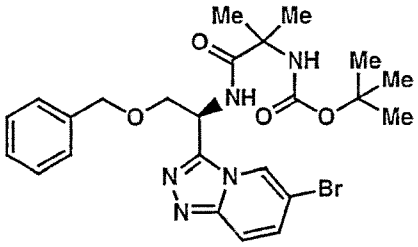
[0132] To a THF (100ml) solution of **1A** (30g, 64.3mmol) was added triphenylphosphine (20.2g, 77.2mmol), and trimethylsilyl azide (10.2ml, 77.2 mmol). To this solution was added diethyl diazacarboxylate (DEAD, 15.2ml, 96.5 mmol) in rapid drops. The solution became hot. After the addition was complete, the solution was allowed to stir at r.t. until all starting material was consumed (<2h). The solvent was removed under reduced pressure to give **1B**

1C



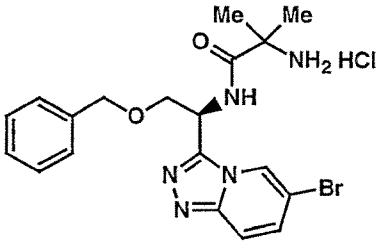
[0133] **1B** (64.3mmol) was suspended in HCl-dioxane (160ml, 4MHCl in dioxane). The suspension was stirred at r.t. until all of the starting material was consumed. The suspension was concentrated to a thick slurry and then diluted with THF (100ml). The solid was collected by filtration and rinsed with excess CH_2Cl_2, diethyl ether, and dried to give **1C** (24.5g, 99%).

1D



[0134] To a THF (100ml) solution of 2-tert-butoxycarbonylamino-2-methyl-propionic acid (9.5g, 47.9mmol) was added EDAC (11.2 g, 58.8mmol) and HOBT (8.0g, 58.8mmol), DMAP (4.8g, 39.2 mmol), and $(i\text{-}Pr)_2NEt$ (20.5ml, 117.6 mmol). This solution was stirred at r.t. for 10min before the addition of **1C** (15 g, 39.2mmol). The reaction was completed in <1h. The solvent was then removed under reduced pressure and the residue was dissolved in EtOAc (200ml). The organic solution was washed with water (200ml), NaOH (0.5N, 200 ml), HCl (0.5N, 200ml), and water (200ml). The organic layer was dried over Na_2SO_4 and concentrated to give a white solid **1D** (20.0g, 90%)

1E

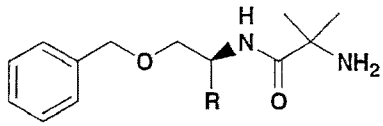


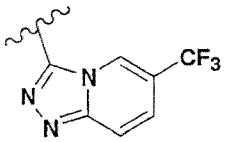
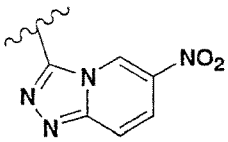
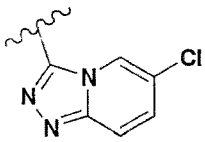
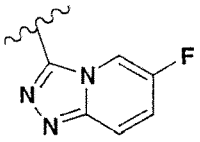
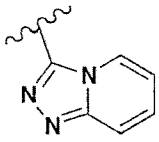
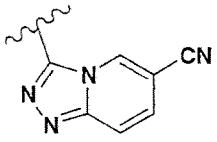
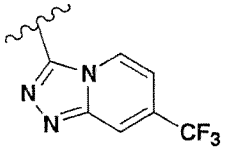
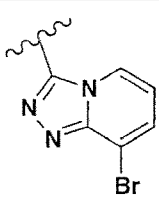
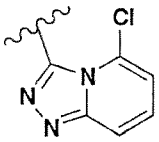
[0135] **1D** (1.0g, 1.8mmol) was dissolved in 4 M HCl-dioxane (5ml). The solution was stirred at r.t. until all starting material was consumed. The solvent was evaporated under reduced pressure and the white solid was triturated with diethyl ether to afford pure product of the title compound(0.84g, <99%). MS (M+H) 433, HPLC retention time 2.07min.

EXAMPLES 2 TO 15

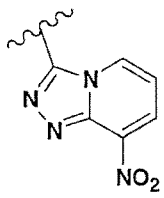
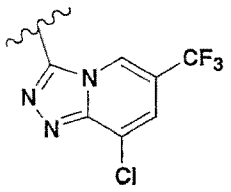
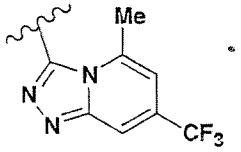
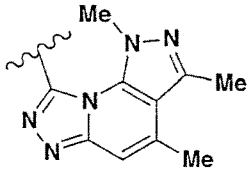
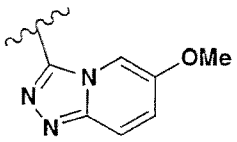
[0136] Examples 2-15 in **Table 1** have been synthesized utilizing the procedures described in **Example 1,** utilizing the appropriate starting materials.

TABLE 1



Compound number	R	HPLC Purity (%)	HPLC Retention (min)	Mass M+H
2		100	2.53	422
3		90	1.93	399
4		90	1.92	388
5		91	1.60	372
6		90	1.29	354
7		99	1.60	379
8		94	2.46	422
9		96	1.80	432
10		94	1.73	388

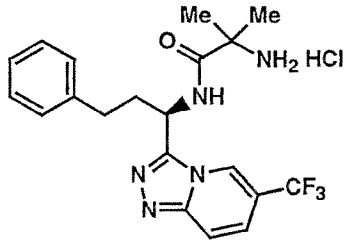
(continued)

Compound number	R	HPLC Purity (%)	HPLC Retention (min)	Mass M+H
11		89	1.73	399
12		91	2.37	456
13		100	2.40	435
14		100	2.12	435
15		88	1.97	384

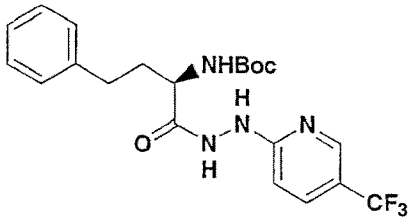
EXAMPLE 16

2-Amino-2-methyl-N-[3-phenyl-1-(6-trifluoromethyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)-propyl]-propionamide

[0137]

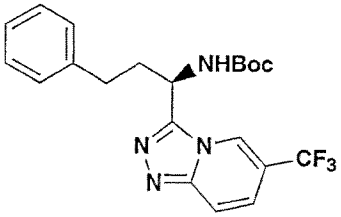


16A



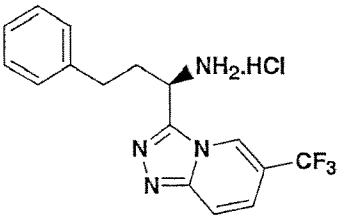
[0138] To a THF (100ml) solution of 2-tert-Butoxycarbonylamino-4-phenyl-butyric acid (2.0g, 7.1 mmol) was added TEA (0.98 ml, 7.1 mmol), followed by the addition of iso-butyl chloroformate (0.98g, 7.1mmol) dropwise. A White suspension was formed. This suspension was stirred at r.t. for 10min and then (5-Trifluoromethyl-pyridin-2-yl)-hydrazine (1.3g, 7.1mmol) was added in three portions. The resulting suspension was stirred at r.t. for 1h and then the solvent was removed under reduced pressure until a thick slurry was formed. Water (200ml) was added and the suspension was stirred to ensure the solid was finely dispersed. The off-white solid was filtered and washed with NaOH (1N, 100ml), water (100ml) and HCl (1N, 100ml) and then water (200ml) dried to give **16A** (1.9g, 100%).

16B



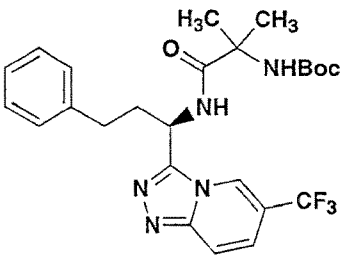
[0139] To a THF (100ml) solution of **16A** (1.9g, 4.3 mmol) was added triphenylphosphine (1.3 g, 5.2 mmol), and trimethylsilyl azide(0.6g, 5.2 mmol). To this solution was added diethyl diazacarboxylate (DEAD, 1.8g, 10.8mmol) in rapid drops. The solution became hot. After the addition was complete, the solution was allowed to stir at r.t. until all starting material was consumed (<2h). The solvent was removed under reduced pressure to give **16B**

16C



[0140] **16B** was suspended in HCl-dioxane (160 ml, 4M HCl in dioxane). The suspension was stirred at r.t. until all of the starting material was consumed. The suspension was concentrated to a thick slurry and then diluted with THF (100 ml). The solid was collected by filtration and rinsed with excess CH_2Cl_2, diethyl ether, and dried to give **16C**

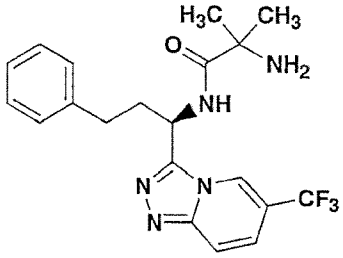
16D



[0141] To a THF (100 ml) solution of 2-tert-butoxycarbonylamino-2-methyl-propionic acid (27.5mg, 0.135mmol) was added EDAC (29.2mg, 0.15mmol) and HOBT (20mg, 0.15mmol), DMAP (1.5mg, 0.01mmol), and pyridine. This solution was stirred at r.t. for 10 min before the addition of **16C** (52mg, 0.123mmol). The reaction was completed in <1 h. The solvent was then removed under reduced pressure and the residue was dissolved in EtOAc (200 ml). The organic solution was washed with water (200 ml), NaOH (0.5 N, 200 ml), HCl (0.5 N, 200 ml), and water (200 ml). The organic layer was dried over Na_2SO_4 and concentrated to give a white solid **16D**

EXAMPLE 16

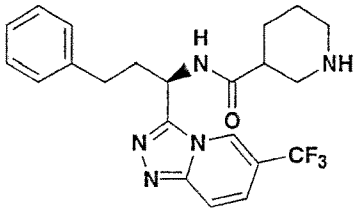
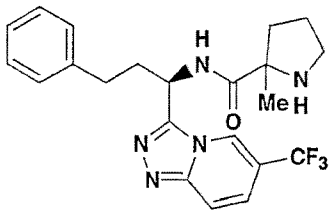
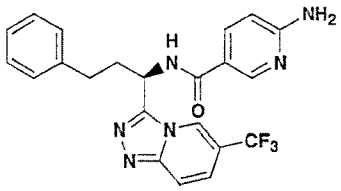
[0142]



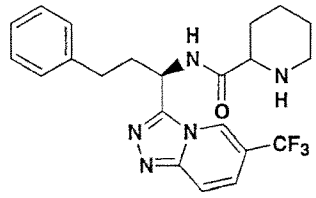
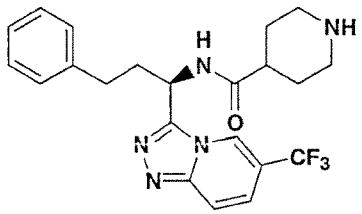
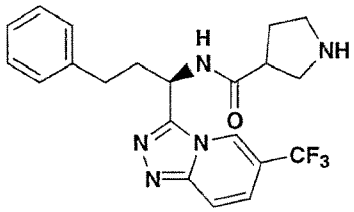
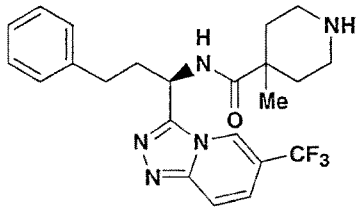
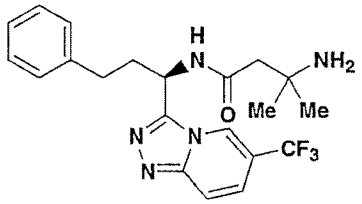
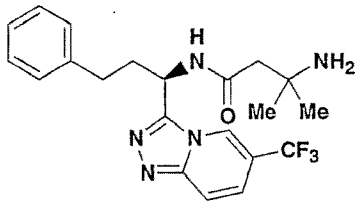
[0143] **16D** was dissolved in 4 M HCl-dioxane (5 ml). The solution was stirred at r.t. until all starting material was consumed. The solvent was evaporated under reduced pressure and the white solid was triturated with diethyl ether to afford pure product (29mg, 94%). MS (M+H) 406, HPLC retention time 2.3min.

[0144] The following compounds have been prepared utilizing the procedures described in **Example 16,** which started with the corresponding acids (step A), hydrazines (step A) and amines (Step D) as depicted in Table 2.

TABLE 2

Compound number		HPLC Purity (%)	HPLC Retention (min)	Mass
17		98	2.28	432
18		91	2.28	432
19		95	2.47	441

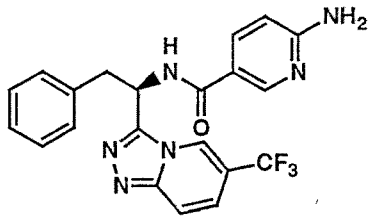
(continued)

Compound number		HPLC Purity (%)	HPLC Retention (min)	Mass
20		98	2.26, 2.42	432
21		98	2.35	432
22		94	2.31	418
23		93	2.47	446
24		95	2.39	420
25		88	2.34	420

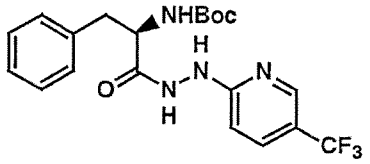
EXAMPLE 26

6-Amino-N-[2-phenyl-1-(6-trifluoromethyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)-ethyl]-nicotinamide

[0145]



26A

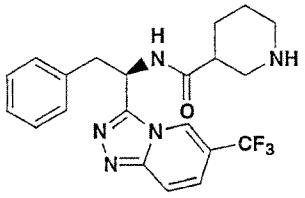
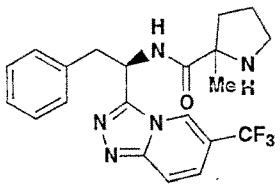
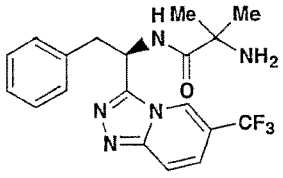


[0146] To a THF (100ml) solution of 2-tert-Butoxycarbonylamino-3-phenylpropionic acid (2.0g, 7.1mmol) was added TEA(0.98 ml, 7.1 mmol), followed by the addition of iso-butyl chloroformate (0.98g, 7.1mmol) dropwise. A White suspension was formed. This suspension was stirred at r.t. for 10min and then (5-Trifluoromethyl-pyridin-2-yl)-hydrazine (1.3g, 7.1mmol) was added in three portions. The resulting suspension was stirred at r.t. for 1h and then the solvent was removed under reduced pressure until a thick slurry was formed. Water (200ml) was added and the suspension was stirred to ensure the solid was finely dispersed. The off-white solid was filtered and washed with NaOH (1N, 100ml), water (100ml) and HCl (1N, 100ml) and then water (200ml) dried to give **26A**(1.9,100%).

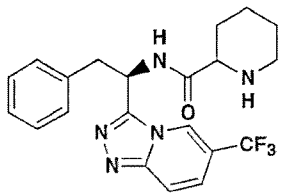
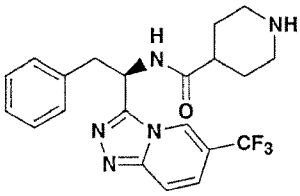
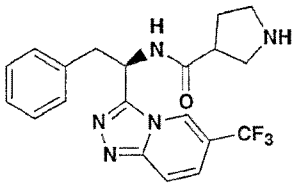
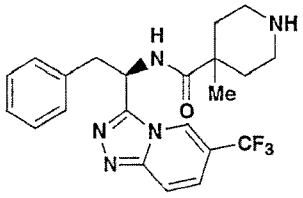
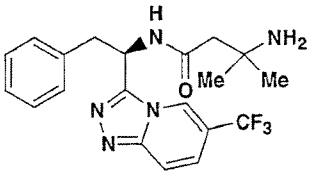
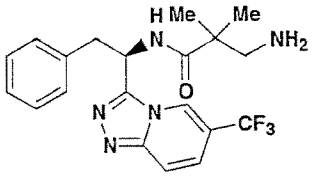
[0147] **Example 26** was prepared utilizing the procedures described in **Example 16,** substituting with **26A** for **16A**, **26B** for **16B**, **26C** for **16C, 26D** for **16D.** Example 26 was obtained as a white foam. MS (M+H) 427, HPLC retention time 2.23min.

[0148] The following compounds have been prepared utilizing the procedures described in **Example 26** as depicted in Table 3.

TABLE 3

Compound number		HPLC Purity (%)	HPLC Retention (min)	Mass
27		95	2.03	418
28		93	2.02	418
29		98	2.00	392

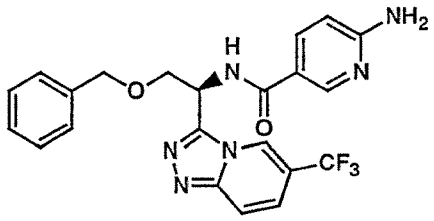
(continued)

Compound number		HPLC Purity (%)	HPLC Retention (min)	Mass
30		98	2.02,2.16	418
31		80	2.08	418
32		88	2.06	404
33		90	2.15	432
34		88	2.14	406
35		76	2.07	406

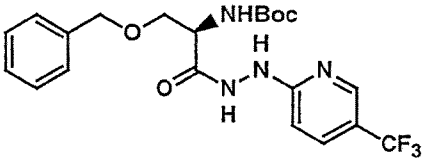
EXAMPLE 36

6-Amino-N-[2-benzyloxy-1-(6-trifluoromethyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)-ethyl]-nicotinamide

[0149]



36A

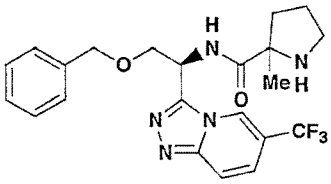
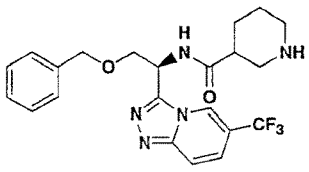
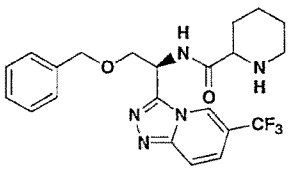


[0150] To a THF (100ml) solution of 3-Benzyloxy-2-tert-butoxycarbonylamino-propionic acid(2.0g, 7.1mmol) was added TEA (0.98 ml, 7.1 mmol), followed by the addition of iso-butyl chloroformate (0.98g, 7.1mmol) dropwise. A White suspension was formed. This suspension was stirred at r.t. for 10min and then (5-Trifluoromethyl-pyridin-2-yl)-hydrazine (1.3g, 7.1mmol) was added in three portions. The resulting suspension was stirred at r.t. for 1h and then the solvent was removed under reduced pressure until a thick slurry was formed. Water (200ml) was added and the suspension was stirred to ensure the solid was finely dispersed. The off-white solid was filtered and washed with NaOH (1N, 100ml), water (100ml) and HCl (1N, 100ml) and then water (200ml) dried to give **36A**(1.9,100%).

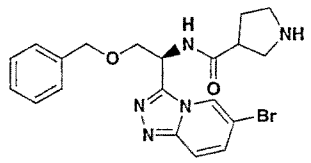
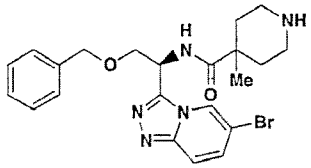
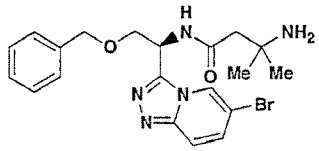
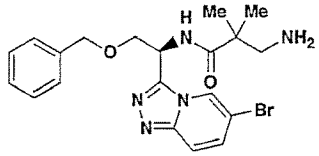
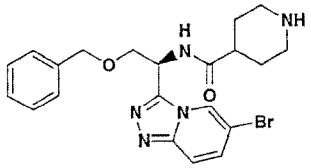
[0151] **Example 36** was prepared utilizing the procedures described in **Example 16,** substituting with **36A** for **16A, 36B** for **16B, 36C** for **16C, 36D** for **16D.** Example 36 was obtained as a white foam. MS (M+H) 456,HPLC retention time 2.4in.

[0152] The following compounds have been prepared utilizing the procedures described in **Example 36** as depicted in **Table 4.**

TABLE 4

Compound number		HPLC Purity (%)	HPLC Retention (min)	Mass
37		98	2.38	447
38		100	2.29	447
39		97	2.31	447

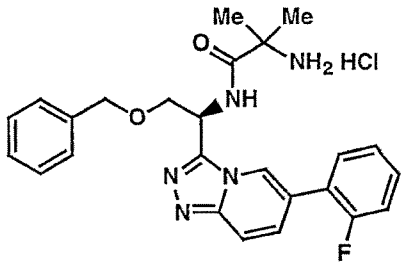
(continued)

Compound number		HPLC Purity (%)	HPLC Retention (min)	Mass
40		95	2.08	445
41		95	2.22	473
42		97	2.11	447
43		90	2.09	447
44		96	2.09	459

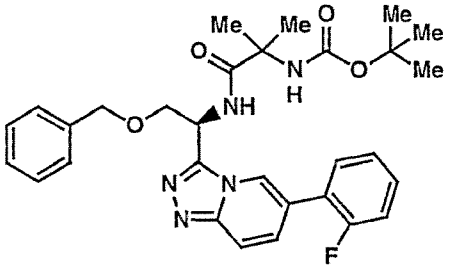
EXAMPLE 45

2-Amino-N-{2-benzyloxy-1-[6-(2-fluoro-phenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl]-ethyl}-2-methyl-propionamide

[0153]



45A



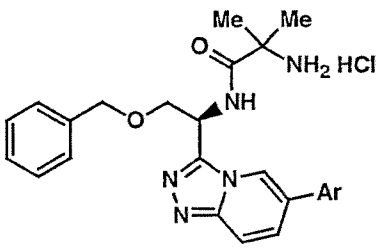
[0154] Compound **1D** (300mg, 0.56mmol), 2-fluorophenylboronic acid(120mg, 0.86 mmol), $Pd(OAc)_2$ (5mg, 0.022 mmol), triphenyl phosphine (100mg, 0.38mmol), and Et_3N (0.24ml, 1.72mmol) were dissolved in DMF (2ml). This solution was heated at 110°C for 12h. The resulted mixture was diluted with water (10ml) and was extracted with EtOAc. The combined organic portion was washed with NH_4OH (10%) and brine and dried over anhydrous MgSO4. The solvent was evaporated under reduced pressure to afford a stick liquid. The products were not purified and used directly for the next step.

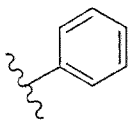
EXAMPLE 45

[0155] **45A** was dissolved in 4 M HCl-dioxane (2ml). The solution was stirred at r.t. until all starting material was consumed. The solvent was evaporated under reduced pressure. The product was purified by preparative HPLC to give the title compound (129mg, 50%). MS (M+H) 447, HPLC retention time 2.47min.

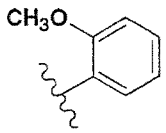
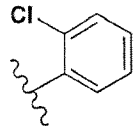
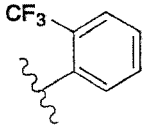
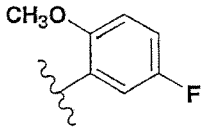
[0156] The following compounds has been prepared by utilizing the intermediates generated in **Example** 1 with chemical sequences described in **Example 45,** utilizing the appropriate starting materials as depicted in **Table 5.**

TABLE 5



Compound number	Ar	HPLC Purity (%)	HPLC Retention (min)	Mass
46		100	2.45	430

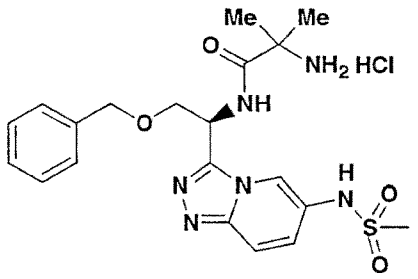
(continued)

Compound number	Ar	HPLC Purity (%)	HPLC Retention (min)	Mass
47		100	2.47	460
48		98	2.63	464
49		99	2.66	497
50		100	2.56	477

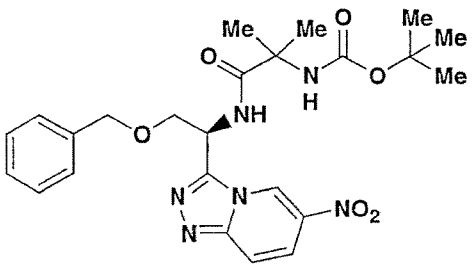
EXAMPLE 51

2-Amino-N-[2-benzyloxy-1-(6-methanesulfonylamino-[1,2,4]triazolo[4,3-a]pyridin-3-yl)-ethyl]-2-methyl-propionamide

[0157]

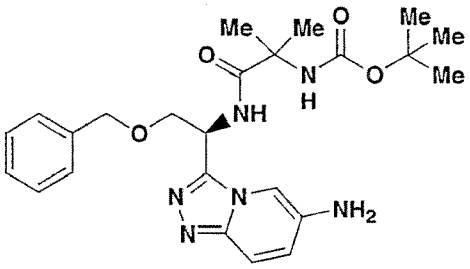


51A



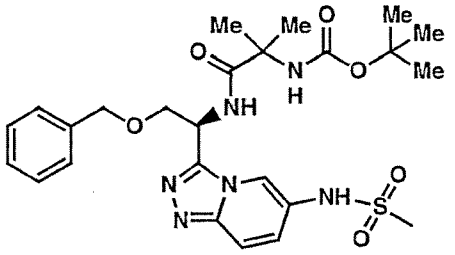
[0158] Compound **51A** was obtained using the same procedures described for the synthesis of **1D** with 5-nitro-2-hydrazinopyridine in place of 5-bromo-2-hydrazinopyridine.

51B



[0159] Compound **51A** (1.3 g, 2.6 mmol) was dissolved in EtOH (60 ml). Pd/C (35mg, 10% Pd by weight) was added under N_2. This mixture was then subjected to hydrogenation at 50 Psi for 3h to afford **51B.** Solvent was removed under reduced pressure and the product was pure enough (>90%) and was used directly for the next reactions.

51C



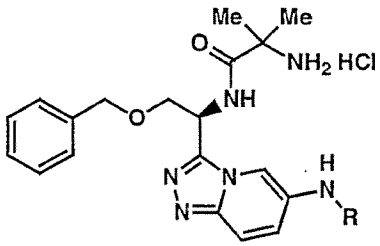
[0160] Compound **51B** (200mg, 0.43 mmol) was dissolved in CH_2Cl_2 (5 ml) and pyridine (0.14ml), 2.1mmol) was added. To this solution was added the corresponding methyl sulfonyl chloride(0.05ml, 0.65mmol). Reactions were completed in 1.5 h. The reactions were then diluted with CH_2Cl_2 (25 ml) and washed with HCl (1N, 20ml), aqueous saturated $NaHCO_3$ (20ml), and water (20ml). Purification by flash chromatography on silica gel (5% CH_3OH/ as elutant) gave **51C** (90mg, 40%).

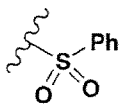
EXAMPLE 51

[0161] Compound **51C** was dissolved in HCl (4ml, 4M in dioxane) and was stirred at r.t. until the reaction was completed. The solvent was removed under reduced pressure. The products were purified by preparative HPLC to give the title compound as a foam (60mg, 82%). MS (M+H) 447, HPLC retention time 1.73min.

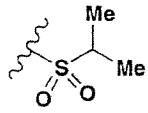
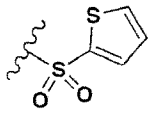
[0162] The following compounds in **Table 6** have been synthesized utilizing the procedures described in **Example 51,** utilizing the appropriate starting materials.

TABLE 6



Compound number	R	HPLC Purity (%)	HPLC Retention (min)	Mass
52		90	2.32	509

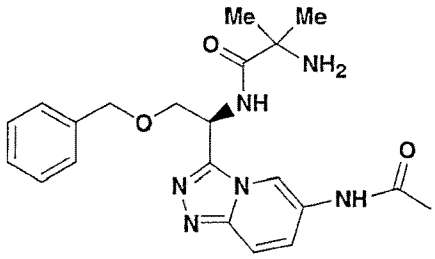
(continued)

Compound number	R	HPLC Purity (%)	HPLC Retention (min)	Mass
53		97	2.02	475
54		97	2.23	515

EXAMPLE 55

N-[1-(6-Acetylamino-[1,2,4]triazolo[4,3-a]pyridin-3-yl)-2-benzyloxy-ethyl]-2-amino-2-methyl-propionamide

[0163]



55A

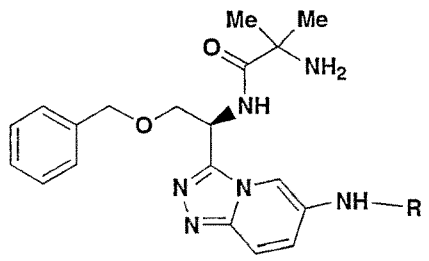
[0164] Compound **51B** (130mg, 0.28mmol) was dissolved in CH_2Cl_2 (2 ml) and Et_3N (0.2ml, 1.4mmol) was added. To this solution was added acetyl chloride(0.026ml,0.36mmol). After stirring overnight at r.t, the reaction was then diluted with CH_2Cl_2 (25 ml) and washed with HCl (1N, 20ml), $NaHCO_3$ (sat. 20ml), and water (20ml). The crude product were purified with flash chromatography (5% CH_3OH/CH_2Cl_2) to give **55A** (80mg, 56%).

Example 55

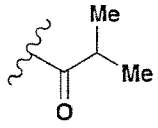
[0165] Compound **55A** was dissolved in HCl (4ml, 4M in dioxane) and was stirred at r.t. until the reaction was completed. The solvent was removed under reduced pressure. The products were purified by preparative HPLC to give the title compound as a foam. MS (M+H) 411, HPLC retention time 1.86min.

[0166] The following compounds in **Table 7** have been synthesized utilizing the procedures described in **Example** 55, utilizing the appropriate starting materials.

TABLE 7



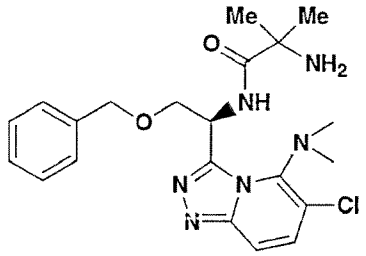
(continued)

Compound number	R	HPLC Purity (%)	HPLC Retention (min)	Mass
56		88	2.24	439

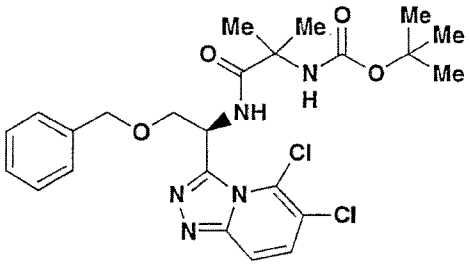
EXAMPLE 57

2-Amino-N-[2-benzyloxy-1-(6-chloro-5-dimethylamino-[1,2,4]triazolo[4,3-a]pyridin-3-yl)-ethyl]-2-methyl-propionamide

[0167]

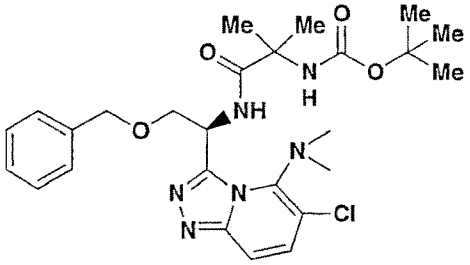


57A



[0168] Compound **57A** was obtained using the same procedures described for the synthesis of **1D** with the corresponding 2-hydrazinopyridine.

57B



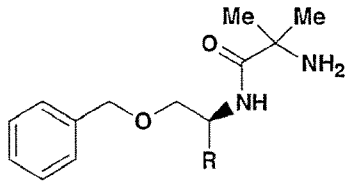
[0169] Compound **57A** (250mg, 0.48mmol) in Dimethylamine (3ml) was heated at 100°C for 1.5h. The reaction was diluted with water (10ml) and extracted with EtOAc. The combined organic portions were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified with flash chromatography (2% CH_3OH/CH_2Cl_2) to give **57B** (140mg, 55%).

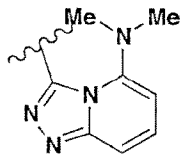
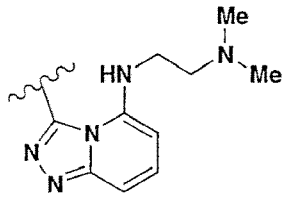
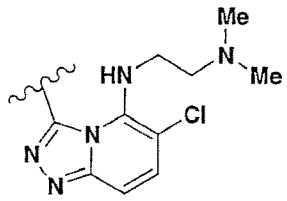
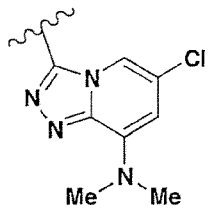
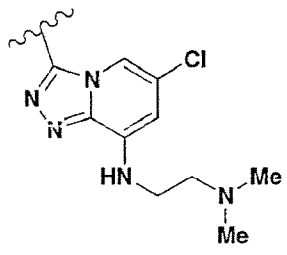
EXAMPLE 57

[0170] **57A** (140mg, 0.26mmol) was dissolved in HCl (5ml, 4 M HCl in dioxane) and stirred at r.t. until all the starting materials was consumed. Purification by preparative HPLC gave the title compound (51mg). MS (M+H) 431, HPLC retention time 2.35min.

[0171] The following compounds in **Table 8** have been synthesized utilizing the procedures described in **Example 57,** utilizing the appropriate starting materials.

TABLE 8

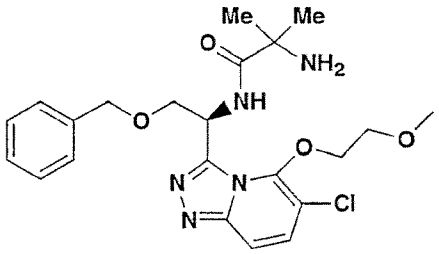


Compound number	Substituted Triazolopyridine (R)	HPLC Purity (%)	HPLC Retention (min)	Mass
58		96	1.51	397
59				
60				
61		98	2.51	431
62		97	1.34	475

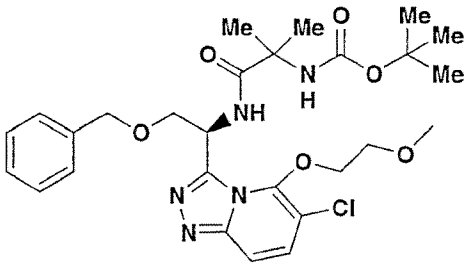
EXAMPLE 63

2-Amino-N-(2-benzyloxy-1-[6-chloro-5-(2-methoxy-ethoxy)-[1,2,4]triazolo[4,3-a]pyridin-3-yl]-ethyl}-2-methyl-propionamide

[0172]



63A



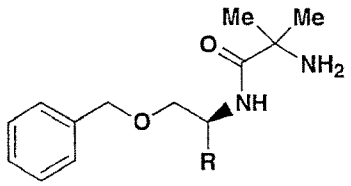
[0173] Compound **57A** (250mg, 0.48mmol) in 2-Methoxy-ethanol(1ml) and Cesium carbonate (155mg, 0.48mmol) was heated at 100°C for 1.5h. The reaction was diluted with water (10 ml) and extracted with EtOAc. The combined organic portions were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to give **63A**.

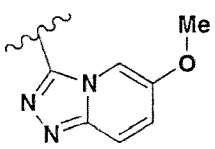
EXAMPLE 63

[0174] **63A** was dissolved in HCl (5 ml 4 M HCl in dioxane) and stirred at r.t. until all the starting materials was consumed. Purification by preparative HPLC gave the title compound (18.6mg). MS (M+H) 462, HPLC retention time 2.23min.

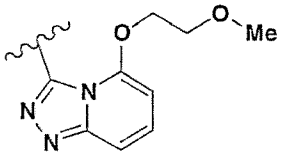
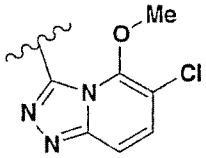
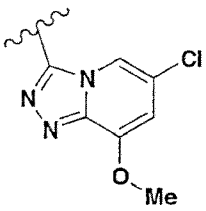
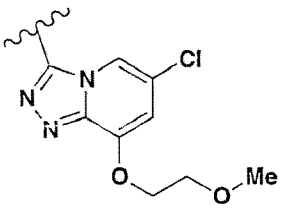
[0175] The following compounds in **Table 9** have been synthesized utilizing the procedures described in **Example 63,** utilizing the appropriate starting materials.

TABLE 9



Compound number	R	HPLC Purity (%)	HPLC Retention (min)	Mass
64		90	1.97	420

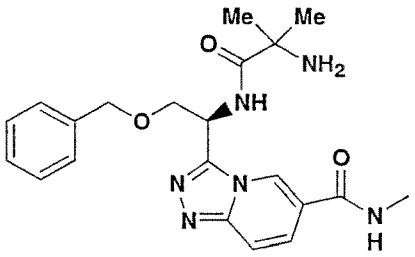
(continued)

Compound number	R	HPLC Purity (%)	HPLC Retention (min)	Mass
65				
66				
67				
68				

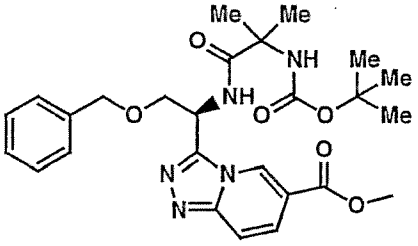
EXAMPLE 69

3-[1-(2-Amino-2-methyl-propionylamino)-2-benzyloxy-ethyl]-[1,2,4]triazolo[4,3-alpyridine-6-carboxylic acid methylamide

[0176]

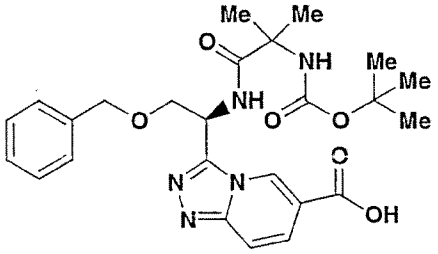


69A



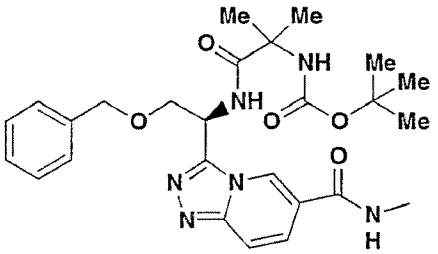
[0177] To **1D** (0.7g, 1.32mmol) in DMF (10ml) and MeOH (5ml) was added 1,3-Bis(diphenylphosphino)-propane (217mg, 0.53mmol), DBU (240mg, 1.58mmol) and palladium acetate (148mg, 0.66mmol). The mixture was degassed and the flushed with carbon monoxide and kept at 20psi. The reaction was heated at 85°C overnight. The catalyst was filtered and the solution concentrated. The residue was taken in EtOAc, washed with water, brine, dried and concentrated. The crude product was purified with flash chromatography to give **69A** as a white foam.

69B



[0178] To **69A** (2.3g, 4.5mmol) in THF (20ml) was added lithium hydroxide (40ml of 2N solution). The mixture was stirred for 3h at r.t. 1NHCl was added to adjust the pH to 2. The solution was extracted with CH_2Cl_2, washed, dried and concentrated to give **69B.**

69C



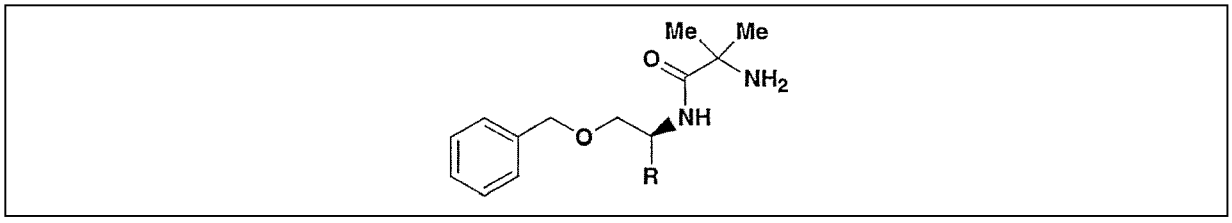
[0179] To a CH_2Cl_2(2ml) solution of **69B**(150mg, 0.3mmol) was added EDAC (86mg, 0.45mmol) and HOBT (60mg, 0.45mmol) and $(i\text{-}Pr)_2NEt$ (58mg,0.45mmol) and then 2M solution of methylamine in THF(0.225ml, 0.45mmol) The reaction was stirred overnight and then extracted with EtOAc .The organic solution was washed with water, brine, dried and concentrated to give a white solid **69C.**

EXAMPLE 69

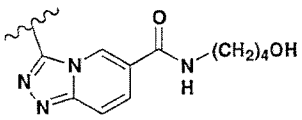
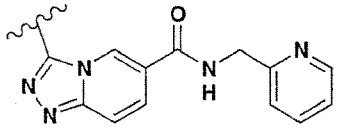
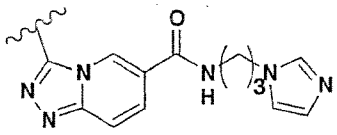
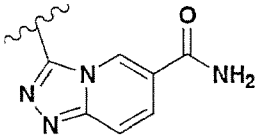
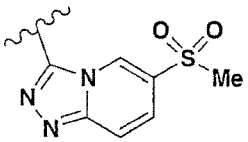
[0180] **69C** was dissolved in HCl (5 ml 4 M HCl in dioxane) and stirred at r.t. until all the starting materials was consumed. Purification by preparative HPLC gave the title compound as an oil. MS (M+H) 410, HPLC retention time 2.4min.

[0181] The following compounds in **Table 10** have been synthesized utilizing the procedures described in **Example 69,** utilizing the appropriate starting materials.

TABLE 10



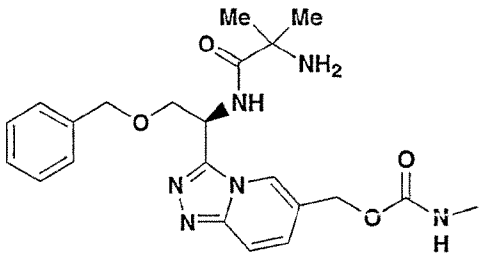
(continued)

Compound number	R	HPLC Purity (%)	HPLC Retention (min)	Mass
70		93	2.56	468
71		90	2.13	487
72		90	2.00	505
73		93	1.39	396
74		95	2.39	432

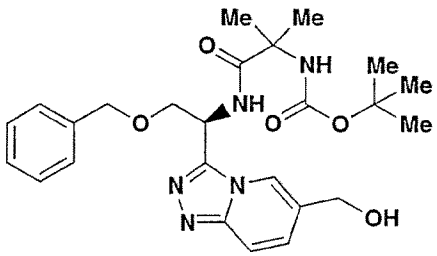
EXAMPLE 75

Methyl-carbamic acid 3-[1-(2-amino-2-methyl-]2ropionylamino)-2-benzyloxy-ethyl]-[1,2,4]triazolo[4,3-a]pyridin-6-ylmethyl ester

[0182]

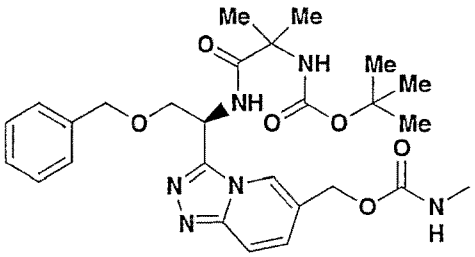


75A



[0183] To a stirred solution of **59A** (50mg,0.098mmol) in CH_2Cl_2 at -78°C was added 1.5M solution of DIBAL in toluene (0.4ml, 0.58mmol) and stirred at r.t. overnight. The solution was cooled to 0°C and then a 1M solution of sodium potassium tartarate was added slowly. Stirred for 1.5h at r.t. The precipitate formed is filtered off through a pad of celite. And then extracted with CH_2Cl_2, washed, dried and concentrated to give **75A.**

75B



[0184] To **75A** (180mg, 0.2mmol) in CH_2Cl_2(2ml) 0°C was added TEA (60mg, 0.6mmol) and methyl isocyanate (24mg, 0.4mmol). Reaction was warmed to r.t. and stirred overnight. The solution was concentrated to give **75B**

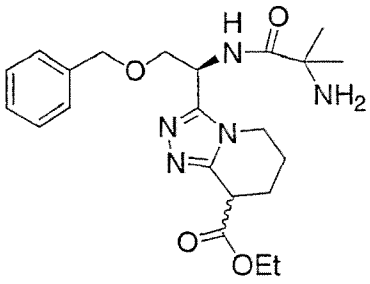
EXAMPLE 75

[0185] **75B** was dissolved in HCl (5 ml 4 M HCl in dioxane) and stirred at r.t. until all the starting materials was consumed. Purification by preparative HPLC gave the title compound as oil. MS (M+H) 441, HPLC retention time 2.48min.

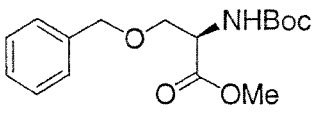
EXAMPLE 76

3-[1-(2-Amino-2-methyl-propionylamino)-2-benzyloxy-ethyl]-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-8-carboxylic acid ethyl ester

[0186]

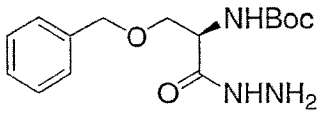


76A



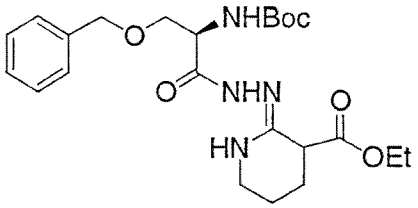
[0187] To a cooled solution of potassium hydroxide (100ml, 40% in water) in ether (500ml) at 0°C was added 1-methyl-3-nitro-1-nitoroguanidine(15g, 0.102mol) slowly over 15min. The upper organic phase was poured into a flask containing 30g potassium hydroxide. After 5min. the ether solution was slowly added to 3-Benzyloxy-2-tert-butoxycarbonylamino-propionic acid (20.5g, 0.069mol) in TBF/CH_2Cl_2 (200ml). After stirring for 5min the solution was concentrated to give **76A.**

76B



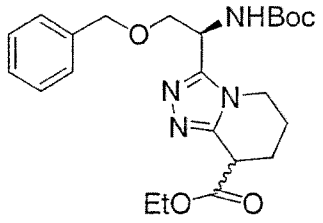
[0188] To a solution of **76A** (22.8mg, 74.8mmol) in 250ml MeOH was added hydrazine (4.8g, 149.8mmol) and the mixture refluxed for 2 days. The solution was concentrated to give crude **76B**.

76C



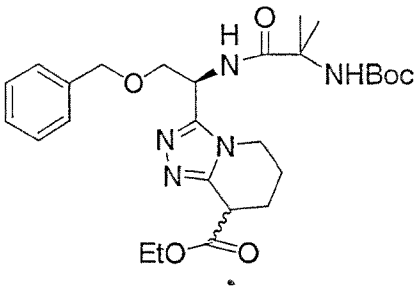
[0189] To a solution of 2-Oxo-piperidine-3-carboxylic acid ethyl ester (0.86g, 5mmol) in CH_2Cl_2 (10ml) was added trimethyloxonium tetrafluoroborate (0.74g, 5mmol)and stirred overnight followed by addition of **76B** (1.5g, 5mmol). The mixture was stirred for 24h.The solution was diluted with CH_2Cl_2, washed with water, brine, dried and concentrated to give **76C** as a white foam (2.5g, <99%).

76D



[0190] The solution of **76C** (1.3g, 2.8mmol) in MeOH (27ml) was refluxed for 4days. The mixture was concentrated to give **76D.**

76E



[0191] To **76D** (1.2g, 2.8mmol) in CH_2Cl_2 was added HCl (5 ml 4 M HCl in dioxane) and stirred at r.t. until all the starting materials was consumed. The solution was concentrated. To a CH_2Cl_2 (15ml) solution of the residue was added EDAC (0.8g, 0.4.16mmol) and HOBT (0.56g, 4.16mmol) and $(i\text{-}Pr)_2NEt$ (7.15g,55.4mmol) and 2-tert-butoxycarbonylamino-2-methyl-propionic acid (0.68g, 3.32mmol). The reaction was stirred overnight and then extracted with EtOAc. The organic solution was washed with water, brine, dried and concentrated. Purification by flash chromatography on silica gel (5% CH_3OH/ CH_2Cl_2 as elutant) gave **76E**.

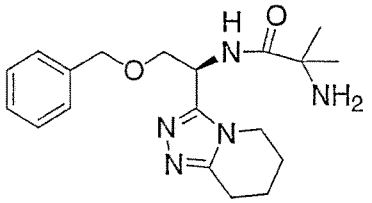
Example 76

[0192] **76E** (50mg, 0.1mmol) in CH_2Cl_2 (5ml) was treated with HCl (2 ml 4 M HCl in dioxane) and stirred at r.t. until all the starting materials was consumed. Purification by preparative HPLC gave the title compound as a salt (22mg, 55%). MS (M+H) 430, HPLC retention time 2.63min.

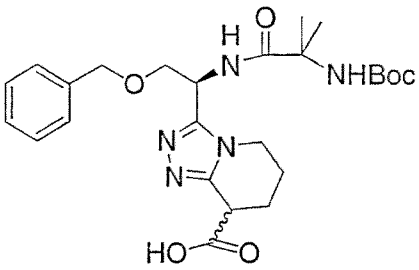
EXAMPLE 77

2-Amino-N-[2-benzyloxy-1-(5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)-ethyl]-2-methyl-propionamide

[0193]



77A



[0194] To a solution of **76E** (0.32g, 0.6mmol) in THF (1ml) was added H_2O (4ml), MeOH (0.5ml) and Lithium hydroxide (6ml of 4N solution). The mixture was stirred at r.t. for 1.5h. The pH of the solution was adjusted to 2 with the slow addition of 1N HCl, followed by extraction with CH_2Cl_2 washed with water, brine, dried and concentrated to give **77A** (270mg, 89%)

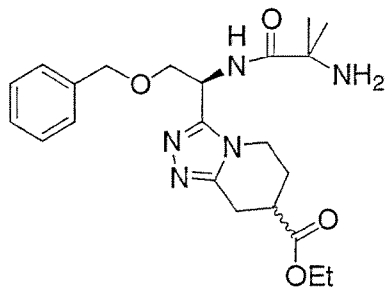
Example 77

[0195] To **77A** (135mg, 0.27mmol) in ether (2.5ml) was added methylamine (0.27ml, 0.54mmol, 2M in THF), HOBT (73mg, 0.54mmol) and EDAC (103mg, 0.54mmol). After stirring for 24h, the solution was extracted with CH_2Cl_2, washed with water, brine, dried and concentrated. The residue in CH_2Cl_2 (2ml) was treated with HCl (1 ml 4 M HCl in dioxane) and stirred at r.t. until all the starting materials was consumed. Purification by preparative HPLC gave the title compound as a foam (61mg, 65%). MS (M+H) 358, HPLC retention time 1.86min.

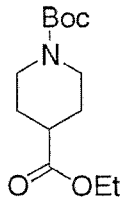
EXAMPLE 78

3-[1-(2-Amino-2-methyl-propionylamino)-2-benzyloxy-ethyl]-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-7-carboxylic acid ethyl eater

[0196]

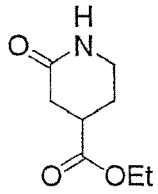


78A



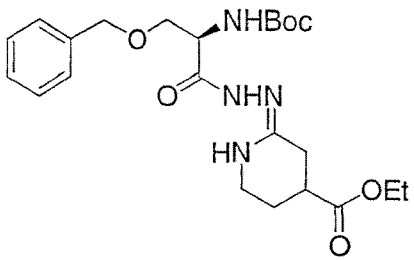
[0197] To a solution of ethyl isonipecotate (20.4g, 0.13mmol) in CH_2Cl_2 (120ml) was added di-tert-butyl dicarbonate (31.1g, 0.13mol). After 5h of stirring at r.t, the reaction was quenched with water and extracted with CH_2Cl_2. washed with water, brine, dried and concentrated. Purification by flash chromatography on silica gel (1:6 EtOAc/hexane as elutant) gave **78A.**

78B



[0198] To a solution of **78A** (10.38g, 40.4mmol) in water (120ml) and acetonitrile (25ml) at r.t. was added sodium periodate (25.9g, 121.1mmol) and ruthinium oxide (0.5g, 3.63mmol). After stirring for 6h the mixture was filtered. The residue was washed with CH_2Cl_2 and the aqueous layer was extracted with CH_2Cl_2, dried and concentrated. The residue in CH_2Cl_2 (100ml) was treated with HCl (14 ml 4 M HCl in dioxane) and stirred at r.t. until all the starting materials was consumed. Purification by flash chromatography on silica gel (5% CH_3OH/CH_2Cl_2 as elutant) gave **78B.**

78C



[0199] **78C** was prepared using the method described in **76C** substituting 2-Oxopiperidine-3-carboxylic acid ethyl ester with 78B (1.2g, 7.1mmol)) and **76B**(2.9g, 7.1mmol). **78C** was obtained as a colorless oil (3.4g, <99%).

[0200] **Example 78** was prepared by using the same methods as described to prepare **76D** substituting **76C** with **78C** to provide the title compound as a foam (17mg). MS (M+H) 430, HPLC retention time 2.56min.

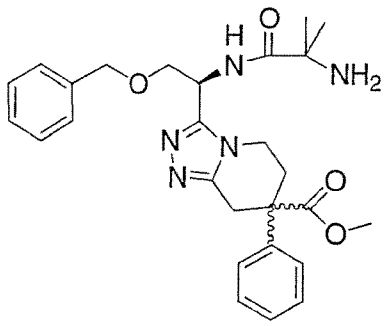
[0201] Preparative HPLC separation of **Example 78** gave the two diastereomers as **Example 78a** MS (M+H) 430,

HPLC retention time 2.55min and **Example 78b** MS (M+H) 430, HPLC retention time 1.89min.

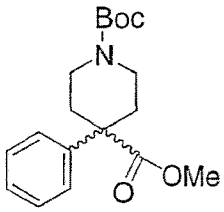
EXAMPLE 79

3-[1-(2-Amino-2-methyl-propionylamino)-2-benzyloxy-ethyl]-7-phenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-7-carboxylic acid methyl ester

[0202]

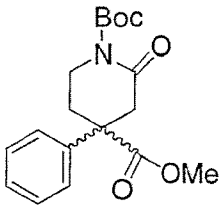


79A



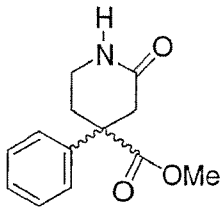
[0203] To a cooled solution of potassium hydroxide (15ml, 40% in water) in ether (100ml) at 0°C was added 1-methyl-3-nitro-1-nitoroguanidine(5g, 34mmol) slowly over 15min. The upper organic phase was poured into a flask containing 30g potassium hydroxide. After 5min the ether solution was slowly added to 4-formyl-4-phenyl-piperidine-1-carboxylic acid tert-butyl ester (4.15g, 13.6mmol) in THF (20ml). After stirring for 5min the solution was concentrated to give **79A** (4.4g, <99%).

79B



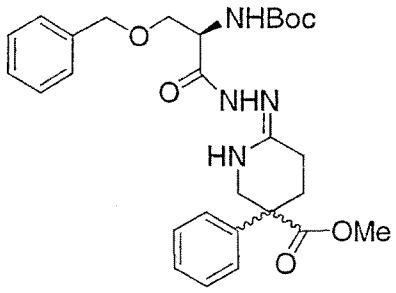
[0204] **79B** was prepared using the method described in **78B** substituting **78A** with 79A (4g, 12.5mmol) and. **79B** was obtained as a colorless oil (3.1g, 75%).

79C



[0205] **79B** (3.1g, 9.3mmol) in CH_2Cl_2/MeOH (6ml/6ml) was treated with HCl (5 ml 4 M HCl in dioxane) and stirred at r.t. until all the starting materials was consumed. Purification by flash chromatography on silica gel (5% CH_3OH/CH_2Cl_2 as elutant) gave **79C**.

79D



[0206] **79D** was prepared using the method described in **76C** substituting 2-Oxopiperidine-3-carboxylic acid ethyl ester with **79C** (830mg, 35.6mmol) and **76B**(2.9g, 7.1mmol). **79D** was obtained as a colorless oil (2.2g, <99%).

[0207] **Example 79** was prepared by using the same methods for **76D, 76E** and **example 76** substituting **76C** with **79D, 76D** with **79E, 76E** with **79F** to provide the title compound as a foam (8.5mg). MS (M+H) 492, HPLC retention time 2.91min.

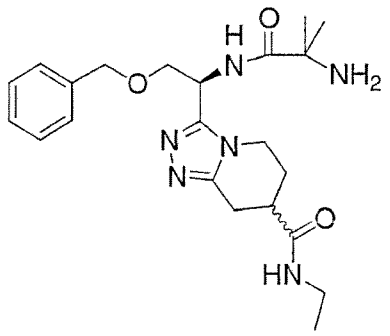
EXAMPLE 80 AND EXAMPLE 81

[0208] **Example 79** was subjected to preparative HPLC to separate the diastereomers to give 24mg of **Example 80** (MS (M+H) 492, HPLC retention time 2.89min) & 34mg of **Example 81** (MS (M+H) 492, HPLC retention time 3.01 min)

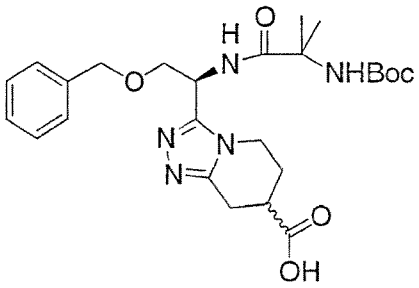
EXAMPLE 82

3-[1-(2-Amino-2-methyl-propionylamino)-2-benzyloxy-ethyl]-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-7-carboxylic acid ethyl amid

[0209]



82A

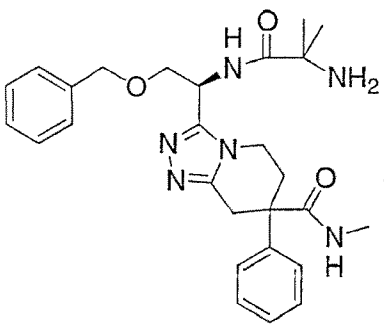


[0210] **82A** was prepared using the method described in **77A** substituting **76E** with 78D (200mg, 0.38mmol) and. **82A** was obtained as a colorless oil (168mg, 89%).

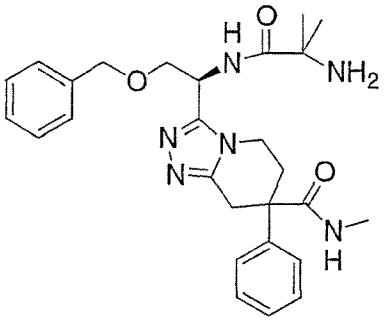
Example 82

[0211] To a solution of **82A** (89mg, 0.18mmol) in CH_2Cl_2 (2ml) at -40°C was added N-methyl morpholine and isobutyl chloroformate (24.3mg, 0.18mmol). The mixture was stirred for 1h at-40°C. Then 2M solution of ethylamine in THF (90µl, 0.18mmol) was added. The reaction was slowly warmed up to r.t. and concentrated. The residue was redissolved in CH_2Cl_2 (2ml) was treated with HCl (1 ml 4 M HCl in dioxane) and stirred at r.t. until all the starting materials was consumed. Purification by preparative HPLC gave the title compound as a salt (14mg, 20%). MS (M+H) 429, HPLC retention time 1.89min.

[0212] Compounds 83 and 83a were synthesized utilizing the procedures described in **Example 82,** utilizing the appropriate starting materials.

83		90	2.42	491

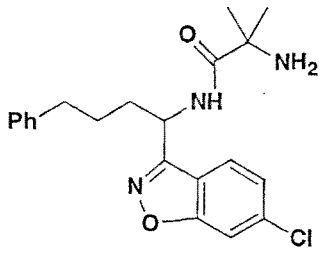
(continued)

83a Other diastereomer		95	2.73	491

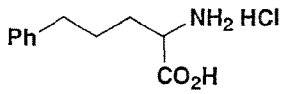
EXAMPLE 84

2-Aznino-N-[1-(6-chloro-benzo[d]isoxazol-3-yl)-4-phenyl-butyl]-2-methyl-propionamide

[0213]

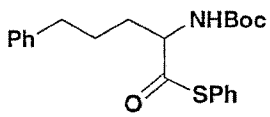


84A



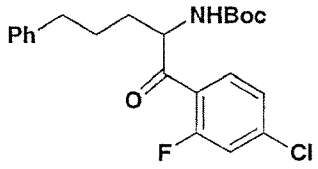
[0214] To 60ml of EtOH was added Na metal (2.3g, 100mmol) slowly & stirred for 30 min. until all the Na metal had dissolved. 2-Acetyl amino-malonic acid diethyl ester (21.7g, 100mmol) was then added. After stirring for 1h at r.t, (3-bromo-propyl)-benzene (15.2ml, 100mmol) was added & then heated at 75°C overnight. The mixture was quenched with water extracted with EtOAc, dried over Na_2SO_4, filtered & concentrated. The residue was triturated with hexane to give a white solid **84A** (18.7g, 81%)

84B



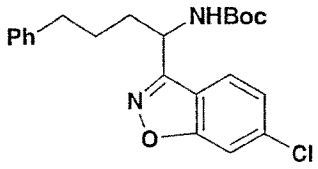
[0215] To a stirred solution of A (4.3g, 18.7mmol) in 1N NaOH (56 ml) and THF (50ml), Di-tert-butyl dicarbonate (4.9g, 22.5mmol) was added at RT. After 3h of stirring benzenethiol (3.1g, 28.1mmol), EDAC (7.1 g, 37 mmol) and HOBT (5.1 g, 37 mmol) were added and the reaction mixture was stirred at r.t. overnight. The mixture was extracted with EtOAc washed with water, dried over Na_2SO_4, filtered & concentrated. Purification by flash chromatography on silica gel (1:9 EtOAc/hexane as elutant) gave a white solid **84B** (3.8g, 53%).

84C



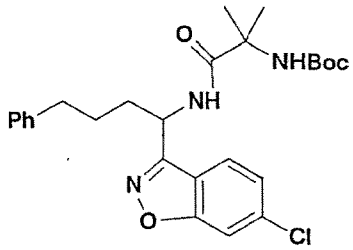
[0216] To **84B** (1.1g, 3.8mmol) in THF (10 ml) under nitrogen was added dichlorobis (triphenylphosphine) Palladium (II) (200mg, 0.28mmol) at 0°C followed by 3-chloro-4-flouro phenylzinc iodide (17ml, 8.5mmol) 0.5M in THF via syringe. After stirring the mixture at r.t. for 3h it was quenched with water extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated. Purification by flash chromatography on silica gel (1:9 EtOAc/hexane as elutant) gave a white solid **84C** (710mg, 45%)

84D



[0217] To a stirred solution of **84C** (700mg, 1.7mmol) in pyridine (5ml) was added Hydroxylamine hydrochloride (240mg, 3.4mmol) & heated in a sealed tube for 2h. The mixture was concentrated, the residue dissolved in DMF (5ml) and potassium hydroxide (450mg, 6.8mmol) added. The mixture was heated at 85°C overnight, quenched with water extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated. Purification by flash chromatography on silica gel (1:9 EtOAc/hexane as elutant) gave a white solid **84D** (390mg, 57%)

84E



[0218] To a stirred solution of **84D** (390mg, 0.97mmol) was added 5ml of 20% TFA/ CH_2Cl_2 and stirred at r.t. for 2 h. The mixture was concentrated, the residue dissolved in 1N NaOH, water brine, dried and concentrated. The residue was taken in 5ml CH_2Cl_2 & Boc-2-Aminoisobutyric acid (390mg, 1.9mmol), 1-Hydroxybenzotriazole hydrate (270mg, 2mmol), EDAC (380mg, 2mmol) were added. The mixture was stirred at r.t. overnight, extracted with EtOAc washed with water, dried over Na_2SO_4, filtered & concentrated. Purification by flash chromatography on silica gel (1:9 EtOAc/hexane as elutant) gave a white solid **84E** (360mg, 76%).

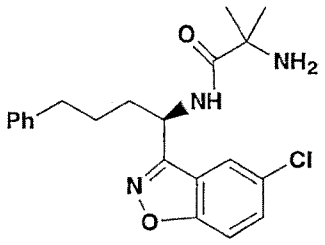
EXAMPLE 84

[0219] A solution of **84E** (13mg, 0.03mmol) in 1ml of 20%TFA/CH_2Cl_2 was stirred for 1h and then concentrated. The residue was purified by preparative HPLC to give the title compound as a white solid (34.5mg, 53%). MS (M+H) 386, HPLC retention time 3.32min.

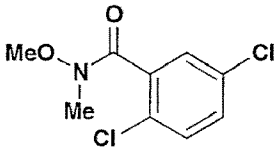
EXAMPLE 85

2-Amino-N-[1-(5-chloro-benzo[d]isoxazol-3-yl)-4-phenyl-butyl]-2-methyl-propionamide

[0220]

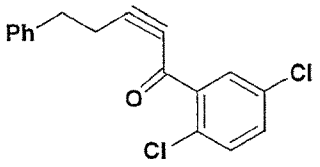


85A



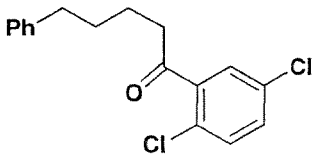
[0221] To a stirred solution of 2,5-Dichloro-benzoic acid (3.5g, 18.3mmol) in CH_2Cl_2 (5ml) was added Oxalyl chloride (18.3ml, 2M in CH_2Cl_2) followed by several drops of DMF. The mixture was stirred at r.t. for 2h and concentrated. The residue was dissolved in CH_2Cl_2 (20ml) & TEA (7.6ml, 55mmol) was added followed by N,O-Dimethylhydroxyamine hydrochloride (3.6g, 36.6mmol). The mixture was stirred at r.t. overnight & extracted with EtOAc washed, dried, filtered & concentrated. Purification by flash chromatography on silica gel (EtOAc/hexane as elutant) gave a pale brown solid **85A** (3g, 67%).

85B



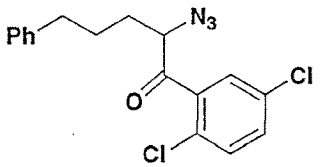
[0222] To But-3-ynyl-benzene (1.5g, 11.5mmol) in THF (15ml) at 0°C was added nbuLi (5.3ml, 2.5M in hexane) via syringe. After stirring for 30min. **85A** (2.4g. 10.3mmol) in 5ml THF was added followed by additional 1h of stirring at 0°C. The mixture was quenched with water, extracted with EtOAc, dried over Na_2SO_4, filtered & concentrated. Purification by flash chromatography on silica gel (1:9 EtOAc/hexane as elutant) gave a yellow liquid **85B** (1.3g, 42%)

85C



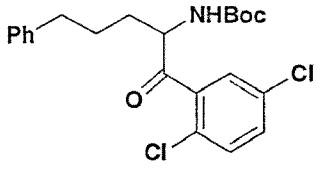
[0223] To **C** (1.3g, 4.3mmol) in MeOH (15ml) and EtOAc (5ml) was added Pd-C catalyst (260mg, 5% by weight of palladium) and stirred at r.t. with a hydrogen balloon for 6h. The catalyst was filtered and concentrated. Purification by flash chromatography on silica gel (5:95 EtOAc/hexane as elutant) gave a yellow liquid **85C** (1.1g, 85%).

85D



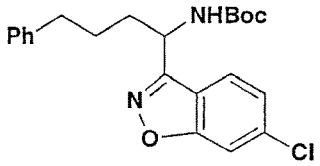
[0224] To a stirred solution of **85C** (900mg, 2.9mmol) in dioxane (5ml) was added bromine (470mg, 2.9mmol) in dioxane (5ml) slowly at r.t. via syringe & then stirred overnight. The mixture was quenched with water extracted with EtOAc, dried over Na_2SO_4, filtered & concentrated & the residue passed through a silica pad to give a pale yellow oil as the intermediate. The intermediate was dissolved in acetone (10ml) and sodium azide (200mg, 3.1mmol) in 2ml water was added. The mixture was stirred at r.t. for 30 min and concentrated, extracted with EtOAc, dried over Na_2SO_4, filtered & concentrated. Purification by flash chromatography on silica gel (1:9 EtOAc/hexane as elutant) gave 85D (710mg, 70%).

85E



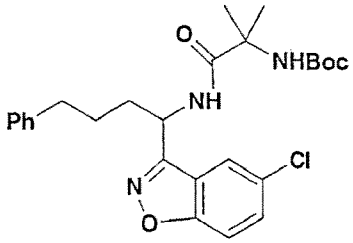
[0225] To **85D** (710mg, 2mmol) in MeOH (10ml) was added di-tert-butyl dicarbonate (1.3g, 6mmol) and Pd-C catalyst (70mg, 5% by weight of palladium) and stirred at r.t. with a hydrogen balloon overnight. The catalyst was filtered & concentrated. Purification by flash chromatography on silica gel (1:9 EtOAc/hexane as elutant) gave a white solid **85E** (250mg, 89%).

85F



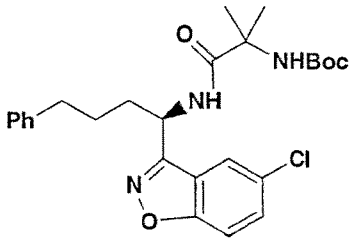
[0226] **85F** was prepared using the method described in **84D** substituting **84C** with **85E** (650mg, 1.5mmol) and hydroxylamine hydrochloride (210mg, 3mmol) & potassium hydroxide (400mg, 6mmol). **85F** was obtained as a colorless oil (490mg, 81%).

85G



[0227] **85G** was prepared using the method described in **84E** substituting **84D** with **85F** (490mg, 1.2mmol) and Boc-2-Aminoisobutyric acid (490mg, 2.4mmol). **85G** was obtained as a colorless oil (540mg, 91%).

85H



[0228] **85G** was subjected to chiral separation using chiral prep HPLC (Chiralpak AD 5cmX50cm 2μm) & 20% IPA/hex-

ane as elutant) to give 265mg of **85H** (rt=6.54min)) & 265mg of **85I** (rt=12.85min).

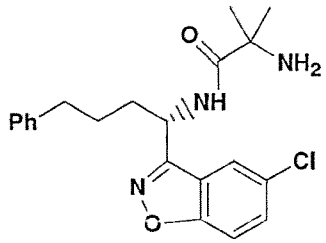
EXAMPLE 85

[0229] **85I** (265mg, 0.55mmol) was treated with 3ml of 20%TFA/CH2Cl2 according to the method for **Example 84** to give the title compound as a white solid (245mg) with 99% purity. MS (M+H) 387, HPLC retention time 3.34min.

EXAMPLE 86

2-Amino-N-[1-(5-chloro-benzo[d]isoxazol-3-yl)-4-phenyl-butyl]-2-methyl-propion amide

[0230]

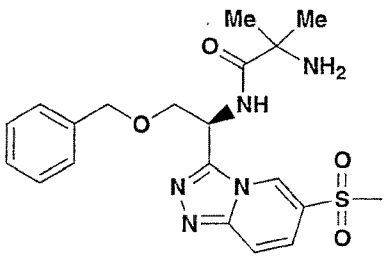


[0231] **86H** (10mg, 0.02mmol)) was treated with 20%TFA/CH2Cl2 (0.7ml) according to the method for **Example 84** to give the title compound as a white solid (7.4mg) with 97%purity. MS (M+H) 386, HPLC retention time 3.37min.

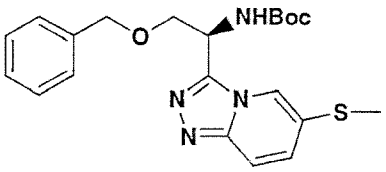
EXAMPLE 87

2-Amino-N-[1-(6-methanesulfonyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)-3-phenylpropyl]-2-methyl-propionamide

[0232]

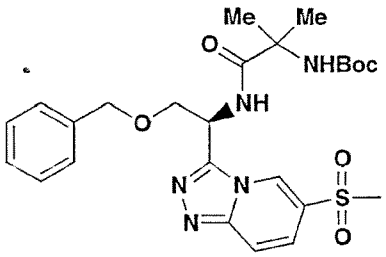


87A



[0233] To **1C** (200mg, 0.447mmol) in THF (3ml) was added isopropyl magnesium chloride (1.34ml, 2.68mmol, 2M solution) at r.t. After 1h of stirring, dimethyldisulphide (94.2mg) was added and stirred overnight. Diluted with water and extracted with CH_2Cl_2, dried and concentrated. Purification by flash chromatography on silica gel (1:1 EtOAc/hexane as elutant) gave a white solid **87A**.

87B



[0234] To **87A** (15mg, 0.03mmol) in CH_2Cl_2 (1ml) was added m-chloro perbenzoic acid (21mg, 0.07) and stirred for 2 h. The mixture was concentrated and redissolved in CH_2Cl_2 washed with 1N NaOH, brine, dried and concentrated. The residue in MeOH (1ml) was treated with 4NHCl (1ml) for 3h at r.t. and then concentrated. The residue was taken in 1.5ml CH_2Cl_2 & Boc-2-Aminoisobutyric acid (390mg, 1.9mmol), 1-HOAT (10mg, 0.07mmol), EDAC (14mg, 0.072mmol) and TEA (20µl, 0.144mmol) were added. The mixture was stirred at r.t. overnight, extracted with EtOAc washed with water, dried over Na_2SO_4, filtered & concentrated to give **87B**

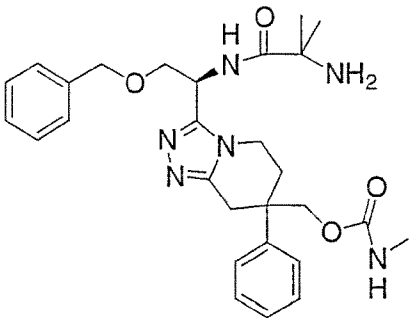
EXAMPLE 87

[0235] A solution of **87B** in MeOH (1ml) was treated with 4N HCl (1ml) and stirred for 1h and then concentrated. The residue was purified by preparative HPLC to give the title compound as a white solid (15mg). MS (M+H) 432, HPLC retention time 2.4min.

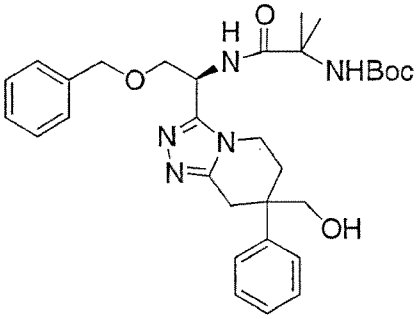
EXAMPLE 88

Methyl-carbamic acid 3-[1-(2-amino-2-methyl-propionylamino)-2-benzyloxy-ethyl]-7-phenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridin-7-ylmethyl ester

[0236]



88A



[0237] To a solution of **79E** (350mg, 0.6mmol) in CH_2Cl_2 (6ml) was added lithium borohydride (1.2ml, 2.4mmol, 2M

solution) at 0°C. The mixture was warmed to r.t. and stirred overnight.The reaction was quenched with pH 3 buffer, stirred for 30min and extracted with CH_2Cl_2, washed with brine, dried, filtered and concentrated to give crude product **88A** (336mg, <99%)

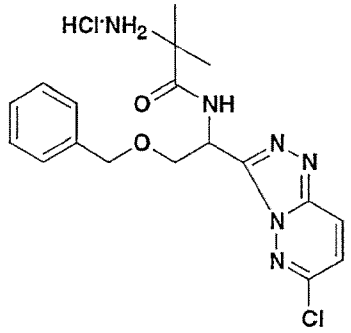
EXAMPLE 88

[0238] To a solution of **88A** in CH_2Cl_2 (3 ml) at 0°C was added TEA (127µl, 0.91mmol) and methylisocyanate (35mg, 0.61mmol). The mixture was warmed to r.t. and stirred overnight. The residue in CH_2Cl_2 (3ml) was treated with HCl (1.5 ml 4 M HCl in dioxane) and stirred at r.t. until all the starting materials was consumed. Purification and separation by Preparative HPLC gave the two diastereomers as Example **88a** MS (M+H) 521, HPLC retention time 2.55min and **Example 88b** MS (M+H) 521, HPLC retention time 2.92min.

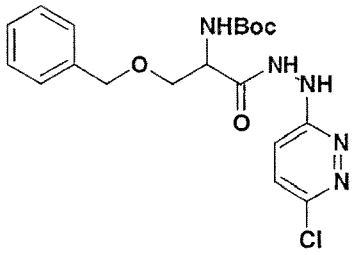
EXAMPLE 89

2-Amino-N-[2-benzyloxy-1-(6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)-ethyl]-2-methyl-propionamide

[0239]

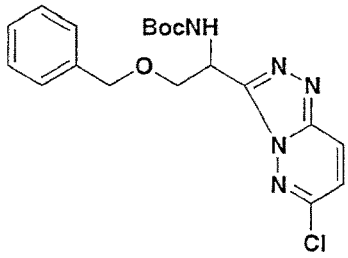


89A



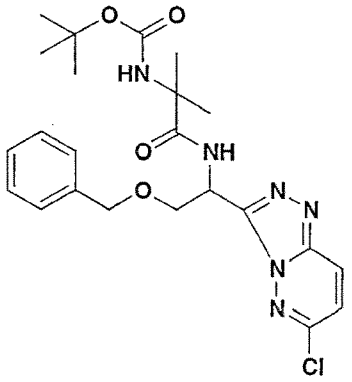
[0240] To a slurry of 3-Benzyloxy-2-butoxycarbonylamino-propionic acid (740 mg, 2.5 mmol) in CH_2Cl_2 (10 mL) was added EDAC (475 mg, 2.5 mmol) at r.t. After stirring for 1 h (6-chloropyridazin-3-yl)hydrazine (362 mg, 2.5 mmol) was added. After 2 h, the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc, dried, filtered and concentrated. Purification by flash chromatography on silica gel (1:2 EtOAc/hexane as elutant) gave **89A** (730mg, 69%) as a yellow foam.

89B



[0241] To a solution of **89A** (210 mg, 0.5 mmol) in acetonitrile (5 mL) at 0°C was added 1,2-dibromo-1,1,2,2-tetrachloroethane (179 mg, 0.55 mmol) followed by triethylamine (0.31 mL, 2.2 mmol) and triphenylphosphine (289 mg, 1.1 mmol). After stirring for 1h, the mixture was warmed to r.t. and stirred for 2 h. The solution was concentrated and the residue was redissolved in EtOAc, washed with 1:1 brine/10% citric acid, brine, dried, filtered and concentrated. Purification by preparative HPLC gave **89B** as an off-white solid (125 mg, 62%).

89C



[0242] To MeOH (3.5ml) at 0°C was added acetyl chloride (0.8 mL) over 3 min. After stirring the solution for 1 h, the solution was added to **89B** (125 mg, 0.31 mmol) in CH_2Cl_2 (0.3ml) at r.t. The mixture was stirred at r.t. for 2 h and then concentrated twice from CH_2Cl_2, The residue was redissolved in CH_2Cl_2 (1 mL) and added to a slurry of Boc-2-aminoisobutyric acid (94.4 mg, 0.46 mmol), HOAT (63.6 mg, 0.46 mmol) and N-methyl morpholine (0.051 ml, 0.5 mmol) in CH_2Cl_2 (2ml). The solution was stirred for 15 h, diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, dried, filtered and concentrated. Purification by flash chromatography on silica gel (1:99 MeOH/EtOAc as elutant) gave **89C** as a colorless foam (69mg, 46%).

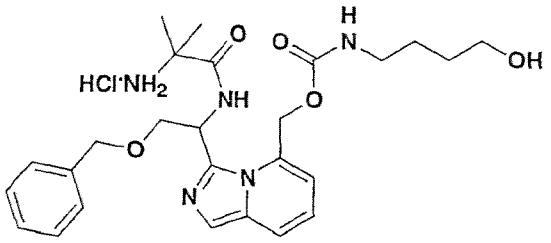
Example 89

[0243] To MeOH (3.5 mL) at 0°C was added acetyl chloride (0.8 mL) over 3 min. After stirring the solution for 1 h, the solution was added to **89C** (69 mg, 0.14 mmol) in CH_2Cl_2 (0.3ml) at r.t. The mixture was stirred at r.t. for 2 h and then concentrated. The residue was dissolved in water, filtered through a 0.45 μ nylon filter and lyophilized to give the title compound as a white amorphous solid. MS (M+H) 389, HPLC retention time 2.92 min.

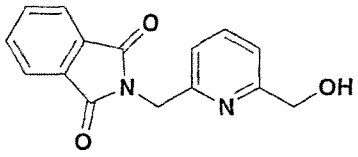
EXAMPLE 90

(4-Hydroxy-butyl)-carbamic acid 3-[1-(2-amino-2-methyl-propionylamino)-2-benzyloxy-ethyl]-imidazo[1,5-a]pyridin-5-ylmethyl ester

[0244]

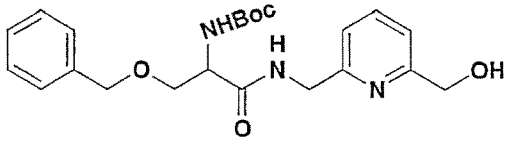


90A



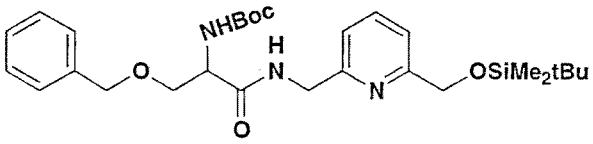
[0245] To a stirred solution of potassium phthalimide (1.04 g, 5.15 mmol) at RT under argon in DMF (40 mL) was added a DMF solution (10 mL) of (6-bromomethylpyridin-2-yl)-methanol(1.03 g, 5.11 mmol) over 5 min. The slurry was warmed at 40°C and stirred overnight. The DMF was then distilled off at 40-55°C (1 Torr). The powdery residue was stirred rapidly in CH_2Cl_2 for 20 min and filtered through Celite. The residue was redissolved in CH_2Cl_2, washed with water, dried and concentrated to give **90A** as an off-white solid (1.16g, 85%)

90B



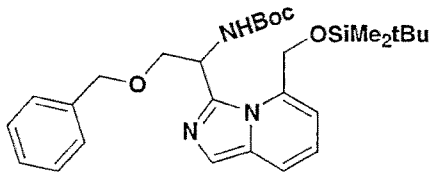
[0246] To a stirred solution of **90A** (1.2 g, 4.32 mmol) in EtOH (60ml) was added hydrazine (0.41 mL, 13.1 mmol) and the reaction mixture was refluxed for 14 h under argon. The solution was cooled, filtered through Celite and the filtrate concentrated. The residue was redissolved in MeOH, cooled, filtered and concentrated to give (6-aminomethyl-pyridin-2-yl)-methanol. To a stirred solution of Boc-(O-benzyl)serine (1.3 g, 4.32 mmol) and N-methyl morpholine (0.484 mL, 4.4 mmol) in THF (10 mL) at -12°C. was added isobutylchloroformate (0.56 mL, 4.35 mmol). After 30 min stirring, a slurry of (6-aminomethylpyridin-2-yl)-methanol in THF was added over 1 min. The solution was stirred at r.t. for 1 h. The reaction was diluted with EtOAc, washed with saturated aqueous sodium bicarbonate solution, dried and concentrated to give **90B** as a yellow oil (1.9 g). The material was used without purification in the following reaction.

90C



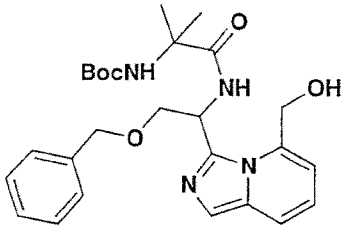
[0247] To a solution of **90B** (1.9 g, 4.3 mmol) in DMF (10ml) was added imidazole (410 mg, 6.02 mmol) and t-butyldimethyl-silylchloride (750 mg, 4.98 mmol). The solution was stirred for 20 h. The reaction was quenched with water, extracted with EtOAc, dried, filtered and concentrated. Purification by flash chromatography on silica gel (19:81 EtOAc/CH_2Cl_2 as elutant) gave **90C** (1.4g, 53%)as a colorless oil.

90D



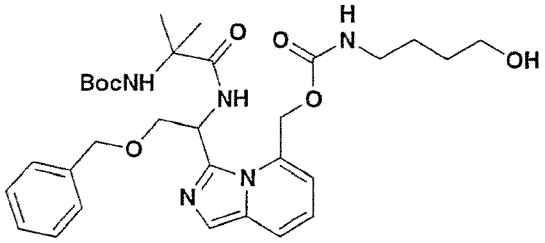
[0248] To a stirred slurry of 90C (1.4 g, 2.6 mmol) and 1,2-dibromo-1,1,2,2-tetrachloroethane (1.9 g, 5.8 mmol) in acetonitrile (15 mL) at 0°C was added triphenylphosphine (1.5 g, 5.8 mmol) and TEA (1.60 mL, 11.6 mmol). After 30 min, the resulting yellow slurry was stirred at r.t. for 16 h. A red solution had formed. This was concentrated, partitioned between water and EtOAc, dried, filtered and concentrated. Purification by flash chromatography on silica gel (3:17 EtOAc/CH_2Cl_2 as elutant) gave **90D** as a tan oil (625 mg, 46%).

90E



[0249] To MeOH (8 mL) at 0°C was added acetyl chloride (2.0 mL) over 3 min. After stirring the solution for 1 h, it was added to **90D** (620 mg, 1.2 mmol) at 0°C. The solution was stirred for 2h and concentrated. The residue was dissolved in CH_2Cl_2(5 mL) and added to a stirred slurry of Boc-2-aminoisobutyric acid (370 mg, 1.82 mmol), HOAt (249 mg, 1.82 mmol) and EDAC (346 mg, 1.82 mmol) followed by addition of N-methylmorpholine (0.3 mL, 2.7 mmol). The mixture was stirred for 15 h, diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, dried and concentrated. Purification by flash chromatography on silica gel (3:17 EtOAc/ CH_2Cl_2 as elutant) gave **90E** as a colorless foam (450mg, 77%).

90F

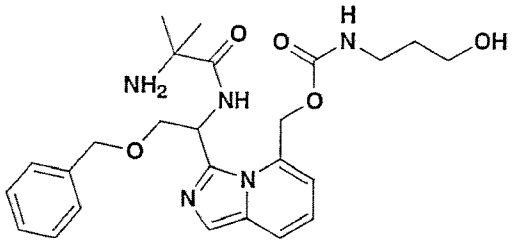


[0250] To a solution of **90E** (279 mg, 0.58 mmol) and pyridine (0.12 mL, 1.4 mmol) in THF, (3 mL) 0°C was added 4-nitrophenyl chloroformate (256 mg, 1.3 mmol) in CH_2Cl_2 (3 mL). The solution was stirred for 1 h and concentrated. The residue was dissolved in THF (5 mL) and 4-aminobutanol (0.5 mL) was added. The solution was stirred for 30 min, diluted with EtOAc, washed with 1N NaOH, dried and concentrated. Purification by flash chromatography on silica gel (EtOAc as elutant) gave **90F** as a yellow oil (207mg, 60%).

EXAMPLE 90

[0251] To MeOH (8 mL) at 0°C was added acetyl chloride (2.0 mL) over 3 min. After stirring the solution for 1 h, it was added to **90F** (204 mg, 0.342 mmol) at 0 °C. The solution was stirred for 2 h and concentrated. The residue was lyophilized to give the title compound as a yellow solid. MS (M+H) 498, HPLC retention time 2.64 min.

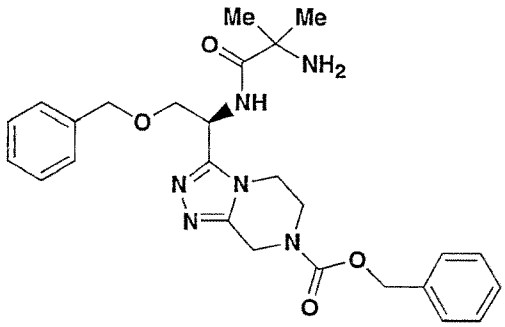
[0252] The following compound has been synthesized utilizing the procedures described in **Example 90,** utilizing the appropriate starting materials. **Example 263** was also prepared by this method.

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
91		584	98	2.6

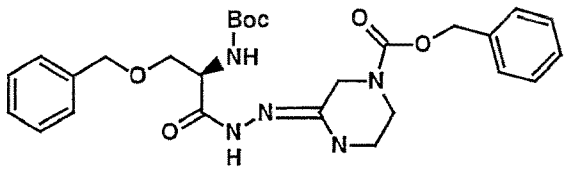
EXAMPLE 92

3-[1-(2-Amino-2-methyl-propionylamino)-2-benzyloxy-ethyl]-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazine-7-carboxylic acid benzyl ester

[0253]

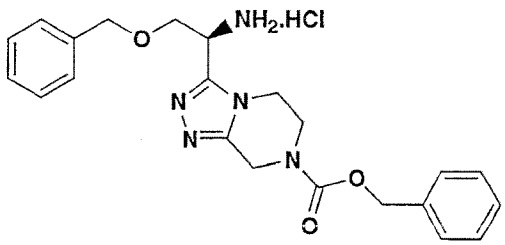


92A



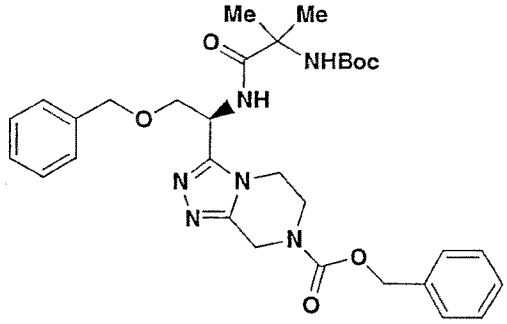
[0254] To a solution of 3-Oxo-piperazine-1-carboxylic acid benzyl ester (1.5g, 6.4mmol) in CH_2Cl_2(20ml) was added trimethyloxonium tetrafluroborate (0.99g, 6.72mmol). The solution was stirred for 60h. A solution of (2-Benzyloxy-1-hydrazinocarbonyl-ethyl)-carbamic acid tert-butyl ester (2.07g, 309.7mmol) in CH_2Cl_2(20ml) was added to give a clear solution. After 2h of stirring the solution was diluted with CH_2Cl_2, washed with water, dried and concentrated to give **92A** as a white foam (3.2g, 95%).

92B



[0255] A solution of **92A** (2.6g, 4.9mmol) in EtOH (26ml) was treated by microwave at 120°C, 60W for 10min. The mixture was treated with 4NHCl in dioxane (30ml) for 30min. The solution was concentrated and coevaporated with ethanol to **92B** (2.8g).

92C



[0256] To a CH_2Cl_2 (100 ml) solution of 2-tert-butoxycarbonylamino-2-methyl-propionic acid (1.34g, 66.1mmol) was added EDAC (1.8g, 9.45mmol) and HOBT (1.27g, 9.45mmol), DMAP (0.77g, 6.3mmol), and TEA (2.63ml, 18.9mmol). This solution was stirred at r.t. for 10 min before the addition of **92B** (2.8g, 6.3mmol). The reaction was completed in 2h. The solution was diluted with CH_2Cl_2, washed with water, 1NHCl, 1N NaOH, dried and concentrated. Purification by flash chromatography on silica gel (5:95 MeOH/ CH_2Cl_2 as elutant) gave **92C** as a foam(3g).

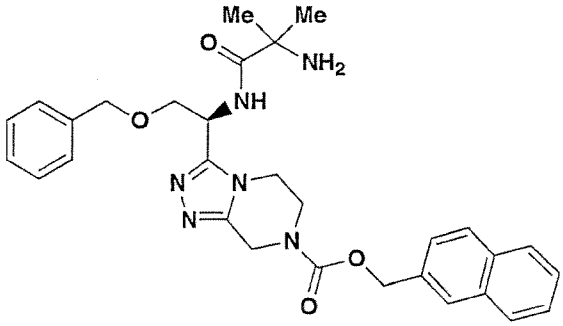
EXAMPLE 92

[0257] To a solution of **92C** (250mg) in CH_2Cl_2 was treated with HCl (30ml 4 M HCl in dioxane) and stirred at r.t for 1h. The solution was concentrated and the residue crystallized using MeOH/ EtOAc to give the title compound as a solid (130mg). MS (M+H) 493, HPLC retention time 2.33min.

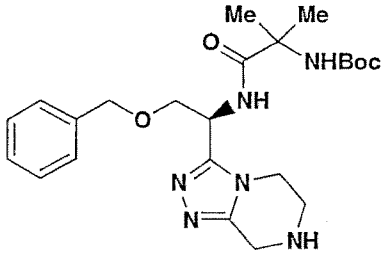
EXAMPLE 93

3-[1-(2-Amino-2-methyl-propionylamino)-2-benzyloxy-ethyl]-5,6-dihydro-8H-f1.2,41triazolof4,3-alpyrazine-7-carboxylic acid naphthalen-2-ylmethyl ester

[0258]

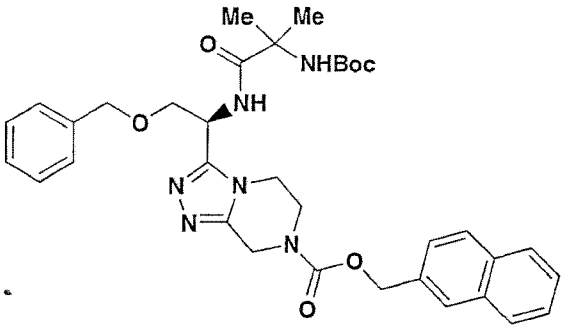


93A



[0259] To a solution of **92C** (2.6g, 4.4mmol) and catalyst palladium on carbon (30mg) in MeOH (70ml) under nitrogen was added ammonium formate (1.3g, 20.9mmol). The solution was stirred for 3h and filtered through celite and concentrated to give **93A**(2.45g)

93B

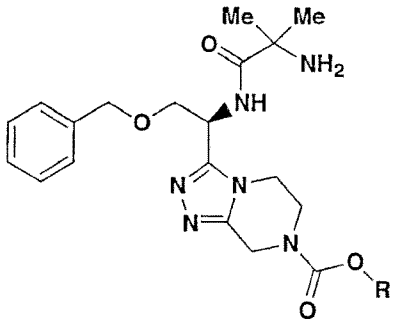


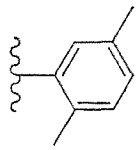
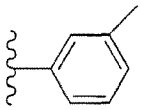
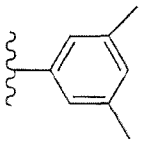
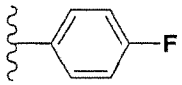
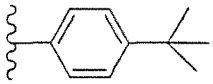
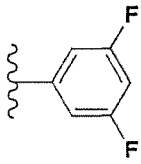
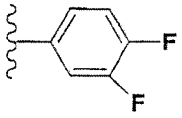
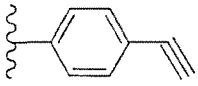
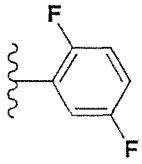
[0260] To a solution of 2-naphthalenmethanol (11mg, 0.07mmol) in CH_2Cl_2 (0.25 ml) was added n-methylmorpholine (12μl, 0.1mmol) and 4-nitrophenyl chloroformate (15mg, 0.0735mmol) in CH_2Cl_2 (0.25 ml). The solution was stirred overnight followed by addition of **93A** (32mg, 0.07mmol) in CH_2Cl_2(0.08 ml) and TEA (0.1ml, 0.7mmol). The solution was stirred overnight and diluted with CH_2Cl_2, washed with 1NHCl, 1NaOH, water, dried and concentrated to give **93B.**

EXAMPLE 93

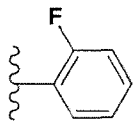
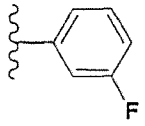
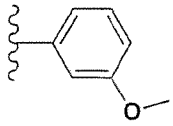
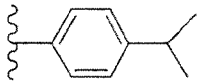
[0261] To a solution of **93B** in CH_2Cl_2 was treated with TFA in CH_2Cl_2 and stirred at r.t for 1h. The solution was concentrated. The residue was purified by preparative HPLC to give the title compound. MS (M+H) 543, HPLC retention time 2.82min.

[0262] The following compounds were synthesized utilizing the procedures as described in **Example 93,** utilizing the appropriate starting materials as know to those skilled in the art.

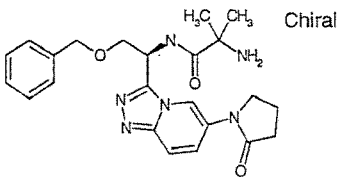
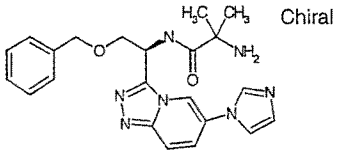
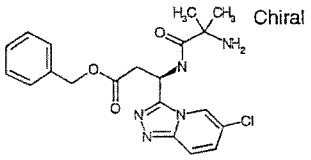
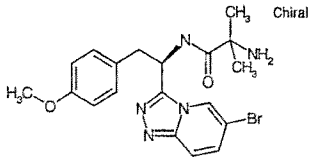
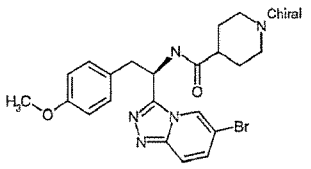


Compound number	R	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
94		523	80	2.77
95		507	90	2.57
96		521	90	2.8
97		511	85	2.4
98		549	81	3.04
99		529	85	2.5
100		529	90	2.48
101		518	97	2.08
102		529	80	2.42

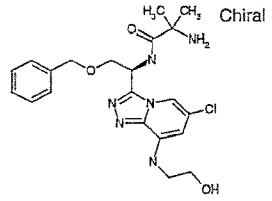
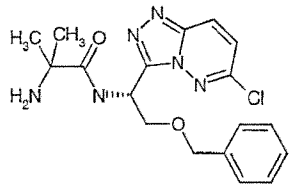
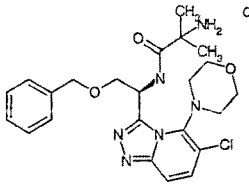
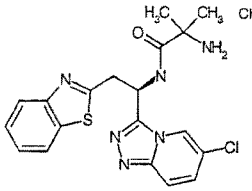
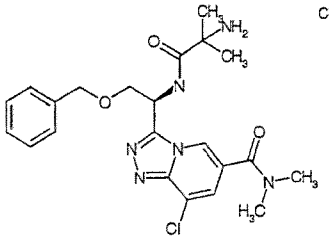
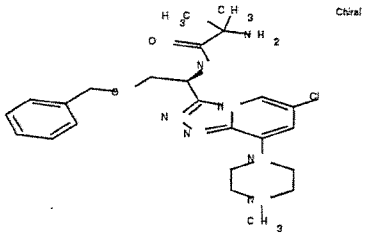
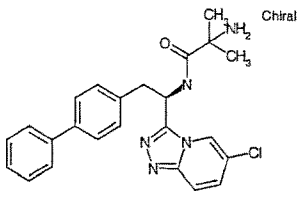
(continued)

Compound number	R	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
103		511	90	2.4
104		511	95	2.37
105		523	90	2.37
106		535	90	2.97

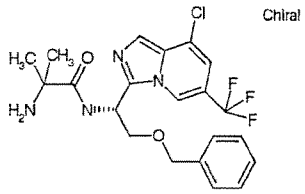
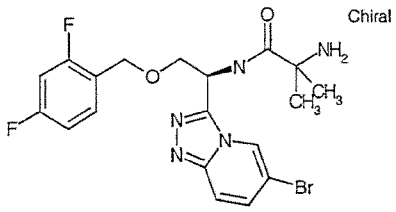
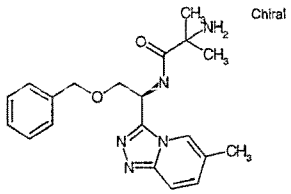
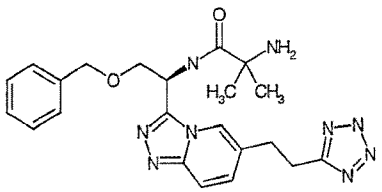
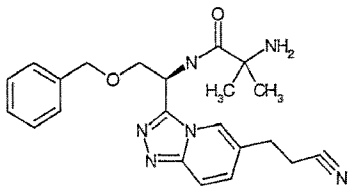
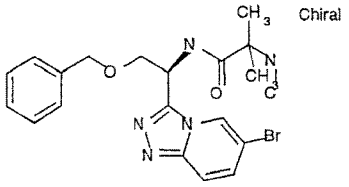
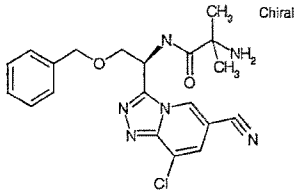
[0263] The following examples were prepared using procedures as described in the general synthetic schemes and working examples above, utilizing the appropriate starting materials as know to those skilled in the art.

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
107		437	92	2.5
108		420	90	1.71
109		416	98	1.9
110		433	96	1.8
111		459	90	1.9

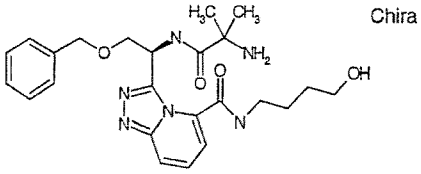
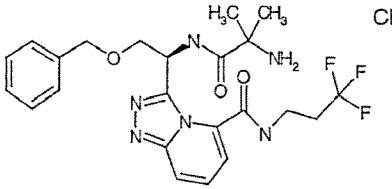
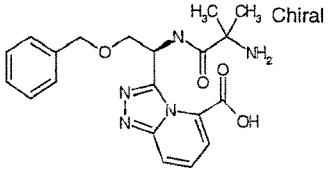
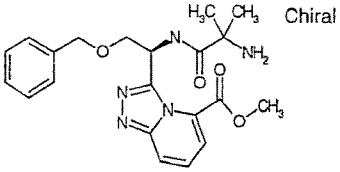
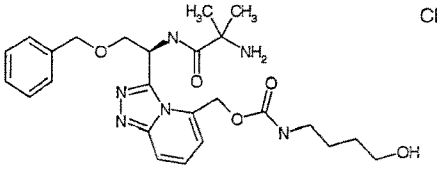
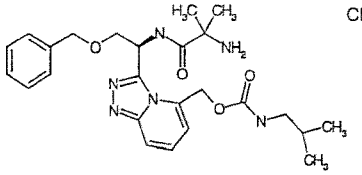
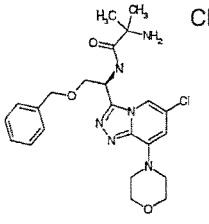
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
112		448	85	2.3
113		390	2.7	99
114		473	88	2.24
115		416	100	1.9
116		459	90	1.87
117		486	100	1.23
118		434	93	2.6

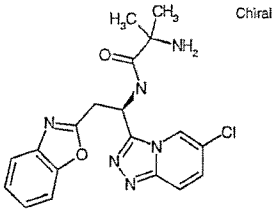
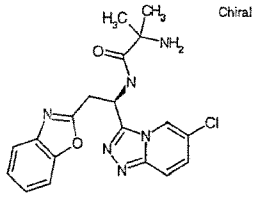
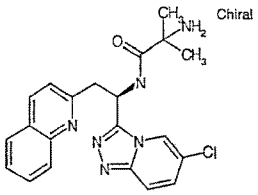
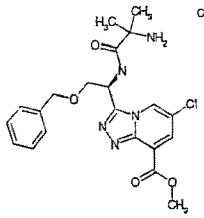
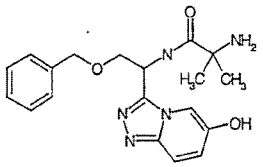
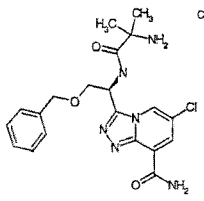
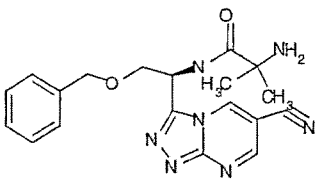
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
119		455	99	4.04
120		469	97	2.73
121		368	92	1.5
122		450	95	2.2
123		407	98	2.2
124		447	95	2.05
125		413	95	1.9

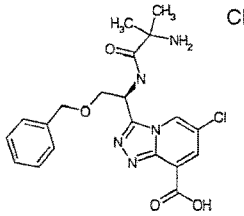
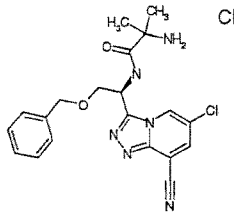
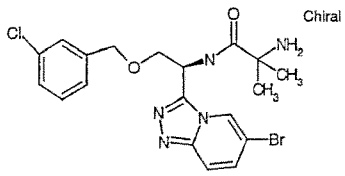
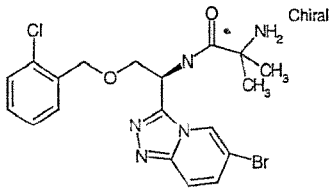
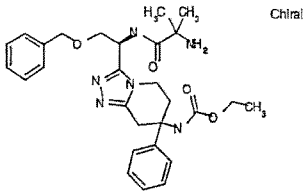
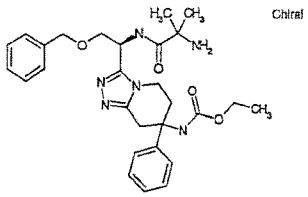
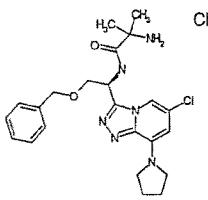
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
126	 Chira	469	90	2.52
127	 Chiral	493		2.98
128	 Chiral	398	90	2.26
129	 Chiral	412	98	2.71
130	 Chiral	499	97	2.6
131	 Chiral	483	85	3.1
132	 Chiral	473	95	2.4

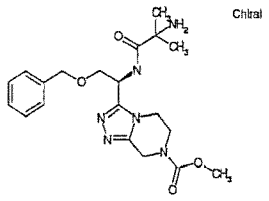
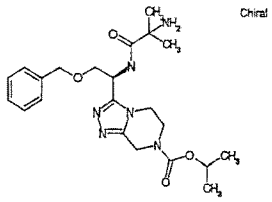
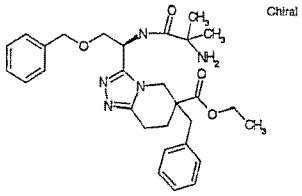
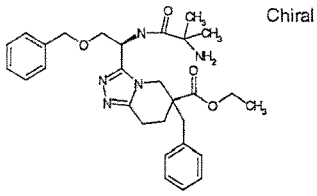
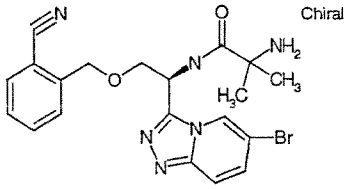
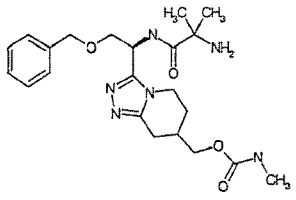
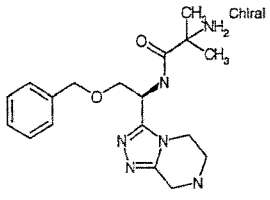
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
133	 Chiral	399	93	1.7
134	 Chiral	502	94	
135	 Chiral	409	86	1.14
136	 Chiral	446	99	2.3
137		370	95	2.07
138	 Chiral	431	99	2.3
139	 Chiral	380	90	

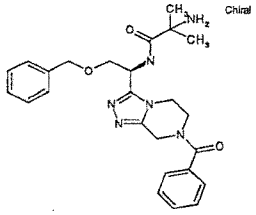
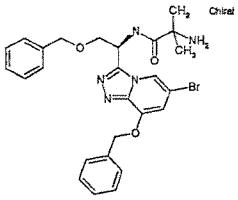
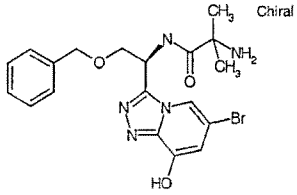
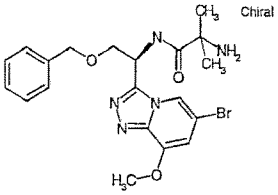
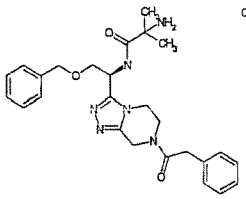
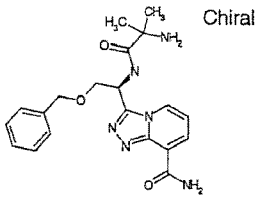
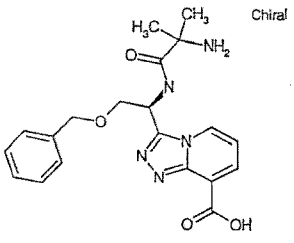
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
140	 Chiral	432	97	2.2
141	 Chiral	413	95	2.4
142	 Chiral	467	93	2.9
143	 Chiral	467	97	2.86
144	 Chiral	521	89	2.8
145	 Chiral	521	85	2.96
146	 Chiral	457	100	2.9

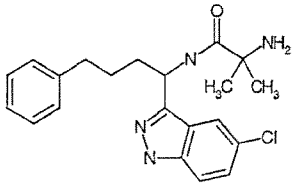
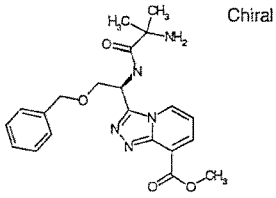
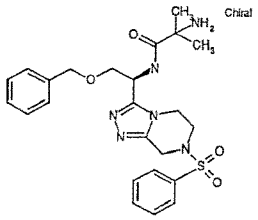
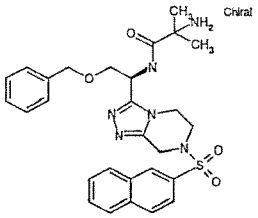
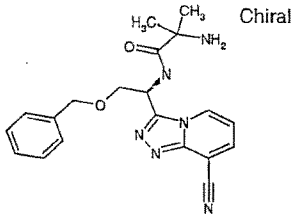
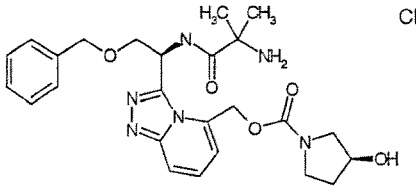
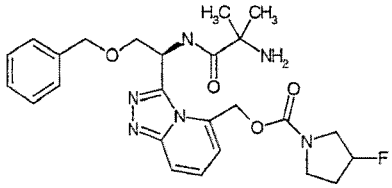
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
147		417	85	1.37
148		445	90	1.95
149		520	95	3.2
150		520	90	3.26
151		458	97	2.4
152		445	90	2.22
153		359	90	0.4

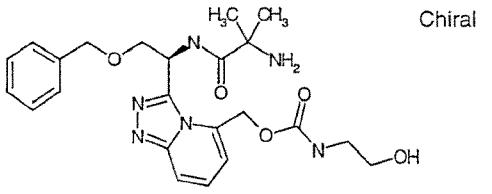
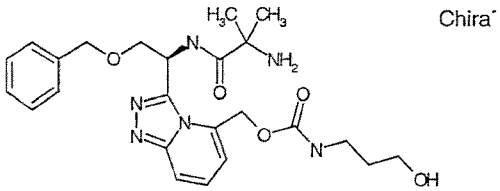
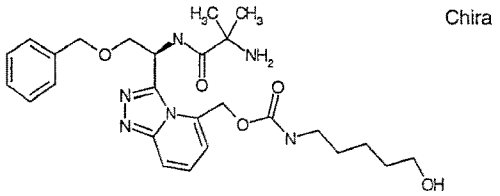
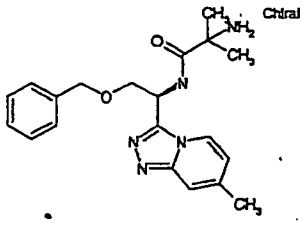
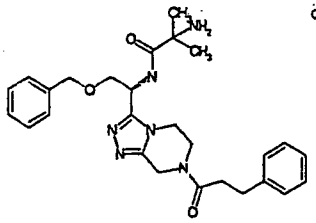
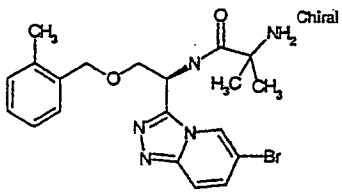
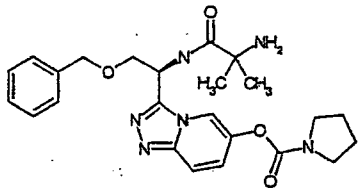
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
154		463	95	1.81
155		539	95	2.9
156		445	95	2.08
157		463	95	2.17
158		477	85	1.95
159		397	98	1.5
160		397	94	1.13

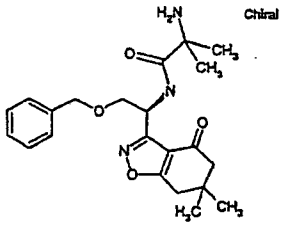
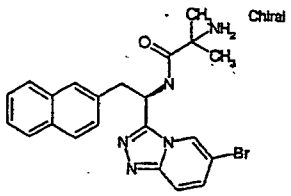
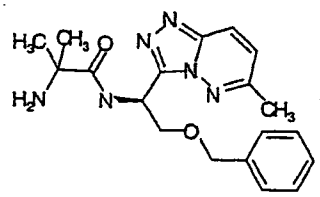
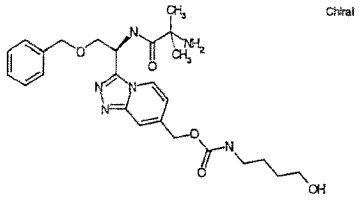
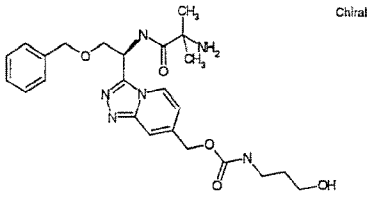
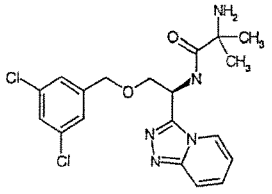
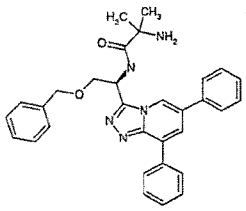
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
161		385	95	
162	 Chiral	412	100	1.6
163	 Chiral	499	95	2.03
164	 Chiral	549	94	2.56
165	 Chiral	379	98	1.5
166	 Chiral	497	96	2.58
167		499	96	2.85

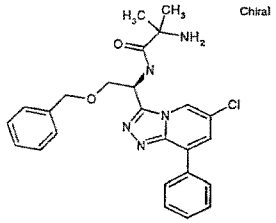
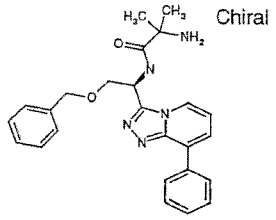
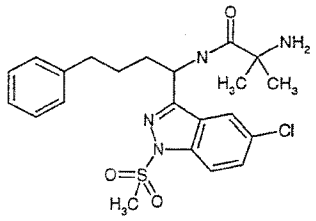
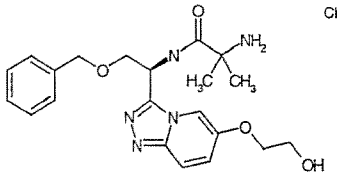
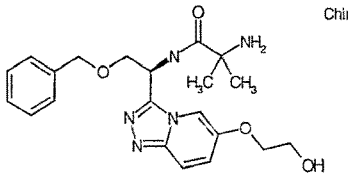
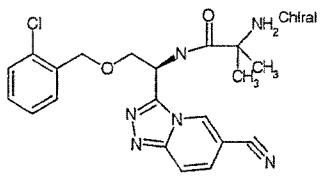
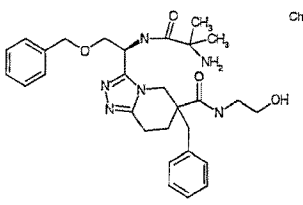
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
168	 Chiral	471	95	2.43
169	 Chiral	485	95	2.5
170	 Chiral	513	94	2.7
171	 Chiral	368	98	1.21
172	 Chiral	491	95	2.21
173	 Chiral	447	97	2.8
174	 Chiral	467	95	2.8

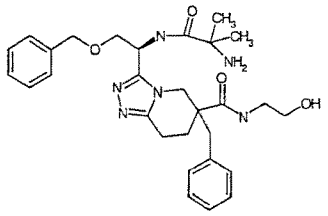
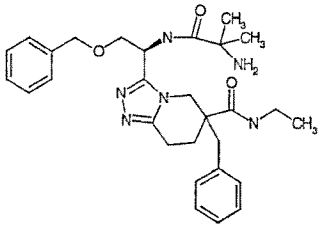
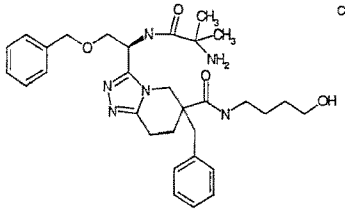
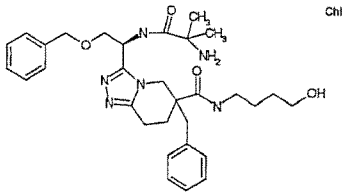
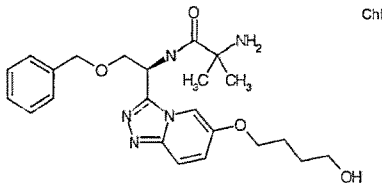
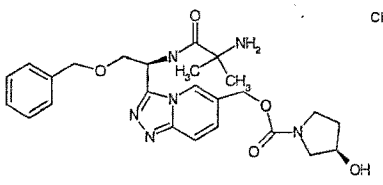
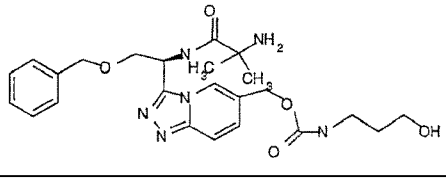
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
* 175		400	95	2.34
176		453	90	2.37
177		369	98	2.58
178		499	95	1.75
179		485	90	1.6
180		423	97	5.80
181		506	94	3.2

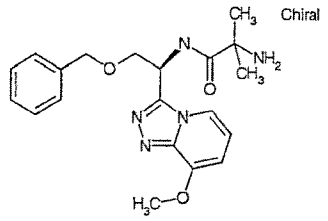
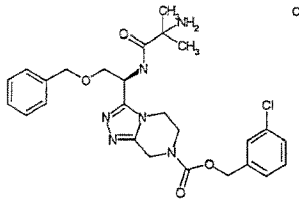
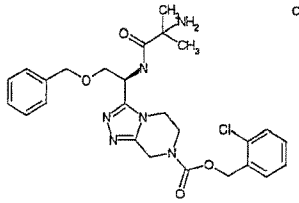
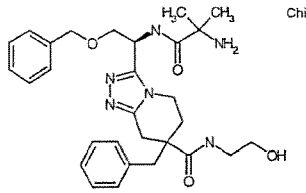
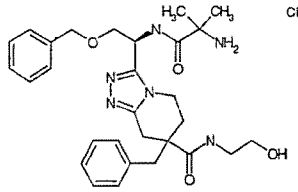
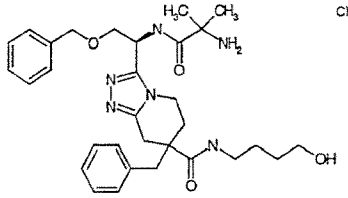
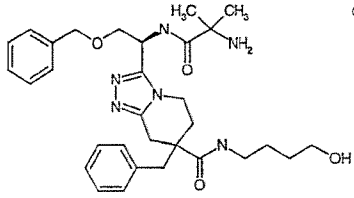
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
182		465	100	2.8
183		430	88	2.4
184		463	94	3.4
185		414	94	2.23
186		414	94	2.23
187		413	97	2.6
188		535	90	2.62

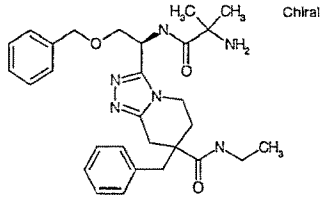
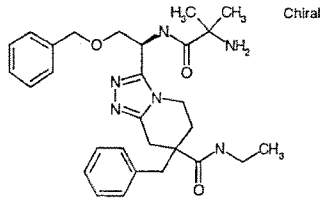
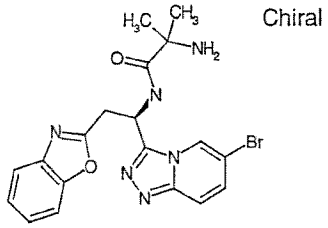
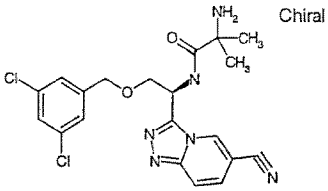
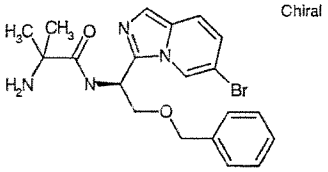
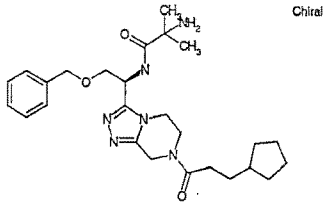
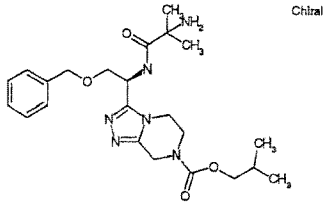
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
189		535	95	2.8
190		519	96	2.88 2.91
191	 Chiral	563	90	2.76
192	 Chiral	563	90	2.87
193	 Chiral	442	98	2.5
194	 Chiral	497	98	
195	 Chiral	485	98	

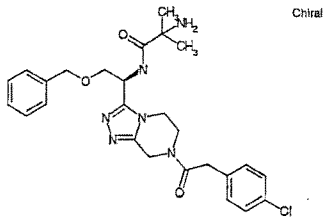
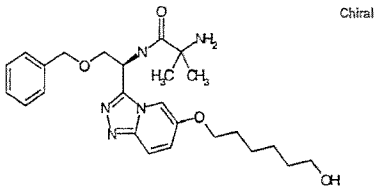
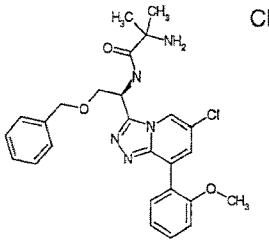
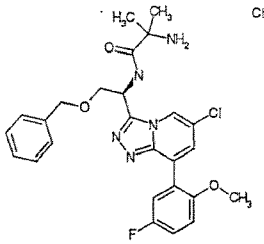
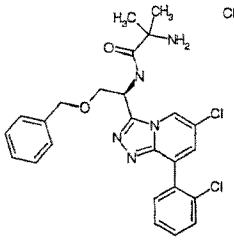
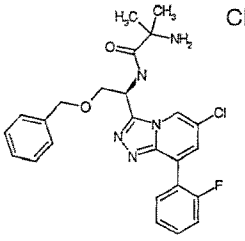
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
196		384	95	1.67
197		527	90	2.64
198		527	84	2.56
199		535	98	2.5
200		535	95	2.8
201		563	98	2.68
202		563	98	2.9

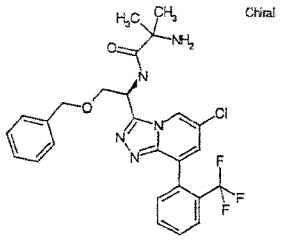
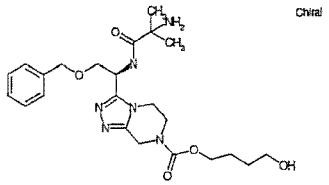
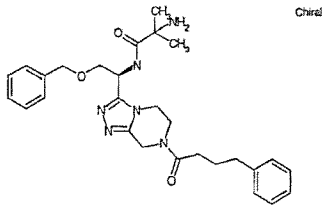
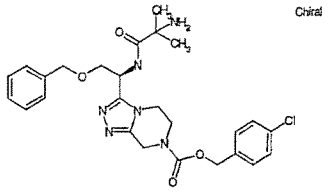
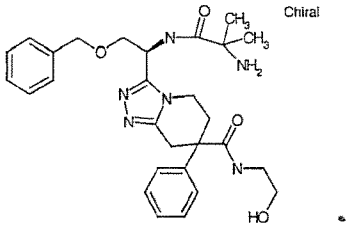
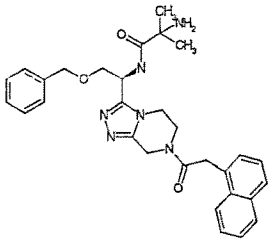
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
203	 Chiral	519	90	2.86
204	 Chiral	519	90	2.94
205	 Chiral	444	90	1.77
206	 Chiral	448	95	6.04
207	 Chiral	432	98	2.94
208	 Chiral	483	90	2.53
209	 Chiral	459	90	2.25

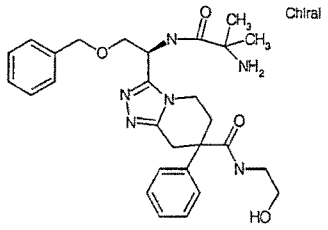
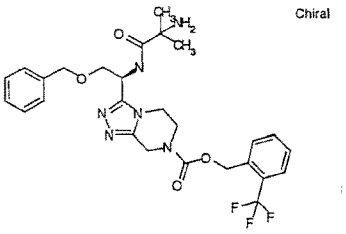
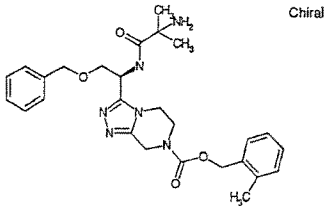
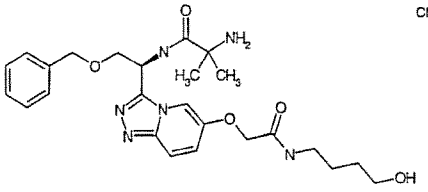
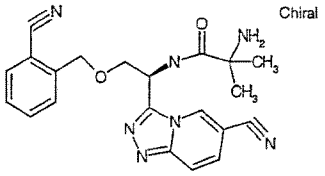
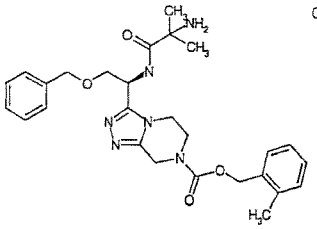
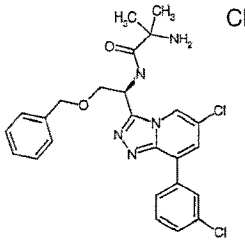
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
210	 Chiral	512	95	2.36
211	 Chiral	470	98	3.07
212	 Chiral	495	100	2.82
213	 Chiral	512	100	2.87
214	 Chiral	499	100	2.87
215	 Chiral	482	100	2.78

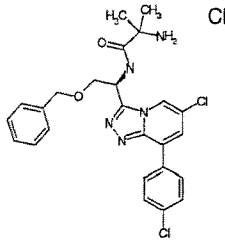
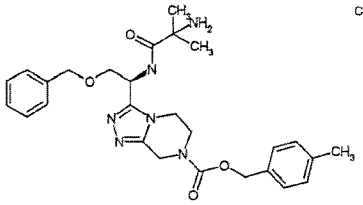
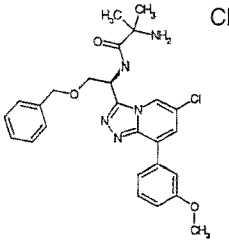
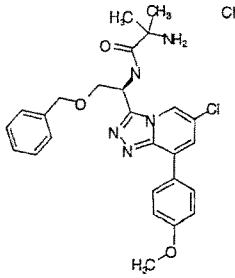
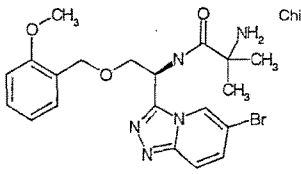
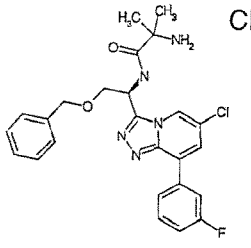
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
216		532	100	2.92
217		475	95	1.61
218		505	85	2.41
219		528	90	2.62
220		521	90	2.32
221		527	90	2.49

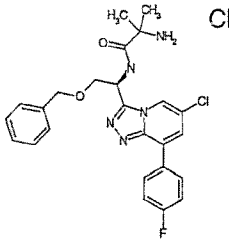
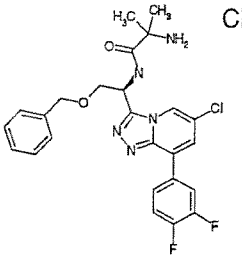
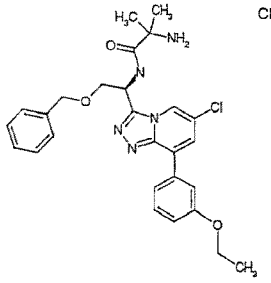
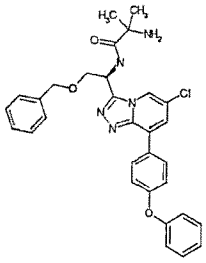
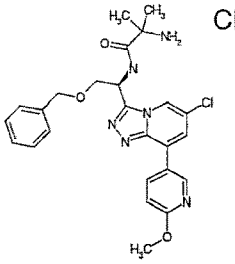
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
222	 Chiral	521	90	2.7
223	 Chiral	561	90	2.63
224	 Chiral	547	90	2.9
225	 Chiral	499	94	2.4
226	 Chiral	404	95	1.45
227	 Chiral	507	92	2.5
228	 Chiral	499	100	3.05

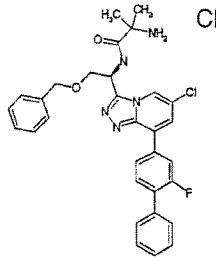
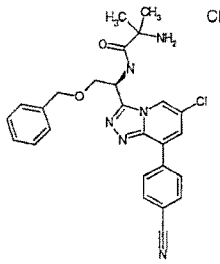
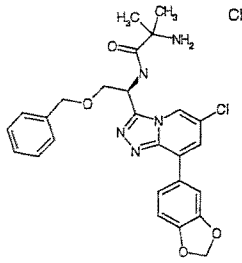
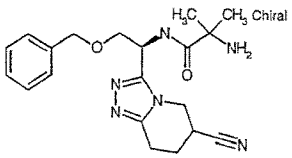
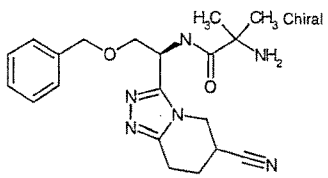
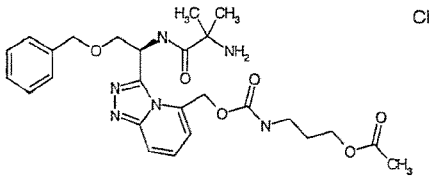
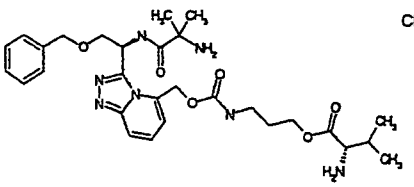
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
229	 Chiral	499	100	3.06
230	 Chiral	507	97	2.51
231	 Chiral	495	94	2.9
232	 Chiral	495	95	2.9
233	 Chiral	463	97	2.85
234	 Chiral	482	93	2.85

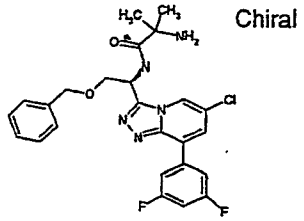
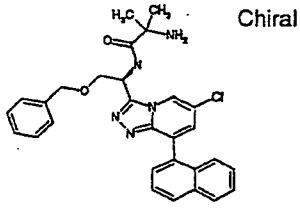
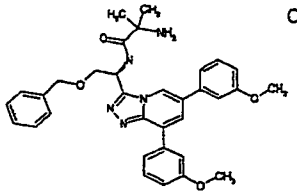
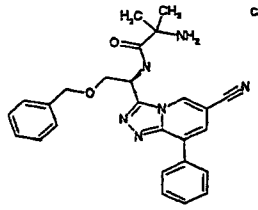
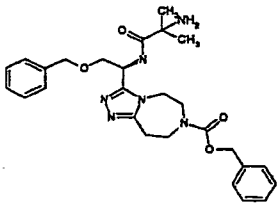
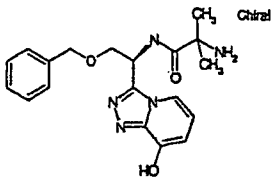
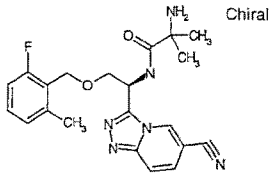
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
235	 Chiral	482	99	2.85
236	 Chiral	500	97	2.9
237	 Chiral	509	97	3.06
238	 Chiral	557	92	3.4
239	 Chiral	495	87	2.68

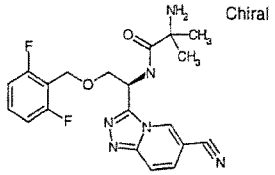
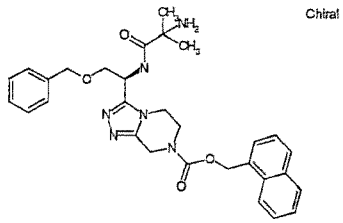
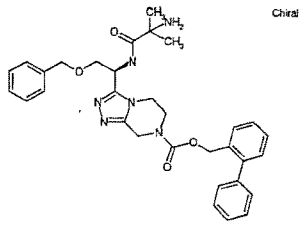
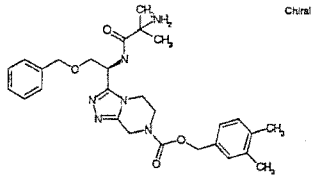
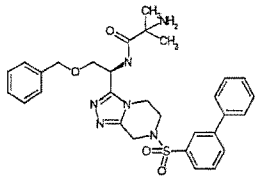
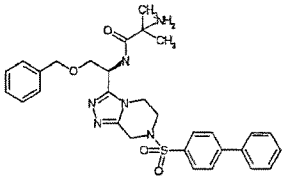
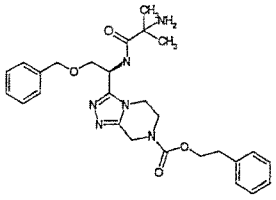
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
240	 Chiral	559	98	3.4
241	 Chiral	489	80	2.6
242	 Chiral	508	90	2.85
243	 Chiral	383	90	1.96
244	 Chiral	383	88	2.19
245	 Chiral	527	96	2.8
246	 Chiral	584	90	2.44

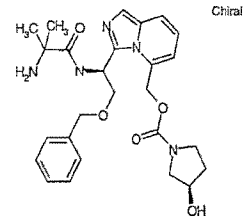
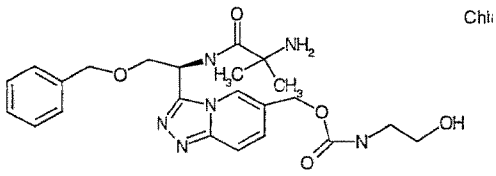
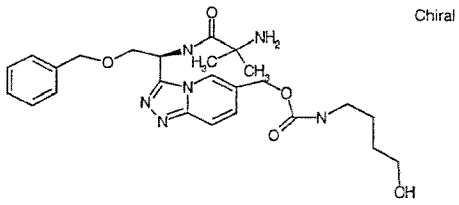
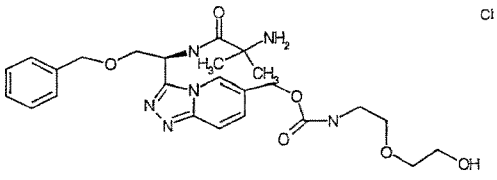
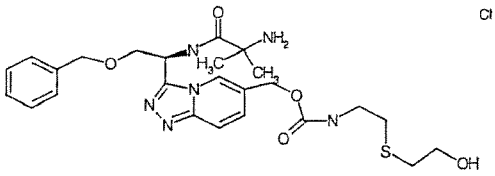
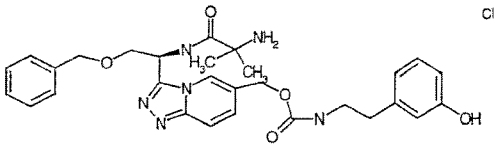
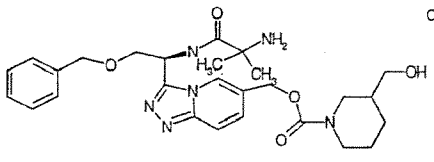
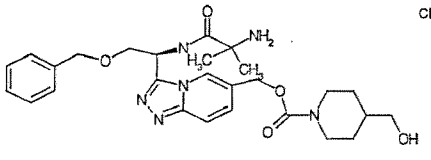
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
247		500	98	2.94
248		514	100	3.1
249		566	94	3.28
250		455	98	2.55
* 251		507	82	2.2
252		370	95	1.38
253		411	96	5.19

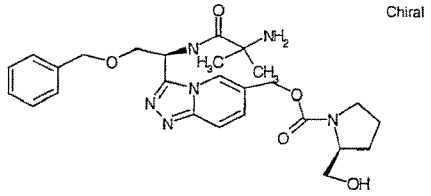
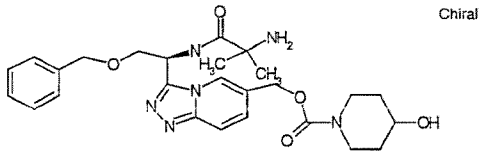
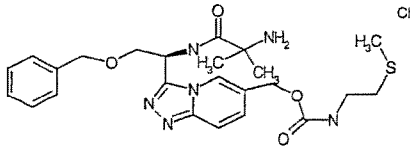
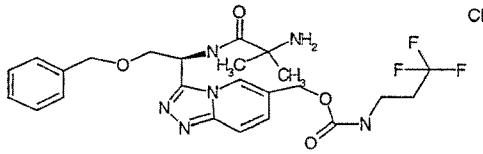
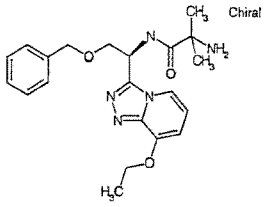
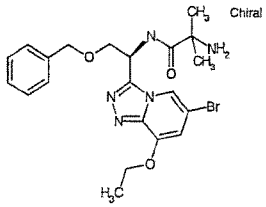
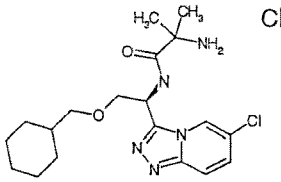
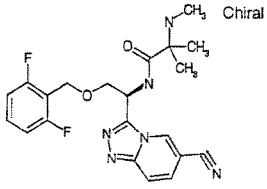
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
254	 Chiral	415	95	4.67
255	 Chiral	543	91	2.76
256	 Chiral	569	94	2.88
257	 Chiral	521	93	2.74
258		575	98	2.79
259		575	92	2.74
260		507	90	2.43

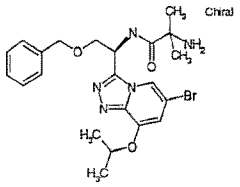
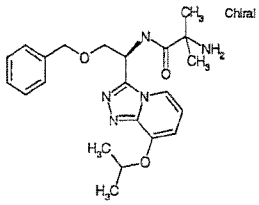
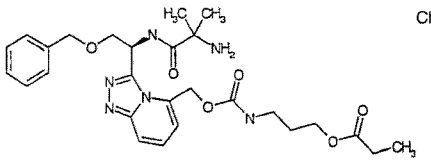
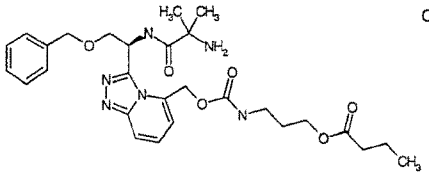
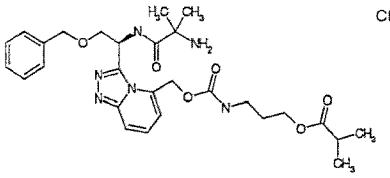
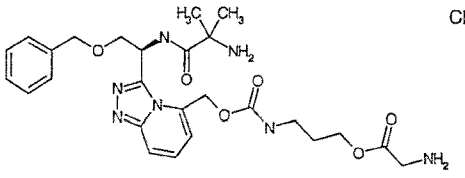
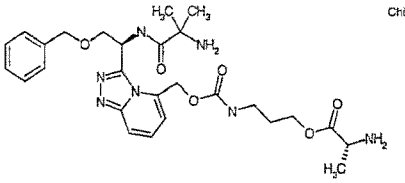
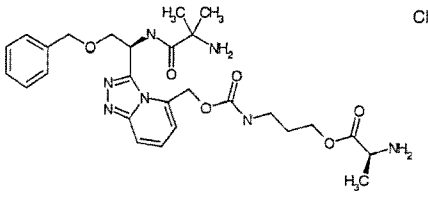
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
261	 Chiral	496	98	2.62
262	 Chi	471	98	2.38
263	 Chiral	499	95	2.58
264	 Cl	515	98	2.50
265	 Cl	531	92	2.62
266	 Cl	547	92	2.93
267	 Chiral	525	98	2.84
268	 Chiral	525	96	2.76

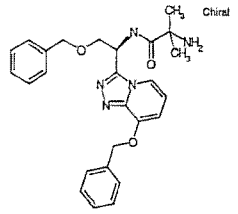
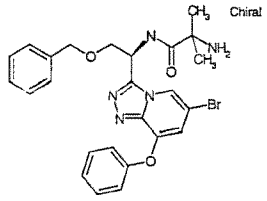
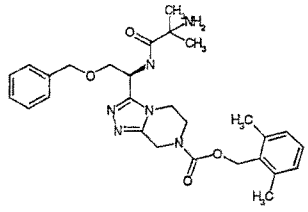
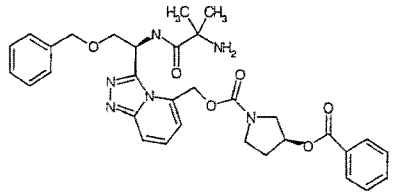
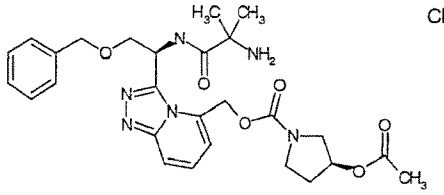
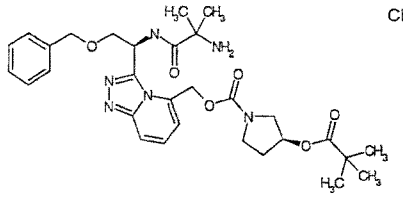
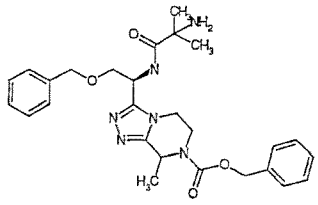
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
269	 Chiral	511	99	2.73
270	 Chiral	511	98	2.62
271	 Chiral	501	95	2.83
272	 Chi	523	96	2.93
273	 Chiral	398	93	1.90
274	 Chiral	477	95	2.41
275	 Chiral	394	95	2.57
276	 Chiral	429	94	4.73

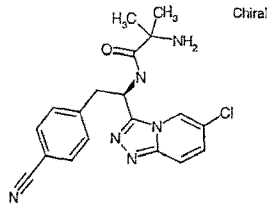
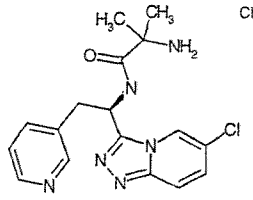
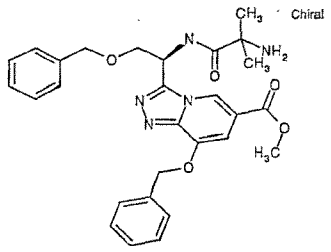
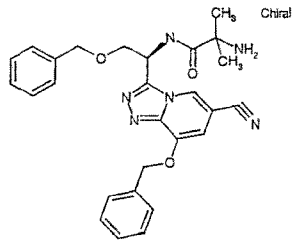
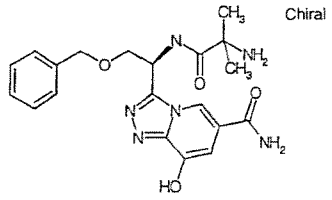
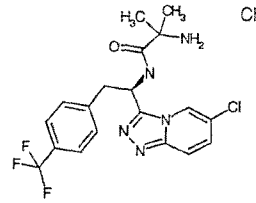
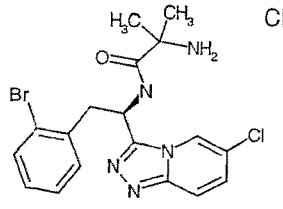
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
277		491	95	2.17
278		412	95	2.07
279		541	95	3.13
280		555	95	3.18
281		555	95	3.13
282		542	90	2.16
283		556	90	2.22
284		556	90	2.22

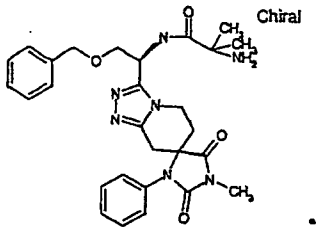
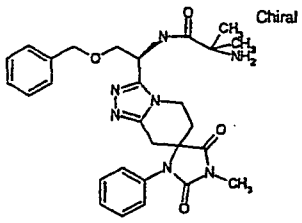
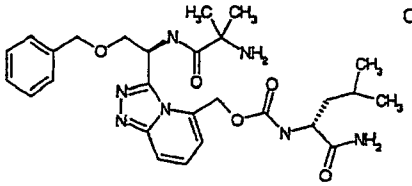
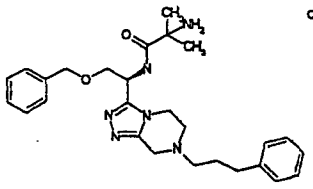
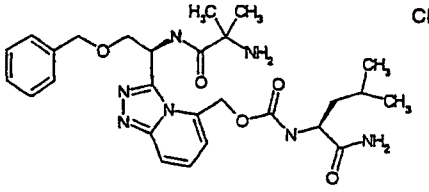
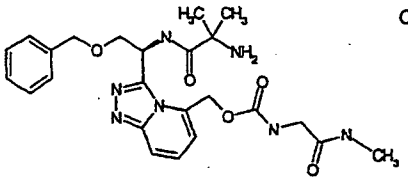
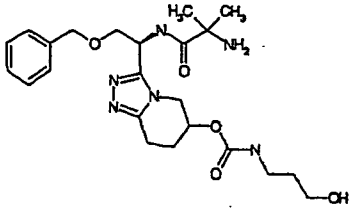
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
285		460	95	2.54
286		525	90	2.07
287		521	90	2.72
288		601	90	3.34
289		539	90	2.85
290		581	90	3.33
291		507	90	2.42

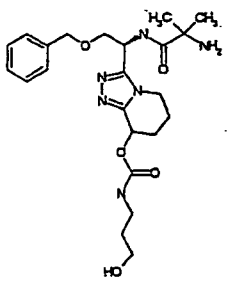
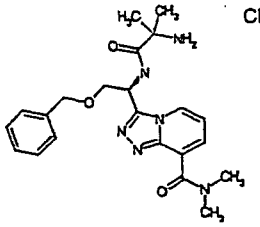
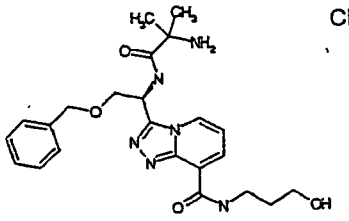
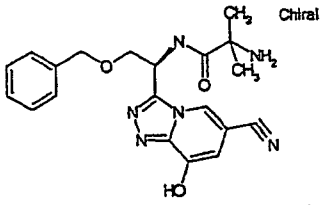
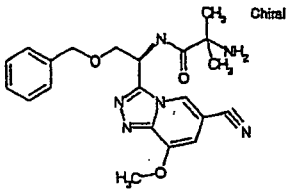
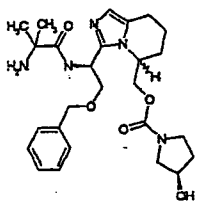
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
292		383	97	1.47
293		359	100	0.22
294		518	95	2.80
295		485	93	2.61
296		413	91	1.39
297		426	100	2.59
298		437	98	2.11

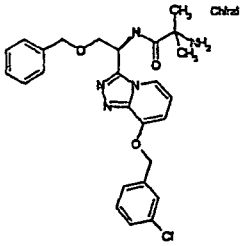
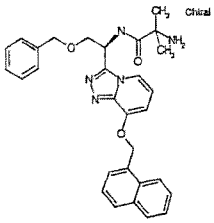
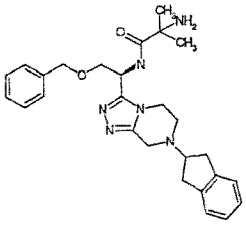
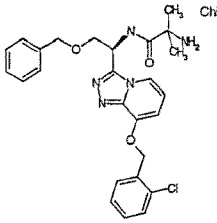
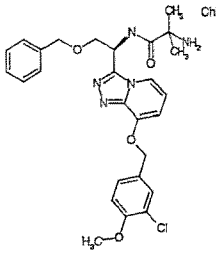
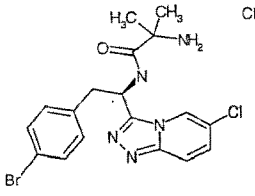
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
* 299		532	80	2.50
* 300		532	100	2.64
301		540	93	2.89
302		477	86	1.89
303		540	95	3.01
304		498	82	2.37
305		475	75	2.30

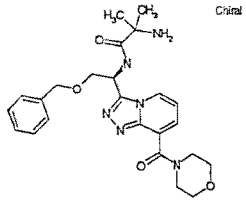
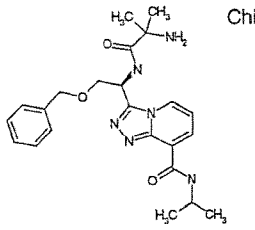
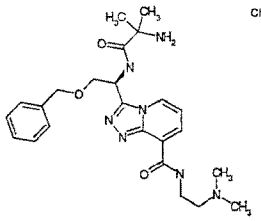
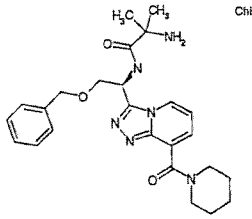
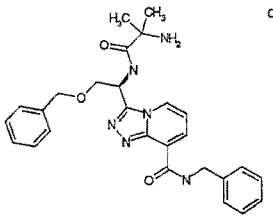
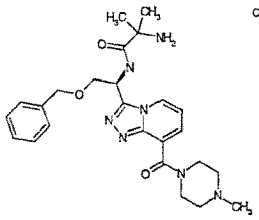
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
306		475	85	2.30
307	 Chiral	425	99	1.56
308	 Chiral	455	93	1.86
309	 Chiral	395	90	1.73
310	 Chiral	409	93	1.82
* 311		500	96	2.64

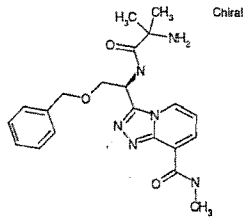
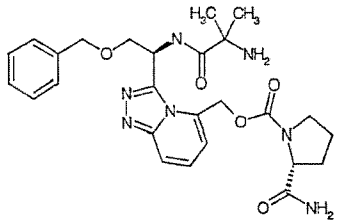
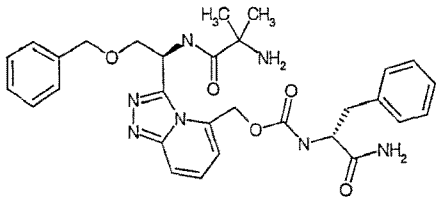
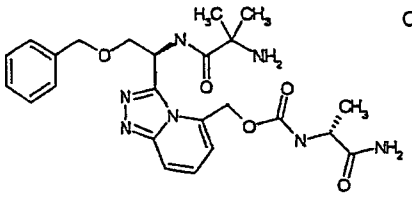
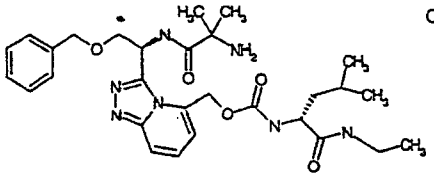
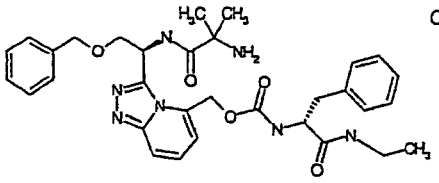
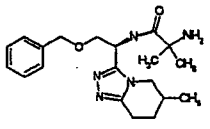
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
312		495	96	2.78
313		510	98	2.92
314		475	89	1.99
315		495	95	2.79
316		525	96	2.92
317		437	100	2.11

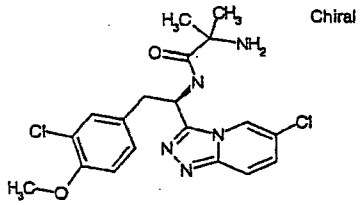
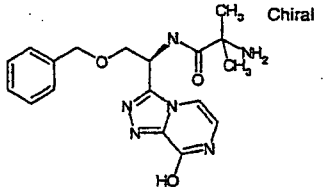
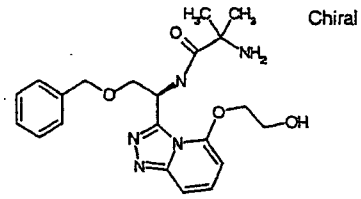
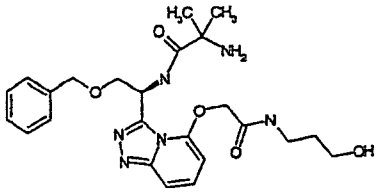
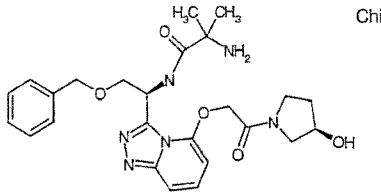
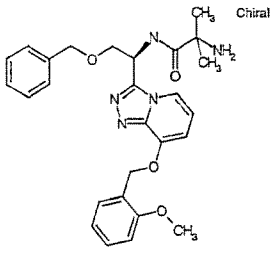
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
318	 Chiral	467	97	1.37
319	 Chiral	439	98	2.26
320	 Chiral	468	98	1.13
321	 Chiral	465	94	1.90
322	 Chiral	487	99	2.57
323	 Chiral	480	83	0.73

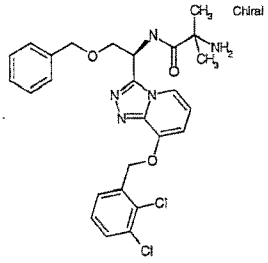
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
324		411	99	1.74
325		524	96	2.56
326		574	95	2.93
327		498	93	1.64
328		568	95	3.05
329		602	93	3.08
330		372	80	1.75

(continued)

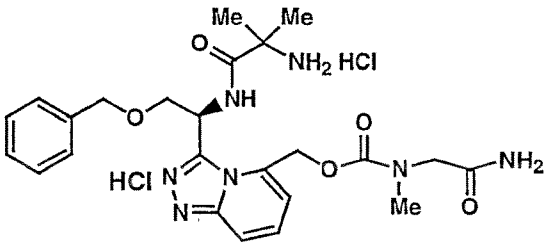
Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
331		423	98	1.14
* 332		371	90	2.14
333		414	83	2.29
334		485	93	2.25
335		497	98	2.63
336		490	98	3.01

(continued)

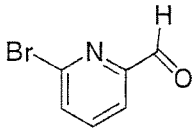
Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
337		529	98	3.01
* Compound not within the definition of the claims				

EXAMPLE 338

[0264]

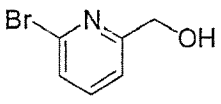


338A



[0265] To a solution n-BuLi (2.5 M in THF, 84 ml, 0.21 mol) in toluene (200 mL) at -10°C was added n-BuMgCl (2.0 M in THF, 52.5 ml, 0.105 mol) over 10 min. The mixture was stirred at -10°C for 30 min, then 2, 6-dibromopyridine (71.07g, 0.3 mol) in toluene (500 mL) was added via an additional funnel over 30 min. The resulting suspension was stirred at -10°C for 2.5 hours, then transferred via a canula to a cooled solution of DMF in toluene (200 mL). The solution was stirred at -10°C for 30 min, then 30% citric acid (300 mL) was added. After stirring for 30 min, the organic phase was washed with water (300 mL), brine (200 mL), and dried over sodium sulfate. After filtratoin the filtrate was concentrated to give **338A** as light yellow colored solid (54.2 g). HPLC(A) retention time 1.88 min.

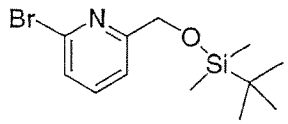
338B



[0266] To a stirred soln of **338A** (29.0 g, 0.151 mol) in methanol (600 mL) cooled to 12°C in a water bath is added sodium borohydride (5.89 g, 0.16 mol) in small batches over 20 min. The temperature is not allowed to rise above 23°C. The reaction mixture was stirred 1 h more and then cautiously quenched with ice cold 10% HCl to pH2 (total of 64 mL). The reaction mixture was concentrated *in vacuo,* generating considerable foaming. The residue was redissolved in methylene chloride (250 mL) and stirred with a 5% potassium carbonate solution (150 mL, at pH 8). The aqueos layer was extracted twice with methylene chloride (250 mL each). The combined organics were dried with sodium sulfate,

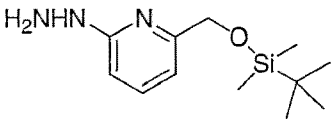
filtered through magnesium sulfate, and concentrated *in vacuo* to give **338B** as a yellow colored oil, (27.65 g). The compound slowly crystallizes to a yellow colored solid. MS (M+H+) 188, 190; HPLC(A) retention time 1.99 min.

338C



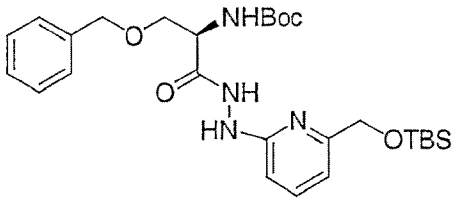
[0267] To a stirred solution of **338B** (25.0 g, 0.129 mol) in DMF (200 mL) at room temperature under argon is added imidazole (17.56 g, 0.258 mol) and then, after the imidazole had dissolved, tert-butyldimethylsilyl chloridel (23.27 g, 0.155 mol) in one portion. A slight endotherm is noted. After stirring for 16 h., the reaction mixture was quenched with ice water (500 mL) and extracted 3x250 mL hexanes. The hexane extracts were combined, washed twice with water (150 mL) and once with brine. After drying the organics over sodium sulfate, they were filtered through magnesium sulfate, and stripped to give **338C** as a light yellow colored oil (39.15 g). MS (M+H) 302, 304; HPLC(A) retention time 4.56 min.

338D



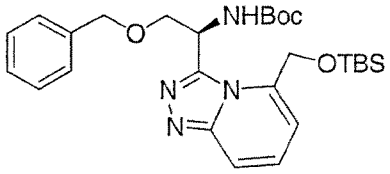
[0268] A 1 L 3-necked flask is charged with a solution of **338C** (38.5 g, 0.127 mol) in pyridine (500 ml) and treated with hydrazine (40 ml, 1.28 mol) in one portion. A slight endotherm is noted. The reaction mixture is stirred and heated to reflux under argon (pot temperature 109-111 °C) for 45 h. After cooling to room temp in an ice bath, solid sodium bicarbonate (11 g) is added. The mixture is stirred for 1 h and stripped to give a yellow oil. Addition of water (200 mL) leads to formation of a solid with the aid of seed crystals. The solid mass is broken up, collected, and washed with water (5x100 mL). In order to expedite drying, the solid is dissolved in ether (500 mL), washed once with brine, dried over sodium sulfate, and filtered through magnesium sulfate. The organics were concentrated *in vacuo* to give **338D** as an off-white solid (31.5 g). MS (M+H+) 254; HPLC(A) retention time 2.53 min.

338E



[0269] A 1 L 3-necked flask (oven-dried) is charged with N-(tert-butoxycarbonyl)-D-serine (35.74 g, 0.12 mol) in THF (250 mL) and cooled to -13°C (isopropanol/ ice bath) under argon. N-Methylmorpholine (13.74 ml, 0.125 mol) is added in one portion (temperature temporarily rises to 2°C). After the temperature cools again to - 13°C, isobutylchloroformate (15.69 ml, 0.12 mol) is added at such a rate as to keep the temperature below -10°C. The reaction mixture is stirred 20 min and then a solution of **338D** (30.4 g, 0.12 mol) in THF (100 mL) is added over 15 min, not allowing the temperature to rise above -5.5°C during this addition process. The addition funnel is rinsed with THF (25 mL) and the yellow reaction slurry is stirred for 90 min. The reaction is quenched at -10°C with saturated sodium bicarbonate (100 mL) and the aqueous layer is extracted twice with ethyl acetate (500 mL). The combined organics were washed once with brine, 10% citric acid, saturated sodium bicarbonate, and dried over sodium sulfate. After filtering through magnesium sulfate, the volatiles were removed *in vacuo,* and the residue restripped from methylene chloride/hexanes to give **338E** as a yellow foam (63.97 g). MS (M+H+) 531; HPLC(A) retention time 3.91 min.

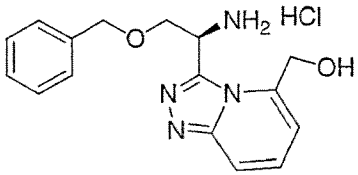
338F



[0270] To a stirred solution of **338E** (93.6 g, 0.177 mol) in THF (800 mL) at -78°C under nitrogen is added triethylamine (196 ml, 1.41 mol). After 10 min, dichlorotriphenylphosphine (194.2 g, 0.583 mol) is added portion wise over 10 min. The mixture was stirred and slowly warmed to room temperature overnight (~20 h). The volatiles were removed and the residue was filtered through a short silicon gel column, rinsing the column with hexane/ethyl acetate (1:2). The combined filtrates were evaporated to give the crude **338F** (200 g, mixed with triphenylphosphine oxide). MS: (M+H+) 513; HPLC (A) retention time 4.30 min.

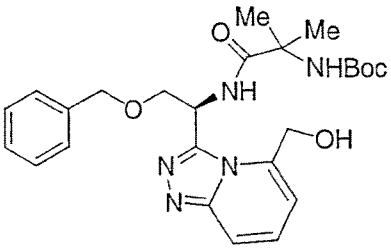
[0271] An alternative procedure: To a stirred solution of **338E** (63.95 g, 0.12 mol) in THF (800 ml) at -73°C under argon is added triethylamine (134 ml, 0.964 mol). After 15 min, dichlorotriphenylphosphine (132.49 g, 0.398 mol) is added portion wise over 30 min, stirred 1 h and then brought to -10°C by displacing the acetone cold bath with room temperature water. The reaction mixture is allowed to warm from -10°C to room temperature *in situ* overnight, then filtered through Celite and concentrated *in vacuo.* The resulting solid was dissolved in methylene chlroide (750 mL), cooled to 0°C and treated with ice-cold 10% citric acid (100 mL). The mixture was stirred rapidly for 5 min, the organics washed once with water, saturated sodium bicarbonate, dried (magnesium sulfate), filtered and restripped to give **338F** as a light tan colored solid (167.74 g, contaminated with triphenylphosphine oxide).

338G



[0272] To methanol (400 ml) at 2°C was added acetyl chloride (100 g) dropwise over 20 min. After stirring 30 min, the solution was brought to room temperature for 45 min.. The methanol solution was added directly to crude **338F** (<167 g, -0.12 mol) and the mixture was stirred for 3 h, concentrated *in vacuo* at temperatures below 30°C, and then the brown colored residue was suspended in THF (500 mL) for 30 min. The resulting solid was collected by filtration, and re-suspended in THF (500 mL) for 30 min. After filtration, the solid was dried *in vacuo* at 40°C to give **338G** as light yellow colored solid (38.6 g). MS (M+H) 299; HPLC(A) retention time 1.65 min.

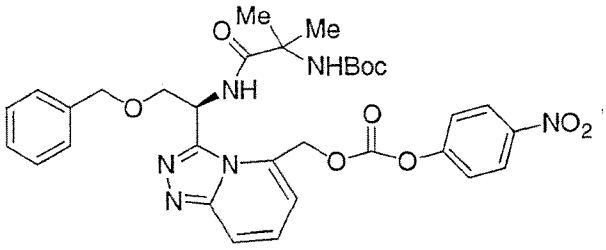
338H



[0273] To a stirred slurry of N-(tert-butoxycarbonyl)-α-methylalanine (24.39 g, 0.120 mol) and HOBt (18.37 g, 0.120 mol) in methylene chloride at room temperature under argon is added EDAC (22.83g, 0.120 mol) as a solid over 10 min. The resulting solution is stirred 1 h and then added (filtering through a cotton plug) to a solution of **338G** (~0.120 mol) and N-methylmorpholine (19.79 ml, 0.18 mol) in methylene chloride at room temperature. After stirring 45 h, the reaction mixture was stirred with saturated sodium bicarbonate (200 mL) for 30 min. The phases were separated and the organic extract was washed once with brine, 10% citric acid (at pH3) and once again with brine. The organics were dried over sodium sulfate, filtered, and the filtrate was partially evaporated (to ~250 mL volume) and ether (~100 mL) was added.

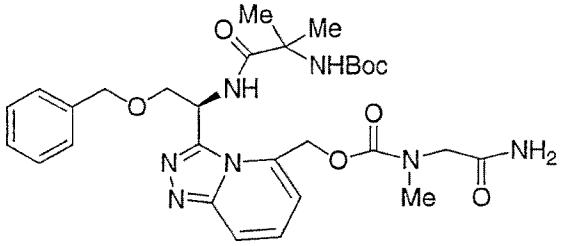
The resulting solids were filtered to give **338H** as a colorless solid (30.10. The mother liquors were concentrated and recrystallized from chloroform (50 mL) and hexanes (sufficient to cause cloudiness in the boiling solution) to obtain an additional 3.45 g. Both solids were combined to give **338H** (33.55 g). mp 155-157 deg°C. MS (M+H+) 484; HPLC(A) retention time 2.85 min.

338I



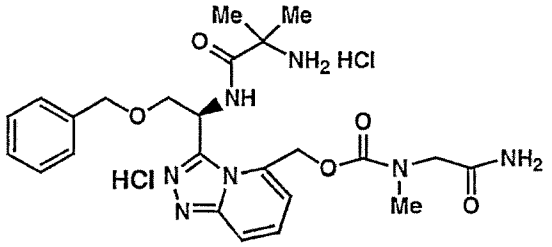
[0274] To a suspension of **338H** (25.63 g, 0.053 mol) in methylene chloride (300 mL) at 0°C was added pyridine (9.0 mL, 0.111 mol). After 10 min, para-nitrophenyl chloroformate (21.4 g, 0.106 mol) was added slowly under nitrogen and the reaction was slowly warmed to room temperature overnight. The mixture was filtered and the solid cake was rinsed with methylene chloride (100 mL). The filtrate was concentrated *in vacuo,* ethyl acetate and ether (200 mL,1:1) were added and the mixture was stirred at room temperature for 30 min. The solids were filtered and the crude solid product was collected. The solid was re-suspended in ethyl acetate and ether (200 mL,1:1) three times to give **338I** as a colorless solid (38.5 g). MS (M+H+) 649; HPLC(A) retention time 3.68 min.

338J



[0275] To a suspension of sarcosinamide (2.61 g, 29.6 mmol) in anhydrous THF (250 mL) at 2°C was added solid **338I** (16.0 g, 24.7 mmol) over 10 min. The yellow mixture was stirred at room temperature for 24 h. After concentration, the resulting yellow foamy residue was diluted with ethyl acetate (600 mL) and washed with cold 1N NaOH (7x100 ml), water (100 ml) and dried over magnesium sulfate. The organic layer was concentrated *in vacuo* to give crude **338J** as colorless solid (14.38 g). The material could be further purified by column chromatography, eluting with 10% methanol/methylene chloride to give pure 338J (10.47 g). MS (M+H+) 531; HPLC(A) retention time 3.91 min.

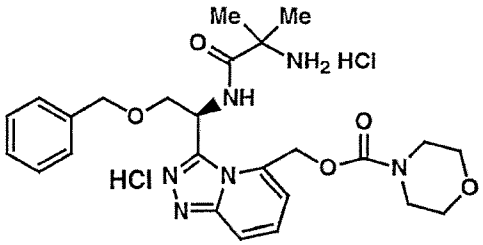
338



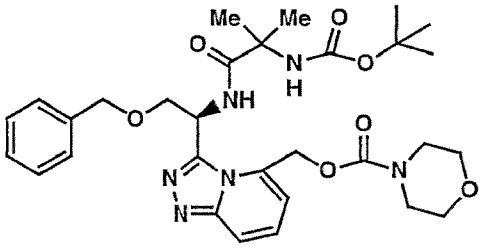
[0276] HCl gas (67.8 g, 1.86 mol) was bubbled into ice-cold isopropanol (200 mL). The resulting solution was cooled to 5°C and solid **338.J** (13.8 g, 23.1 mmol) was added in portions over 5 min. After 30 min at 0°C, the reaction mixture was stirred at room temperature an additional 30 min before concentration *in vacuo.* The resulting viscous liquid was stirred with isopropanol (100 mL) and the resulting colorless solid was collected by filtration to give **338** (12.65 g). mp 151.4-152.6°C; MS (M+H+) 498; HPLC(A) retention time 1.723 min.

EXAMPLE 339

[0277]

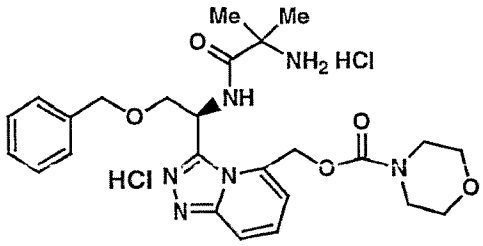


339A



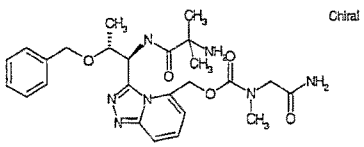
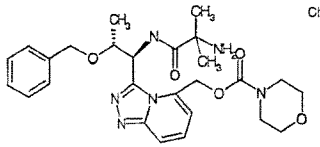
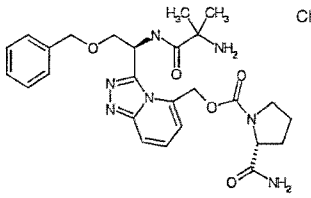
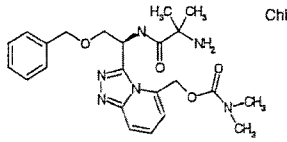
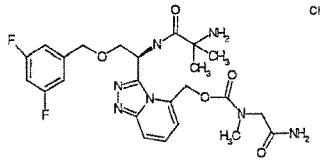
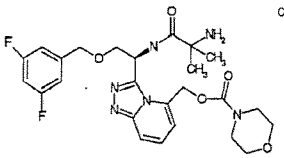
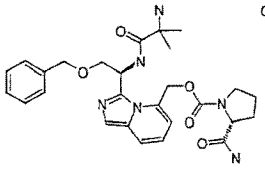
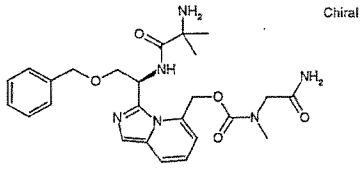
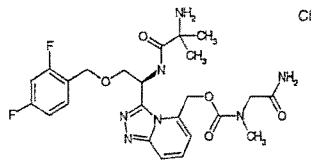
[0278] To a stirred slurry of intermediate **338I** (37.41g, 0.058 mol) and triethylamine (12.06 ml, 0.087 mol) in THF (300 ml) at room temperature under argon was added morpholine (5.53 ml, 0.063 mol) over 2 minutes. A yellow solution forms within 5 min and the reaction was stirred overnight. After 15 h, the reaction solution was concentrated *in vacuo* and re-dissolved in EtOAc (800 mL). The organic layer was washed with saturated sodium bicarbonate (5x125 mL), once with 5% potassium hydrogensulfate (200 mL), brine and once with saturated sodium bicarbonate (100 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated to give a colorless foam, 37.5 g. This material is recrystallized twice from 5:4 ethyl acetate: hexane to give **339A** as a colorless solid (30.95 g). mp 104-106°C, MS (M+H+) 597; HPLC(A) retention time 3.58 min.

339



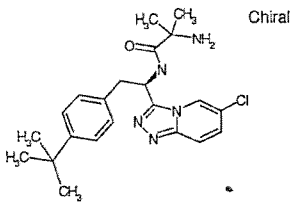
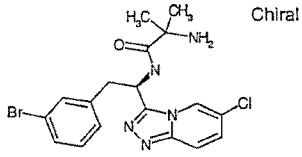
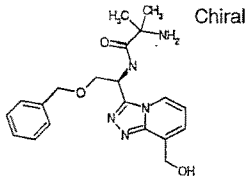
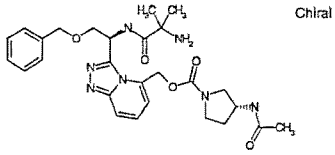
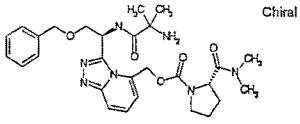
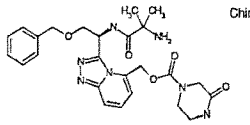
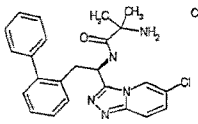
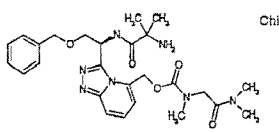
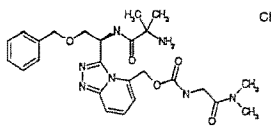
[0279] Acetyl chloride (50 ml, 0.637 mol) was added dropwise over 30 min to dry methanol (200 mL) at 0°C. After 30 min, the mixture was warmed to room temperature, stirred 1 h, then added to solid **339A** (30.2 g, 0.051 mol). After 4 h, the reaction mixture was concentrated and the resulting colorless amorphous solid was suspended in THF and sonicated for 30 min. Filtration gave a colorless amorphous solid which was dried at 45°C for 15 h to give **339** (25.75 g). MS (M+H) 497; HPLC(A) retention time 2.73 min. CHN elemental analysis: C25H32N6O52HCl

[0280] The following examples were prepared using procedures as described in the general synthetic schemes and working examples above, utilizing the appropriate starting materials as known to those skilled in the art.

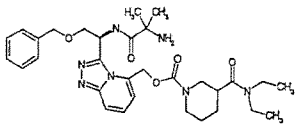
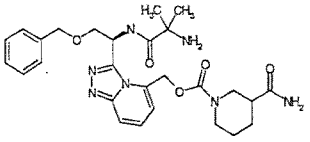
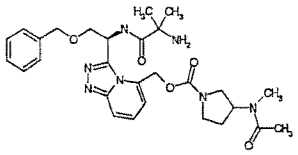
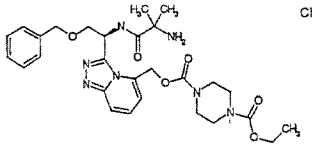
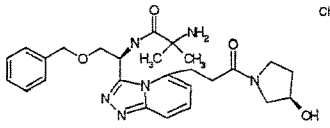
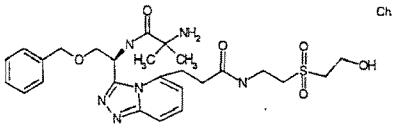
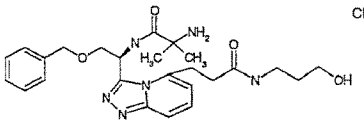
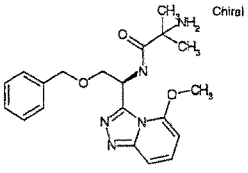
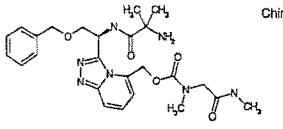
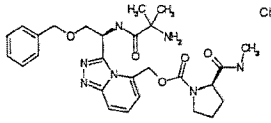
Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
340		512	95	1.73
341		511	95	2.07
342		524	96	2.56
343		455	95	3.33
344		534	97	1.85
345		533	98	2.3
346		523	96	4.10
347		497	97	4.73
348		534	97	4.73

[0281] The following examples were prepared using procedures as described in the general synthetic schemes and

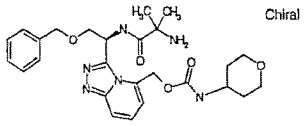
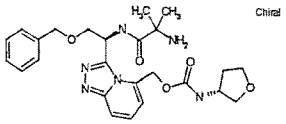
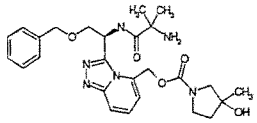
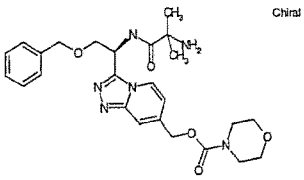
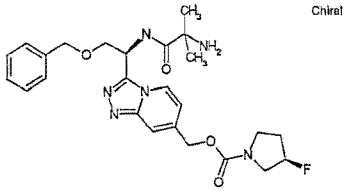
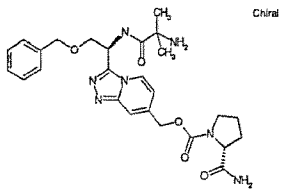
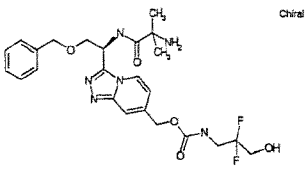
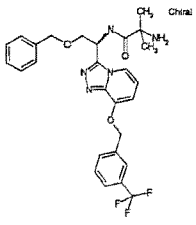
working examples above, utilizing the appropriate starting materials as known to those skilled in the art.

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
349		414	94	2.67
350		437	97	2.13
351		384	99	1.28
352		538	95	2.53
353		552	92	2.70
354		510	92	2.47
355		434	99	2.60
356		526	95	2.60
357		512	95	2.54

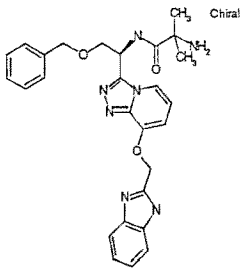
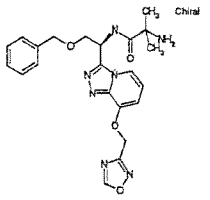
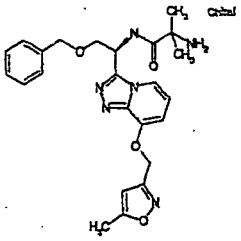
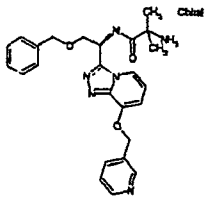
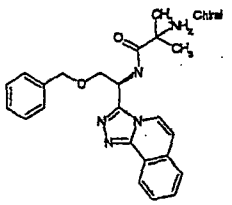
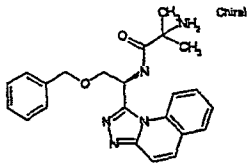
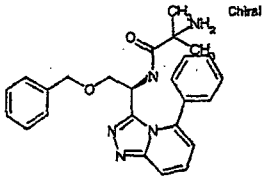
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
358		594	95	3.07
359		538	95	2.68
360		552	95	2.64
361	 Chiral	568	95	3.06
362	 Chiral	495	97	2.35
363	 Ch	561	90	2.28
364	 Chiral	483	98	2.36
365	 Chiral	384	95	1.96
366	 Chiral	512	95	2.48
367	 Chiral	538	95	2.63

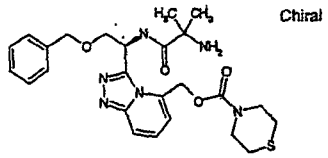
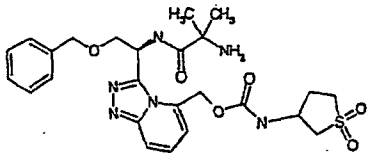
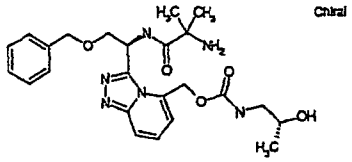
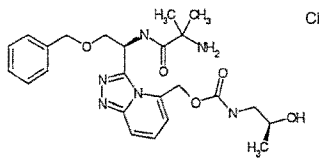
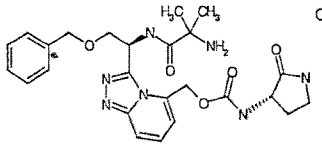
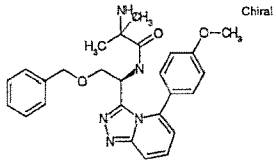
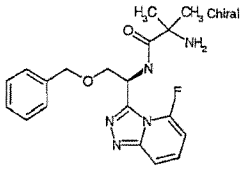
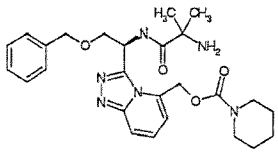
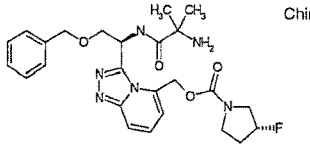
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
368		511	95	2.71
369		497	95	2.63
370		511	95	2.74
371		497	98	1.87
372		499	95	2.13
373		524	95	1.73
374		521	90	1.77
375		528	98	2.93

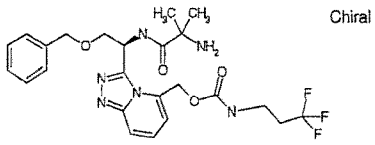
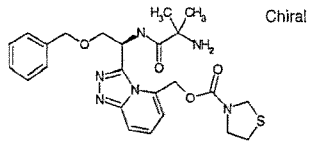
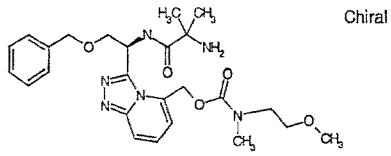
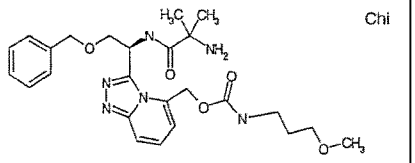
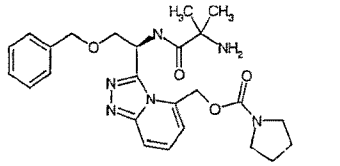
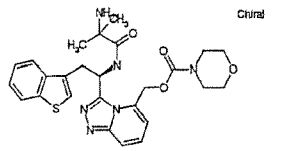
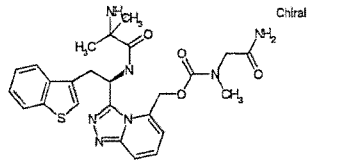
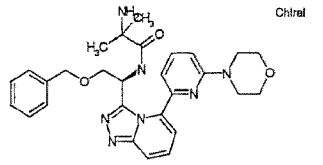
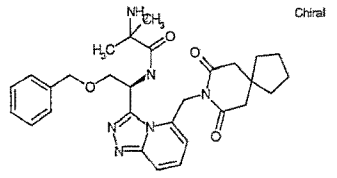
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
376		500	95	1.85
377		452	90	1.78
378		465	95	2.15
379		461	95	1.47
* 380		404	96	2.74
* 381		404	97	2.65
382		430	98	2.77

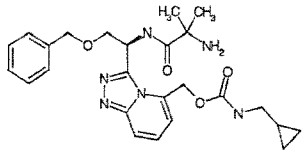
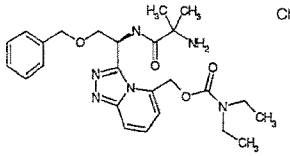
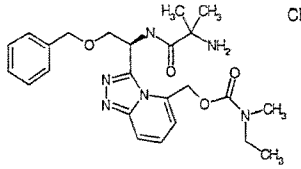
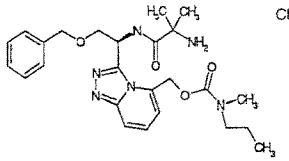
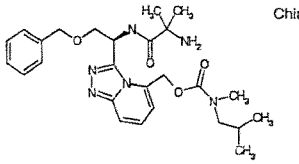
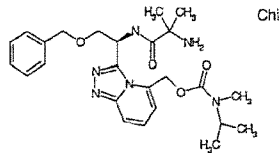
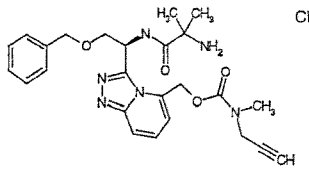
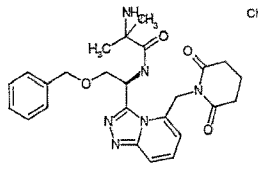
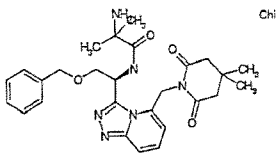
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
383		513	95	3.12
384		545	95	2.49
385		485	92	2.56
386		485	93	2.55
387		510	92	2.42
388		460	100	2.87
389		372	80	1.51/1.64
390		495	95	3.19
391		499	95	2.86

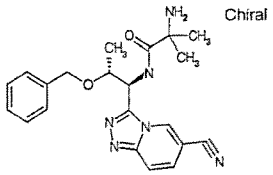
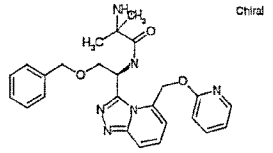
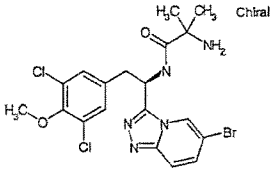
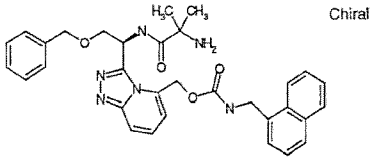
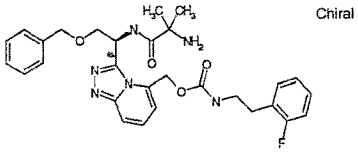
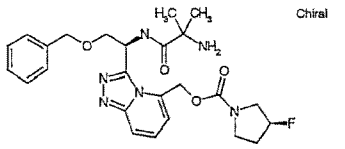
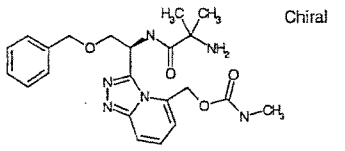
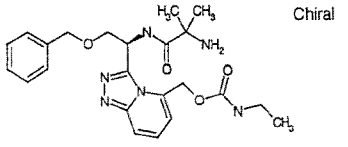
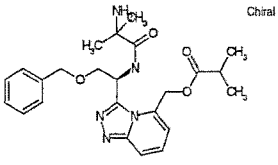
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
392	 Chiral	523	95	2.97
393	 Chiral	499	93	2.99
394	 Chiral	499	95	2.81
395	 Chi	499	95	2.75
396		481	95	3.01
397	 Chiral	523	93	2.20
398	 Chiral	524	97	1.89
399	 Chiral	516	99	2.21
400	 Chiral	533	100	2.40

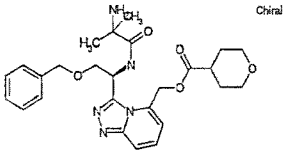
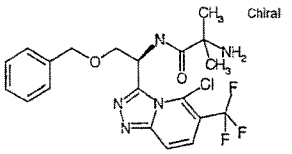
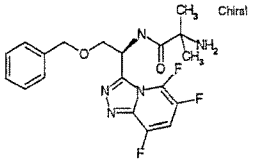
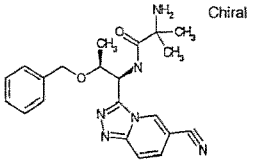
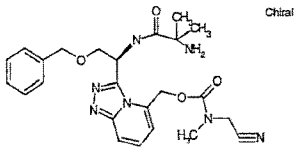
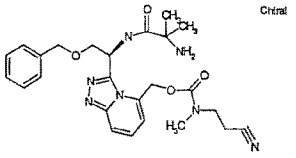
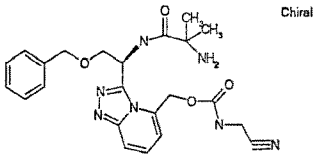
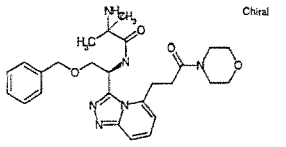
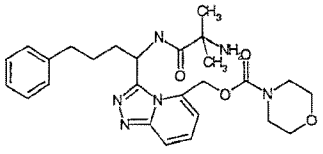
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
401	 Chiral	481	95	3.52
402	 Chiral	483	95	3.72
403	 Chiral	469	95	3.59
404	 Chiral	483	95	2.56
405	 Chiral	497	90	2.74
406	 Chiral	483	90	2.56
407	 Chiral	479	90	2.28
408	 Chiral	479	92	1.57
409	 Chiral	507	99	2.04

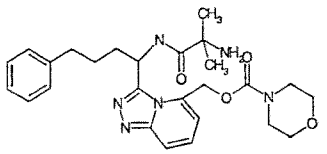
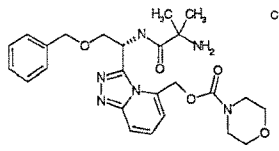
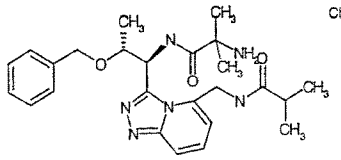
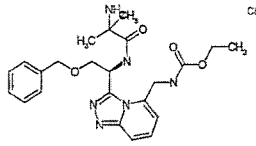
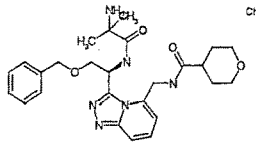
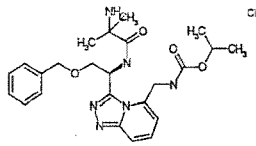
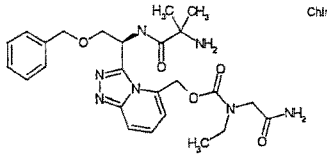
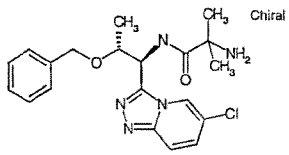
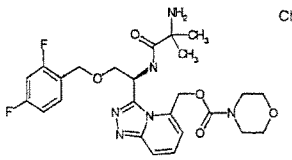
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
410		393	98	4.84
411		461	89	2.32
412		502	96	2.34
413		567	90	3.78
414		549	90	3.60
415		499	90	3.08
416		441	90	2.64
417		455	90	2.91
418		454	93	2.37

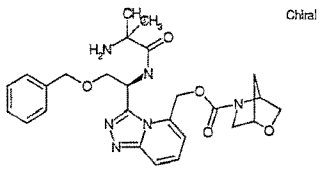
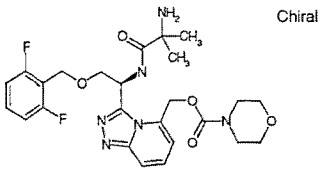
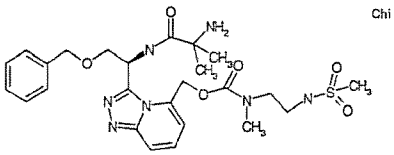
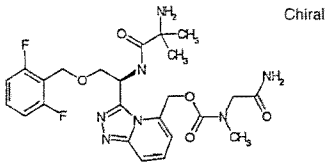
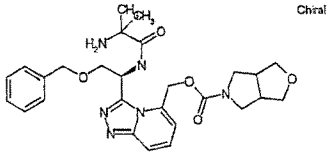
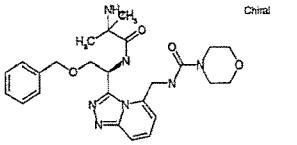
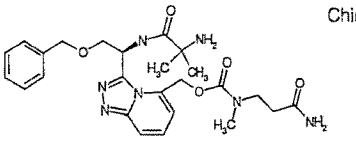
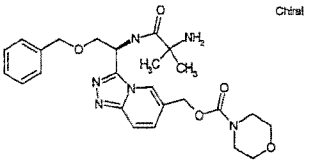
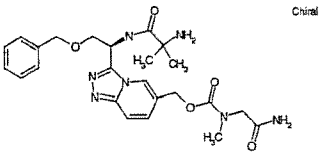
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
419		496	94	2.03
420		456	93	2.44
421		408	95	1.87
422		393	97	4.93
423		480	75	2.01
424		494	80	2.00
425		466	80	1.80
426		495	97	1.62
427		495	98	2.31

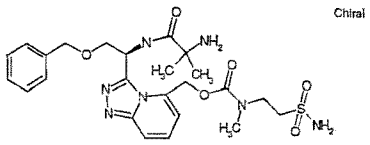
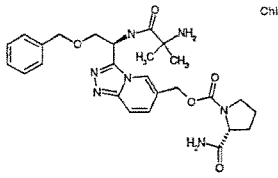
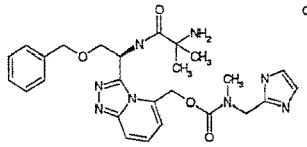
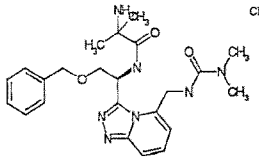
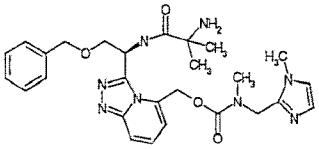
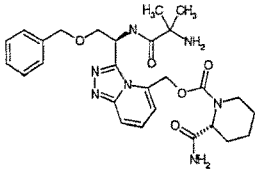
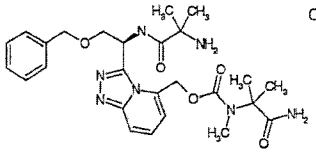
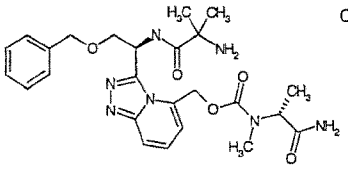
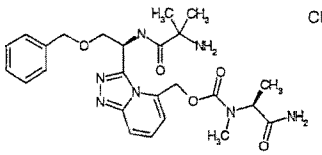
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
428		495	98	2.31
429		497	95	2.17
430		467	90	2.00
431		455	93	2.43
432		495	98	2.06
433		469	98	2.07
434		512	90	1.94
435		402	95	2.12
436		533	99	4.18

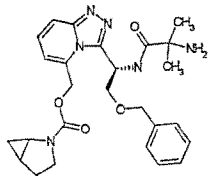
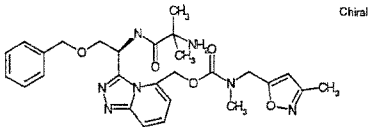
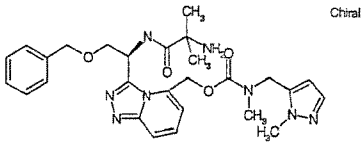
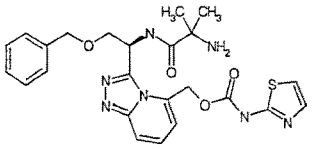
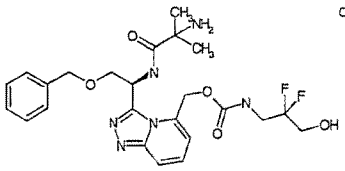
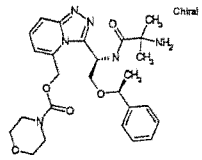
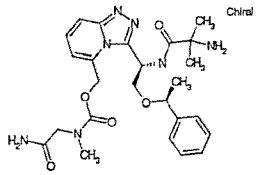
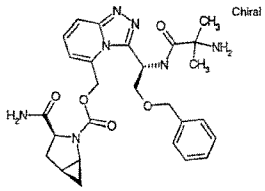
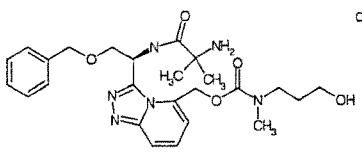
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
437	 Chiral	509	98	3.02
438	 Chiral	533	98	4.13
439	 Chi	562	98	1.98
440	 Chiral	534	96	1.96
441	 Chiral	523	98	3.08
442	 Chiral	496	85	1.45
443	 Chiral	512	96	1.89
444	 Chiral	497	95	2.09
445	 Chiral	498	97	1.75

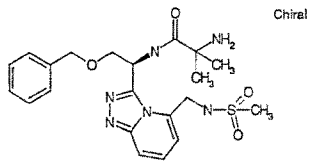
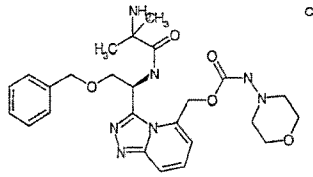
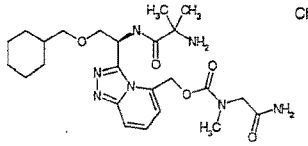
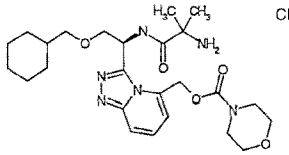
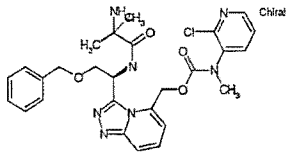
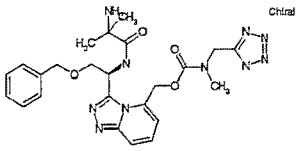
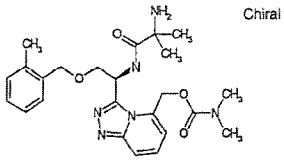
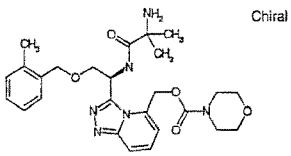
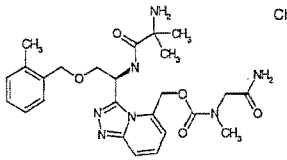
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
446	 Chiral	548	98	1.89
447	 Chiral	524	96	1.88
448	 Chiral	521	97	1.38
449	 Chiral	454	96	1.39
450	 Chiral	535	95	1.34
451	 Chiral	538	92	2.26
452	 Chiral	526	94	2.11
453	 Chiral	512	90	2.04
454	 Chiral	512	94	2.02

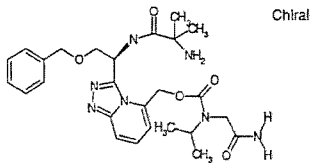
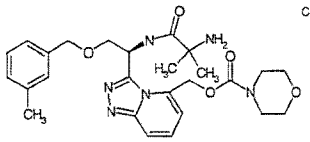
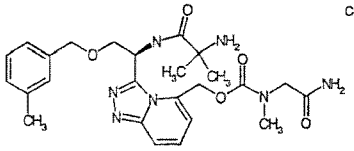
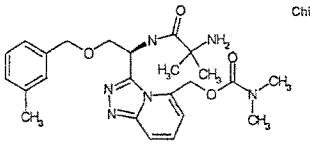
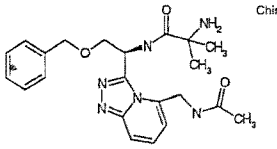
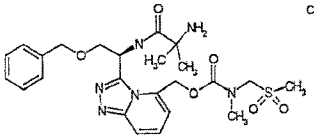
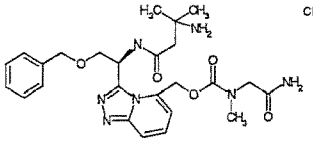
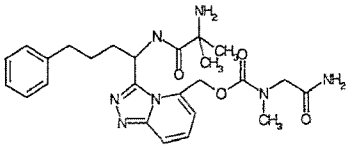
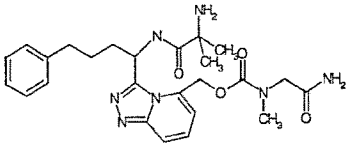
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
455		493	98	2.62
456		536	98	2.20
457		535	98	2.19
458		510	90	2.40
459		521	97	
460		511	99	3.11
461		512	99	2.76
462		536	96	2.92
463		499	96	2.07

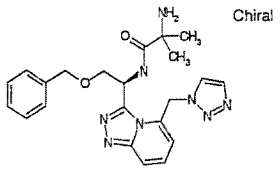
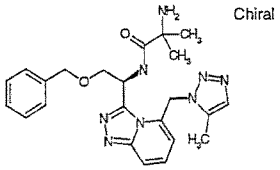
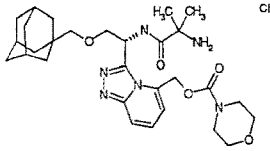
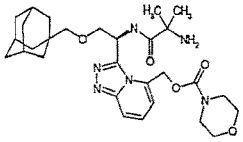
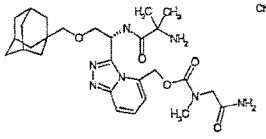
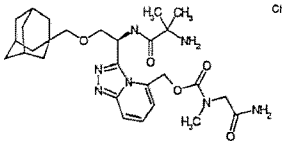
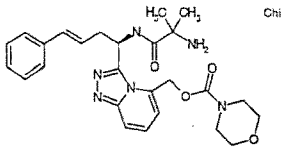
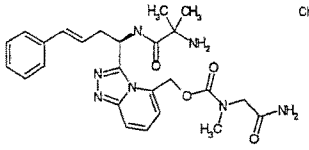
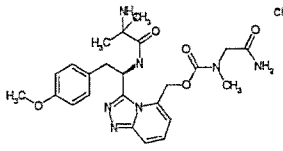
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
464	 Chiral	461	97	1.58
465	 Chiral	512	89	1.65
466	 Chiral	504	92	2.33
467	 Chiral	503	92	2.66
468	 Chiral	553	94	2.16
469	 Chiral	523	89	1.69
470	 Chiral	469	97	5.71
471	 Chiral	511	97	5.53
472	 Chiral	512	97	4.97

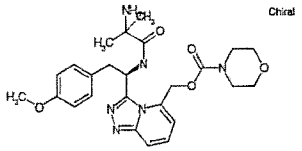
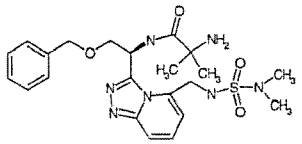
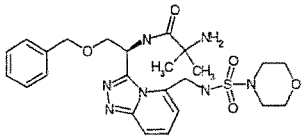
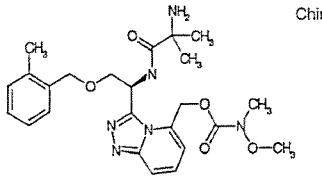
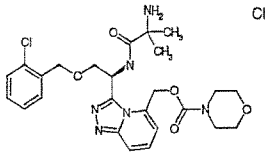
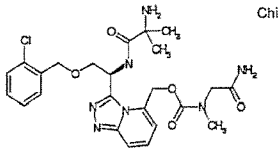
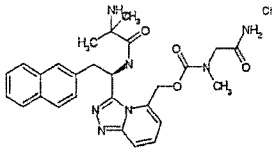
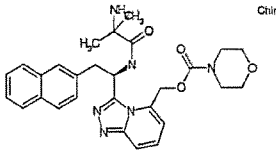
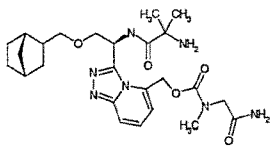
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
473	 Chiral	526	99	2.09
474	 Chiral	511	98	2.55
475	 Chiral	512	97	2.18
476	 Chiral	469	97	2.62
477	 Chiral	425	97	1.43
478	 Chiral	533	95	2.03
479	 Chiral	512	95	1.71
480		496	95	1.96
481		496	98	1.96

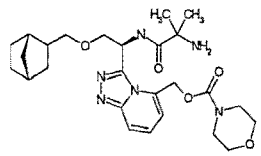
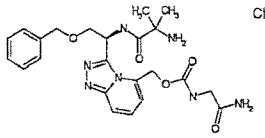
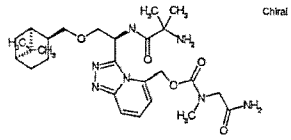
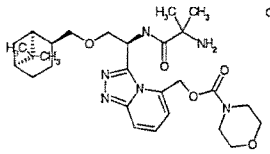
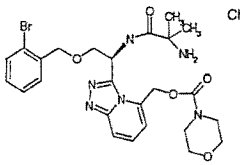
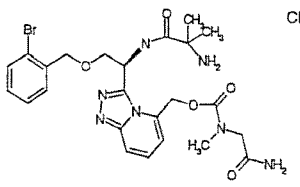
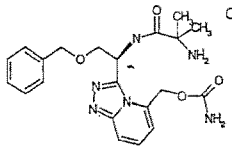
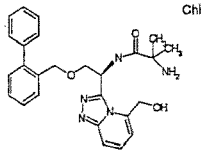
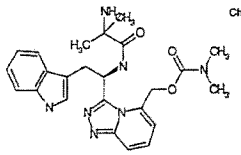
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
482	 Chiral	435	96	4.41
483	 Chiral	449	99	4.66
484	 Chiral	555	92	3.14
485	 Chiral	555	92	3.12
486	 Chiral	556	92	2.86
487	 Chiral	556	93	2.88
488	 Chiral	493	99	2.26
489	 Chiral	494	99	1.92
490	 Chiral	498	96	1.41

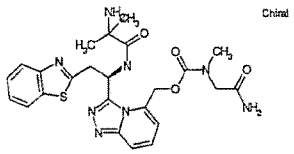
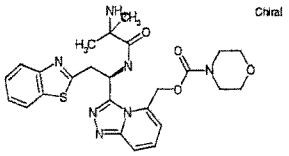
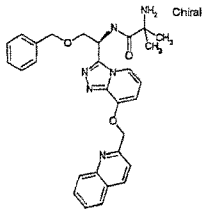
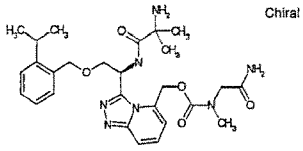
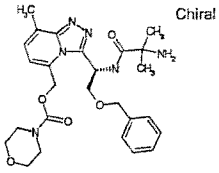
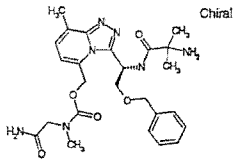
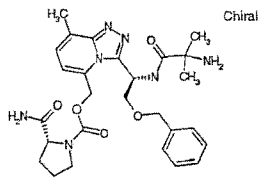
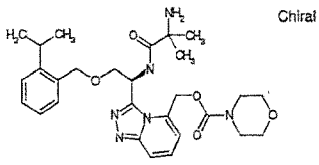
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
491	 Chiral	497	89	1.79
492		490	99	1.92
493		532	99	1.94
494	 Chiral	485	97	5.83
495	 Chiral	532	99	5.69
496	 Chiral	533	98	5.07
497	 Chiral	518	96	1.97
498	 Chiral	517	90	2.25
499		516	90	2.37

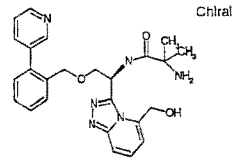
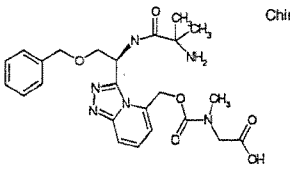
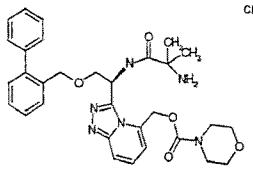
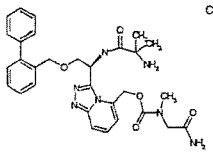
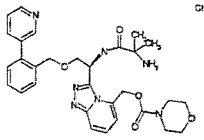
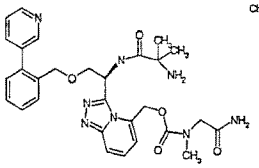
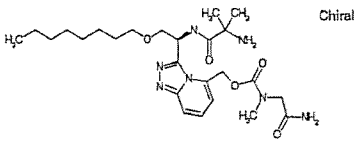
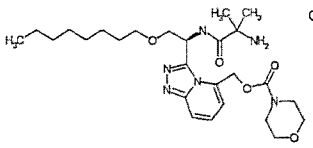
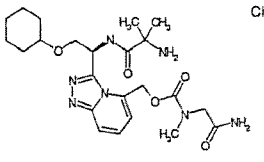
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
500		515	95	2.68
501		484	95	1.69
502		544	95	2.79
503		543	92	3.01
504		576	96	2.44
505		577	88	2.13
506		427	90	1.76
507		460	100	2.56
508		464	95	1.84

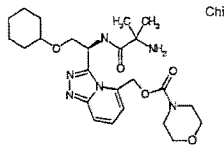
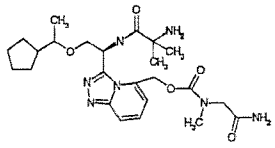
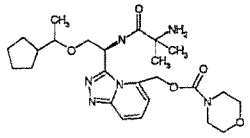
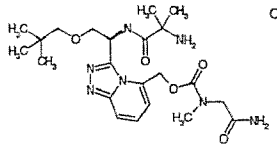
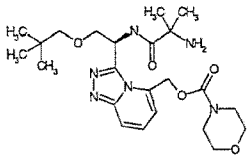
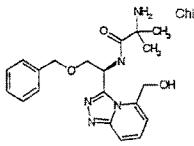
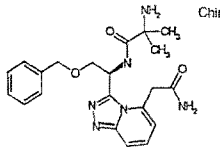
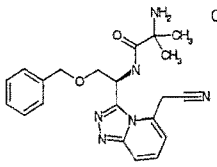
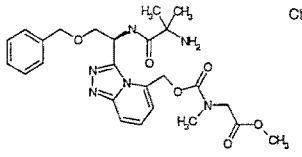
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
509		525	91	1.59
510		524	90	1.96
511		511	94	2.21
512		540	98	4.73
513		511	99	3.28
514		512	94	2.91
515		538	97	3.10
516		539	99	5.35

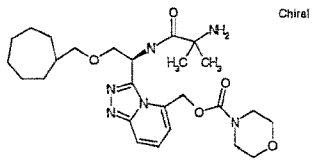
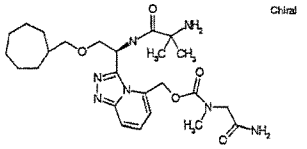
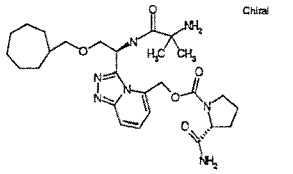
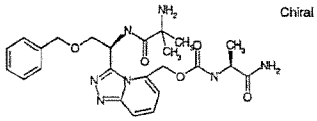
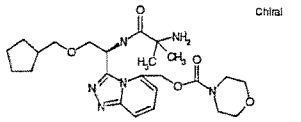
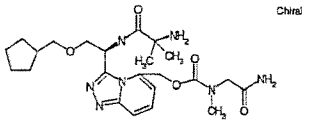
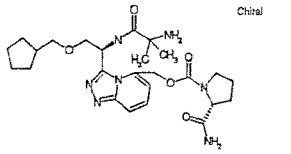
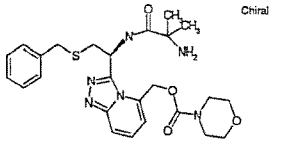
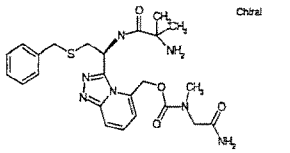
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
517		461	95	0.197/0.97
518		499	99	2.03
519		573	97	2.79
520		574	95	2.58
521		574	93	1.59
522		575	95	0.197/1.21
523		520	95	2.80
524		519	95	3.00
525		490	95	2.00

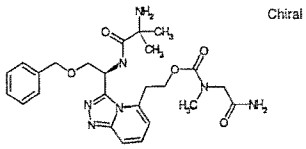
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
526	 Chiral	489	95	2.40
527		504	95	2.16
528		503	95	2.45
529	 Chiral	478	92	2.03
530	 Chiral	477	93	2.39
531	 Chiral	384	97	3.21
532	 Chiral	411	98	2.74
533	 Chiral	393	98	3.85
534	 Chiral	513	95	2.17

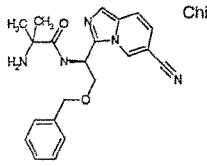
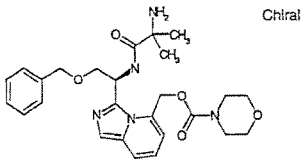
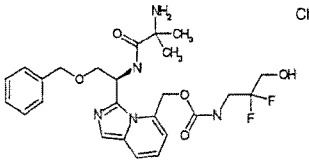
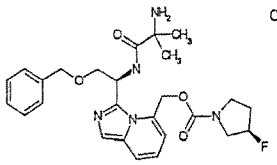
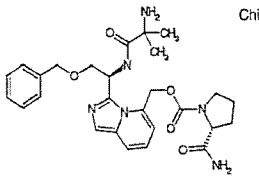
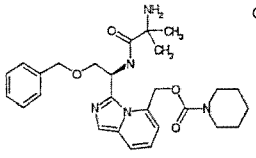
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
535	 Chiral	517	95	2.67
536	 Chiral	518	97	2.38
537	 Chiral	544	95	2.47
538	 Chiral	498	92	1.71
539	 Chiral	489	95	3.05
540	 Chiral	490	97	2.67
541	 Chiral	516	97	2.83
542	 Chiral	513	95	2.31
543	 Chiral	514	99	1.87

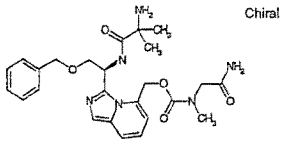
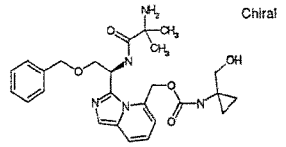
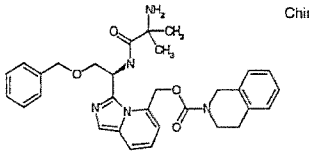
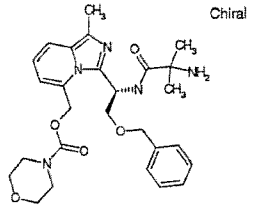
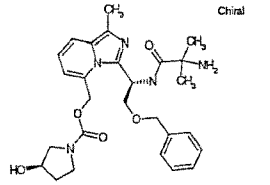
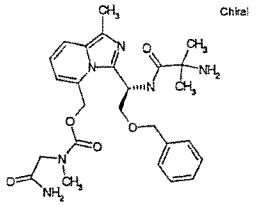
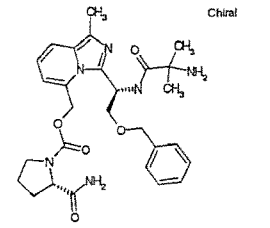
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
544	 Chiral	512	90	3.80
* Compound not within the definition of the claims				

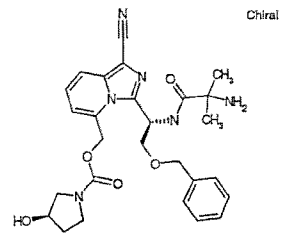
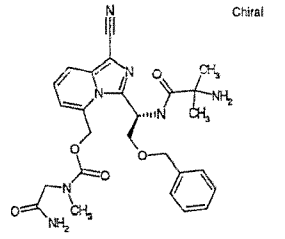
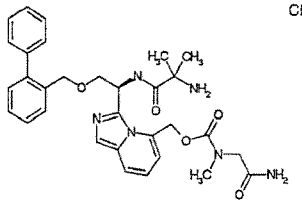
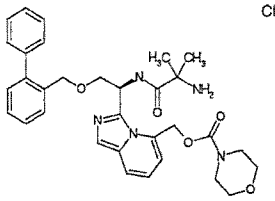
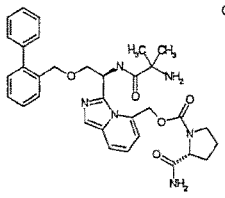
[0282] The following examples were prepared using procedures as described in Example 90, as well as described in the general synthetic schemes and working examples above, utilizing the appropriate starting materials as known to those skilled in the art.

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
545	 Chiral	378	97	3.03
546	 Chiral	496	94	5.67
547	 Chiral	520	94	5.08
548	 Chiral	498	99	5.88
549	 Chiral	523	96	4.10
550	 Chiral	494	98	6.78

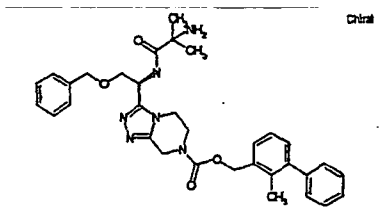
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
551	 Chiral	497	91	4.73
552	 Chiral	496	95	5.19
553	 Chiral	542	96	7.27
554	 Chiral	510	97	3.10
555	 Chiral	510	96	2.85
556	 Chiral	511	98	2.84
557	 Chiral	537	98	2.84

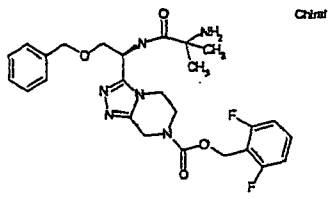
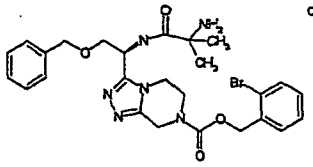
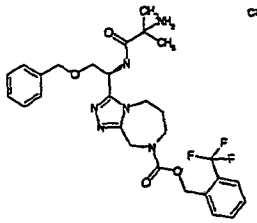
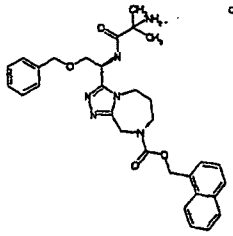
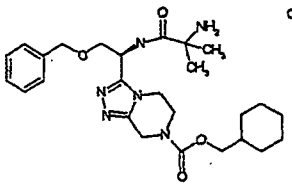
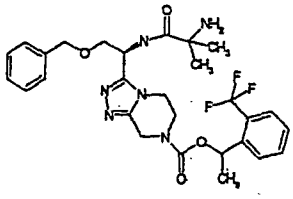
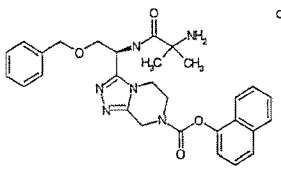
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
558	 Chiral	521	98	3.56
559	 Chiral	522	97	3.38
560	 Chiral	573	98	2.75
561	 Chiral	572	98	2.97
562	 Chiral	599	97	2.80

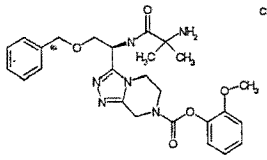
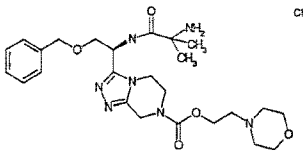
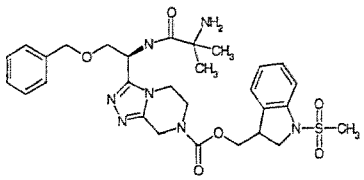
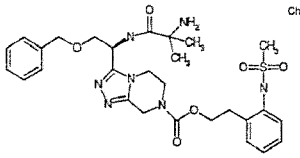
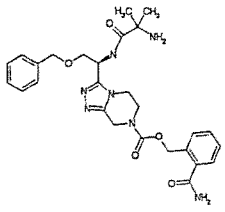
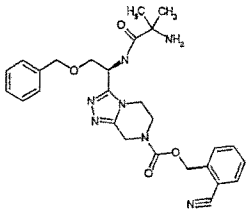
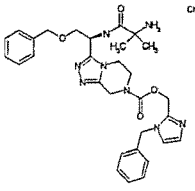
[0283] The following examples were prepared using procedures as described in Example 92 and Example 93 above, and as described in the general synthetic schemes and working examples above, utilizing the appropriate starting materials as known to those skilled in the art.

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
563	 Chiral	583	95	3.09

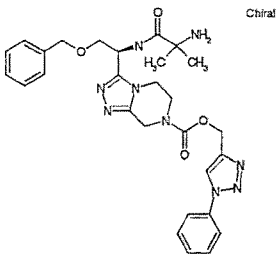
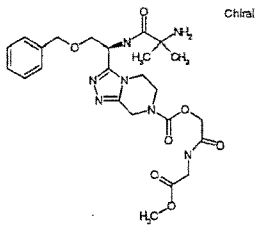
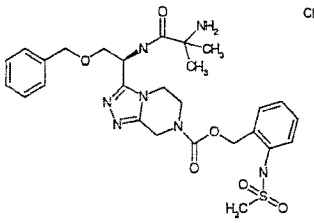
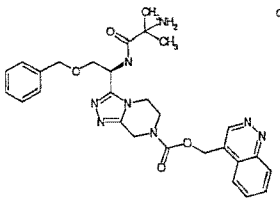
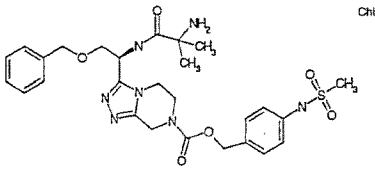
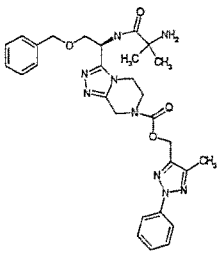
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
564		529	95	3.10
565		572	95	3.20
* 566		575	90	2.61
* 567		557	84	3.42
568		499	95	2.77
569		575	95	3.40
570		529	97	3.21

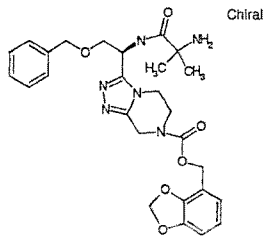
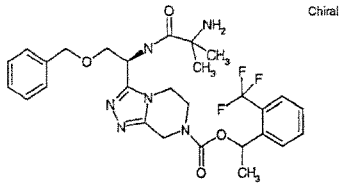
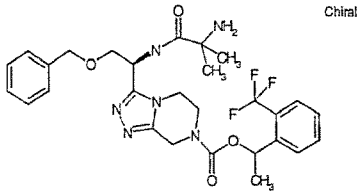
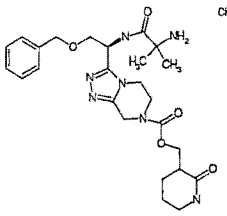
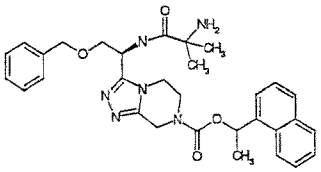
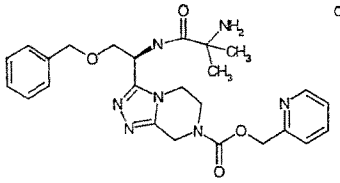
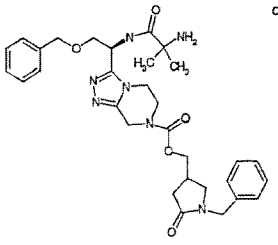
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
571		509	98	2.89
572		516	93	0.19
573		612	95	2.89
574		600	95	2.70
575		536	95	2.60
576		518	95	2.93
577		573	99	2.62

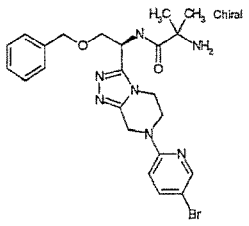
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
578		560	98	3.43
579		532	95	2.64
580		586	97	3.20
581		545	98	
582		586	95	1.99
583		574	99	

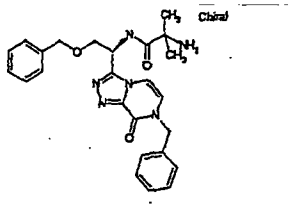
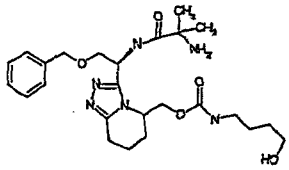
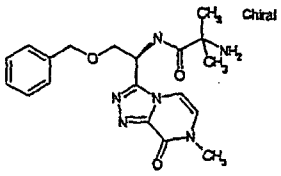
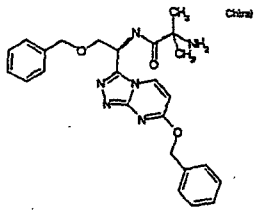
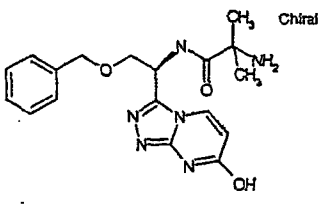
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
584	 Chiral	537	90	3.64
585	 Chiral	575	95	2.79
586	 Chiral	575	95	2.80
587	 Chiral	514	97	1.84
588		557	95	2.84
589	 Chiral	494	97	2.85
590	 Chiral	590	98	2.37

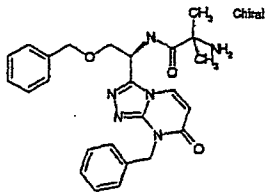
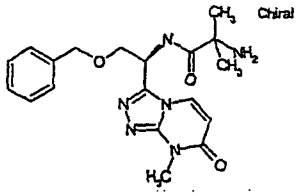
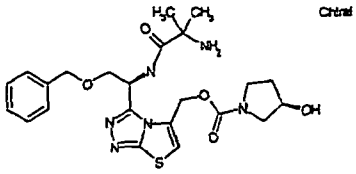
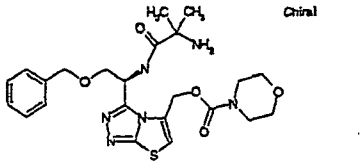
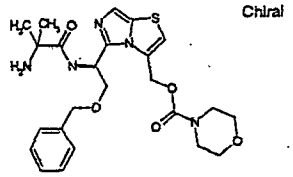
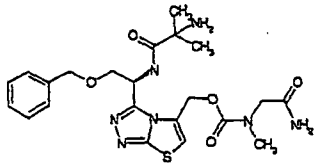
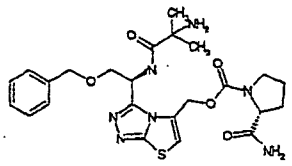
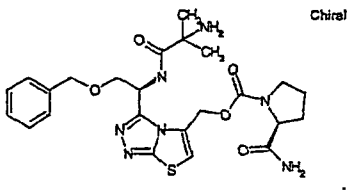
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
591		515	90	2.68
* Compound not within the definition of the claims				

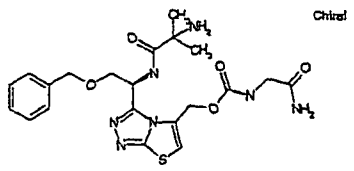
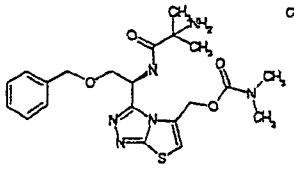
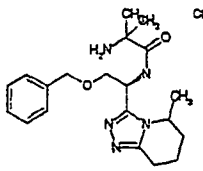
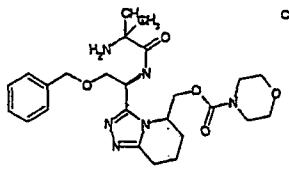
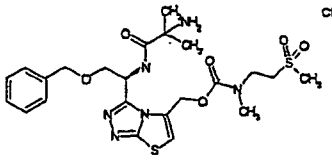
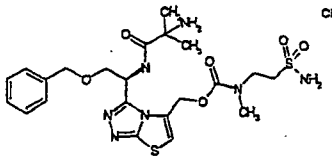
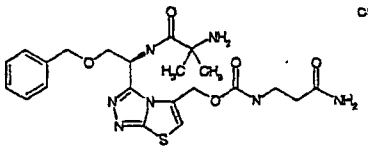
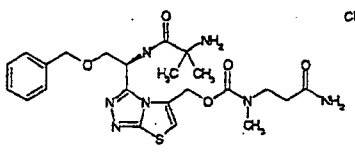
[0284] The following examples were prepared using procedures as described in the general synthetic schemes and working examples above, utilizing the appropriate starting materials as known to those skilled in the art.

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
* 592		461	94	3.01
593		503	95	2.39
* 594		385	95	1.26
* 595		461	96	2.52
596		371	90	1.26

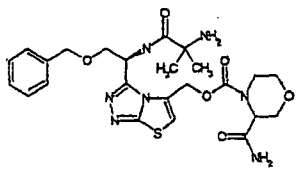
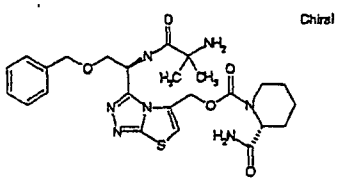
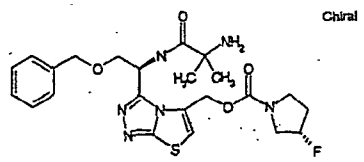
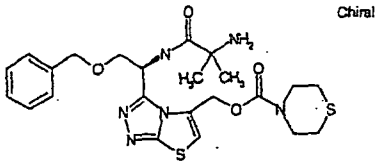
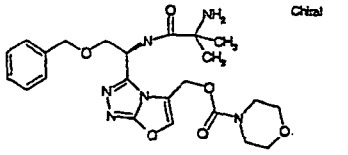
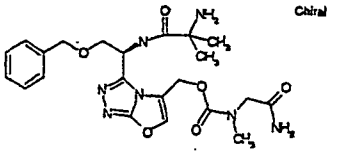
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
* 597		461	97	2.43
* 598		385	90	1.47
* 599		503	97	2.00
* 600		503	98	2.21
* 601		502	96	2.66
* 602		504	91	
* 603		530	95	
* 604		530	91	

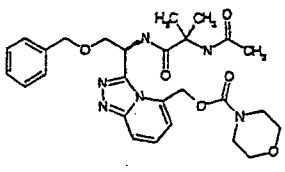
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
* 605		490	90	
* 606		461	91	
607		372	97	3.03
608		501	98	3.28
* 609		553	95	
* 610		554	90	
* 611		504	96	1.77
* 612		518	96	1.85

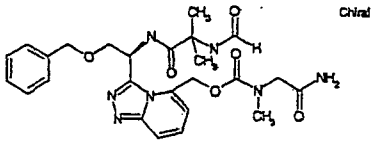
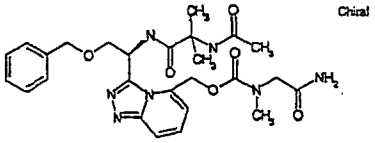
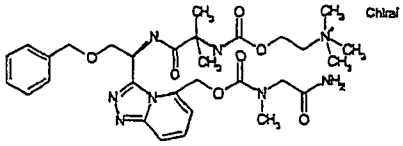
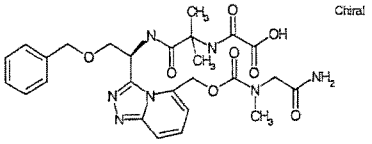
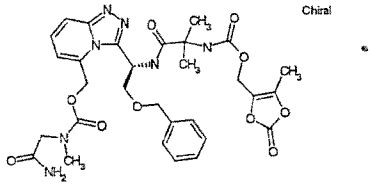
(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
* 613		546	90	1.87
* 614		544	96	2.20
* 615		505	95	2.26
* 616		519	95	2.54
* 617		487	95	
* 618		488	90	
* Compound not within the definition of the claims				

[0285] The following pro-drug examples were prepared using procedures as described in the general synthetic schemes and working examples above, utilizing the appropriate starting materials as known to those skilled in the art.

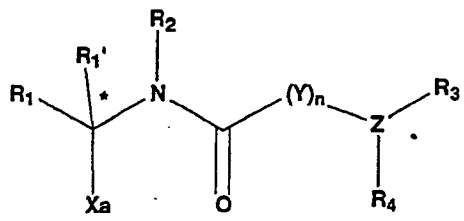
Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
619		539	99	3.27

(continued)

Compound number	Structure	Mass M+H	HPLC Purity (%)	HPLC Retention (min)
620		526	92	2.11
621		540	92	2.12
622		628	94	1.81
623		570	94	2.08
624		654	99	3.46

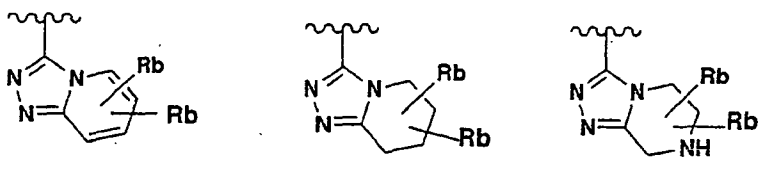
Claims

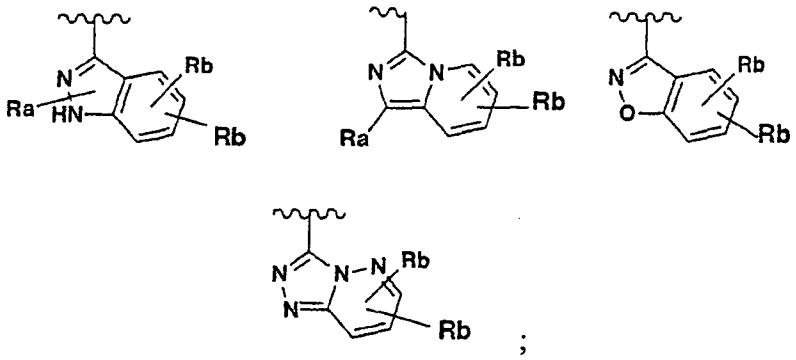
1. A compound of the formula I



I

wherein Xa has the structure





;

R_1 is a substituted or unsubstituted functional group selected from the group consisting of alkyl, aryl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heterocycle, alkoxyalkyl, arylalkyloxyalkyl, aryloxyalkyl, heteroaryl, cycloalkylalkoxyalkyl, heteroarylalkoxy, heteroarylalkyl and heterocycloalkyl;

R_2, R_3 and R_4 are each independently a substituted or unsubstituted functional group selected from the group consisting of hydrogen, alkyl, aryl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heterocycle, alkoxyalkyl, arylalkyloxyalkyl, aryloxyalkyl, heteroaryl, cycloalkylalkoxyalkyl, heteroarylalkyl and heterocycloalkyl, or R_3 and R_4 taken together can form a 3 to 8 membered cycloalkyl or heterocyclic ring, or one or more of R_3 and R_4 can be taken together with one or more of Y and Z to form a mono- or bicyclic cycloalkyl or heterocyclic ring;

R_1' is a substituted or unsubstituted functional group selected from the group consisting of hydrogen, alkyl, cycloalkyl, heterocycle, aryl and heteroaryl;

Y is a linking group selected from the group consisting of alkylene, alkenylene, alkynylene, arylene and heteroarylene, said linking group may optionally be substituted with one or more functional group selected from the group consisting of alkyl, aryl, cycloalkyl, heterocycle, alkoxyalkyl, heteroaryl, arylalkyl, arylalkyloxyalkyl, aryloxyalkyl, cycloalkylalkoxyalkyl, heteroarylalkyl, $-OR_5$, $-OC(O)R_5$, $-CF_3$, $-OCF_3$, $-N(R_5)C(O)R_s$' and $-NR_5R_5$';

R_5 and R_5' for each occurrence are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, heterocycle and aryl, wherein R_5 and R_5' for each occurrence may optionally be substituted with one or more Rb;

Ra and Rb for each occurrence may be absent or are each
independently selected from the group
consisting of alkyl, alkenyl, alkynyl, halogen, cyano, carbonyl, -CN, aryl, arylalkyl, arylalkenyl, arylalkynyl, cycloalkyl, alkoxy, alkoxyalkyl, aryloxy, aryloxyalkyl, heterocycle, heteroaryl, heteroarylalkyl, $-OR_2$, $-NR_5R_5$', $-CF_3$, $-SO_2R_6$, $-OC(O)R_5$,$-SO_2NR_6R_6$', $-(CH_2)_mR_8$ and R_9;

R_6 and R_6' for each occurrence are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkylthioalkyl, alkoxyalkyl, aryl, arylalkyl, heterocycle, heteroaryl, heteroarylalkyl, heterocycloalkyl and cycloalkyl, wherein R_6 and R_6' for each occurrence may optionally be substituted with 1 to 3 substituents selected from the group consisting of halogen, OR_2, alkoxy, heterocycloalkyl, $-NR_5C(O)NR_5R_5$', $-C(O)NR_5R_5$', $-NR_5C(O)R_5$', -CN, $-NR_5SO_2R_5$',$-OC(O)R_5$, $-SO_2NR_5R_5$', $-SOR_7$, -COOH and $-C(O)OR_7$, or R_6 and R_6' taken together can be cyclized to form $-(CH_2)_qX(CH_2)_s-$;

R_7 for each occurrence is independently selected from the group consisting of C_1 to C_6 alkyl, aryl and heteroaryl, wherein R_7 may optionally be substituted with - $(CH_2)_wOH$;

R_8 is selected from the group consisting of alkoxy, alkoxycarbonyl, - $C(O)NR_6R_6$', $-NR_5R_5$', $-C(O)R_6$, $-NR_5C(O)NR_5R_5$' and -N-heteroaryl;

R_9 is selected from the group consisting of heterocycloalkyl, heteroaryl, -CN, $-(CH_2)_pN(R_6)C(O)R_6$', $-(CH_2)_pCN$, $-(CH_2)_pN(R_6)C(O)OR_6$', $-(CH_2)_pN(R_6)C(O)NR_6R_6$', $-(CH_2)_pN(R_6)SO_2R_6$, $-(CH_2)_pC(O)NR_6R_6$', $-(CH_2)_pC(O)OR_6$, $-(CH_2)_pOC(O)OR_6$, $-(CH_2)_pOC(O)R_6$, $-(CH_2)_pOC(O)NR_6R_6$', $-(CH_2)_pN(R_6)SO_2NR_6R_6$', $-(CH_2)_pOR_6$, $-(CH_2)_pOC(O)N(R_6)(CH_2)_mOH$, $-(CH_2)_pSOR_6$ and $-(CH_2)_pOCH_2C(O)N(R_6)(CH_2)_mOH$;

X is selected from the group consisting of $-CR_5R_5$'-, -O-, -S-, -SO-, $-SO_2$-,$-NC(O)OR_7$-, $-NC(O)NR_5$- and $-NR_5$-;

Z is nitrogen;

m is an integer between 1 and 6;

n is an integer from 1 to 6;

p is an integer from 0 to 5;

w is an integer between 0 and 5; and

q and s are each independently an integer between 1 and 3,

with the proviso that R_5, R_5', R_6 or R_6' cannot be hydrogen when either is connected to a carbonyl group or sulfone group.

2. The compound as defined in claim 1 wherein when Ra or Rb are R_9, R_6 is heterocycle or alkyl, optionally substituted with hydroxyl or halogen.

3. The compound as defined in claim 2 wherein R_9 is $(CH_2)_pC(O)OR_6$, $(CH_2)_pOC(O)R_6$, or $(CH_2)_pOC(O)N(R_6)(CH_2)_mOH$.

4. The compound as defined in claim 1 wherein when Ra or Rb are R_9, R_6 and R_6' are independently hydrogen, alkyl, or cycloalkyl, where the alkyl or cycloalkyl is optionally substituted with $-C(O)OR_7$ or $-C(O)NR_5R_5$', or R_6 and R_6' taken together can be cyclized to form $-(CH_2)_qX(CH_2)_s-$.

5. The compound as defined in claim 4 wherein R_9 is $-(CH_2)_pN(R_6)C(O)OR_6$', $-(CH_2)_pN(R_6)C(O)NR_6R_6$', or $(CH_2)_pOC(O)NR_6R_6$', where R_6 and R_6' are independently hydrogen or alkyl, where the alkyl is optionally substituted with $-C(O)NR_5R_5$', where R_5 and R_5' are independently hydrogen or alkyl.

6. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 5 and a pharmaceutically acceptable carrier therefor.

7. The pharmaceutical composition of claim 6 further comprising at least one additional therapeutic agent selected from the group consisting of other compounds of formula I, parathyroid hormone, bisphosphonates, estrogen, testosterone, selective estrogen receptor modulators, selective androgen receptor modulators, progestin receptor agonists, anti-diabetic agents, anti-hypertensive agents, anti-inflammatory agents, anti-osteoporosis agents, anti-obesity agents, cardiac glycosides, cholesterol lowering agents and thyroid mimetics.

8. A compound as defined in any one of claims 1 to 5 for use for increasing levels of endogenous growth hormone.

9. A compound as defined in any one of claims 1 to 5 for use in treating or delaying the progression or onset of HIV wasting syndrome, muscular atrophy, lipodistrophy, long term critical illness,
osteoporosis, sarcopenia, frailty or ARFD in the elderly, obesity, renal disease, anorexia, sleep disorders, depression, Syndrome X, diabetes, congestive heart failure, cardiac myopathy, cardiac dysfunction associated with valvular disease and cachexia.

10. The compound for use according to claim 9, wherein the use comprises administering, concurrently or sequentially, a therapeutically effective amount of at least one additional therapeutic agent selected from the group consisting of other compounds of formula I, parathyroid hormone, bisphosphonates, estrogen, testosterone, selective estrogen receptor modulators, selective androgen receptor modulators, progestin receptor agonists, anti-diabetic agents, anti-hypertensive agents, anti-inflammatory agents, anti-osteoporosis agents, anti-obesity agents, cardiac glycosides, cholesterol lowering agents and thyroid mimetics.

11. A compound as defined in any one of claims 1 to 5 for use for stimulating wound healing and/or the immune system.

12. A compound as defined in any one of claims 1 to 5 for use for increasing muscle mass and/or strength or maintaining muscle strength and function in the elderly, increasing lean body mass, or for improving the cognitive function, or for improving the immune response to vaccination, or for accelerating the recovery of hip fracture.

13. The pharmaceutical composition of claim 6 further comprising at least one nutritional supplement

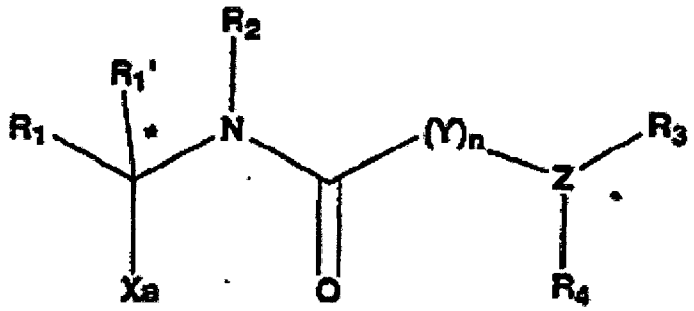
14. A compound as defined in any one of claims 1 to 5 for the preparation of a pharmaceutical composition for increasing levels of endogenous growth hormone; for increasing muscle mass and/or strength or maintaining muscle strength and function in the elderly, increasing lean body mass, or for improving cognitive function, or for improving the immune response to vaccination, or for accelerating the recovery of hip fracture; for stimulating wound healing and/or the immune system; for treating or delaying the progression or onset of HIV wasting syndrome, muscular atrophy, lipodistrophy, long term critical illness, osteoporosis, sarcopenia, frailty or ARFD in the elderly, obesity, renal disease, anorexia, sleep disorders, depression, Syndrome X, diabetes, congestive heart failure, cardiac myopathy, cardiac dysfunction associated with valvular disease and cachexia.

15. The use according to claim 14, wherein the use comprises administering, concurrently or sequentially, a therapeutically effective amount of at least one additional therapeutic agent selected from the group consisting of other compounds of formula I, parathyroid hormone, bisphosphonates, estrogen, testosterone, selective estrogen receptor

modulators, selective androgen receptor modulators, progestin receptor agonists, anti-diabetic agents, anti-hypertensive agents, anti-inflammatory agents, anti-osteoporosis agents, anti-obesity agents, cardiac glycosides, cholesterol lowering agents and thyroid mimetics.

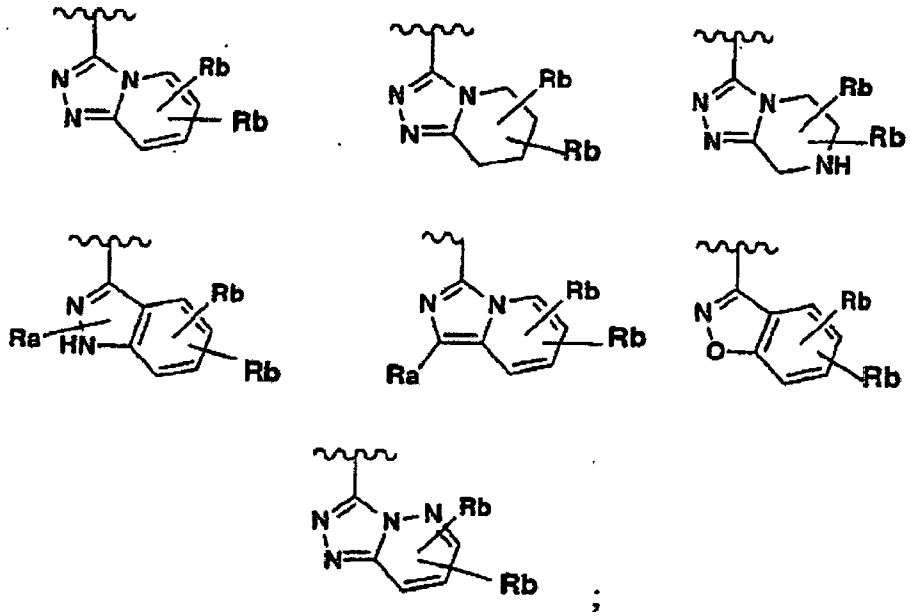
Patentansprüche

1. Verbindung der Formel I:



I

wobei Xa folgende Struktur aufweist:



;

R_1 eine substituierte oder unsubstituierte funktionelle Gruppe ist, die ausgewählt wird aus Alkyl, Aryl, Alkenyl, Alkinyl, Arylalkyl, Cycloalkyl, Heterocyclus, Alkoxyalkyl, Arylalkyloxyalkyl, Aryloxyalkyl, Heteroaryl, Cycloalkylalkoxyalkyl, Heteroarylalkoxy, Heteroarylalkyl und Heterocycloalkyl;

R_2, R_3 und R_4 jeweils unabhängig voneinander eine substituierte oder unsubstituierte funktionelle Gruppe sind, die ausgewählt werden aus Wasserstoff, Alkyl, Aryl, Alkenyl, Alkinyl, Arylalkyl, Cycloalkyl, Heterocyclus, Alkoxyalkyl, Arylalkyloxyalkyl, Aryloxyalkyl, Heteroaryl, Cycloalkylalkoxyalkyl, Heteroarylalkyl und Heterocycloalkyl oder R_3 und R_4 zusammen einen 3- bis 8-gliedrigen Cycloalkyl- oder heterocyclischen Ring bilden können oder eines oder mehrere von R_3 und R_4 mit einem oder mehreren von Y und Z zusammengenommen werden können, um einen mono- oder bicyclischen Cycloalkyl- oder heterocyclischen Ring zu bilden;

R_1' eine substituierte oder unsubstituierte funktionelle Gruppe ist, die ausgewählt wird aus Wasserstoff, Alkyl, Cycloalkyl, Heterocyclus, Aryl und Heteroaryl;

Y eine Verknüpfungsgruppe ist, die ausgewählt wird aus Alkylen, Alkenylen, Alkinylen, Arylen und Heteroarylen,

wobei die Verknüpfungsgruppe gegebenenfalls mit einer oder mehreren funktionellen Gruppen substituiert sein kann, die ausgewählt werden aus Alkyl, Aryl, Cycloalkyl, Heterocyclus, Alkoxyalkyl, Heteroaryl, Arylalkyl, Arylalkyloxyalkyl, Aryloxyalkyl, Cycloalkylalkoxyalkyl, Heteroarylalkyl, $-OR_5$,$-OC(O)R_5$, $-CF_3$, $-OCF_3$, $-N(R_5)C(O)R_5$' und $-NR_5R_5$';

R_5 und R_5' für jedes Vorkommen jeweils unabhängig voneinander ausgewählt werden aus Wasserstoff, Alkyl, Cycloalkyl, Heterocyclus und Aryl, wobei R_5 und R_5' für jedes Vorkommen gegebenenfalls mit einem oder mehreren Rb substituiert sein können;

Ra und Rb für jedes Vorkommen fehlen können oder jeweils unabhängig voneinander ausgewählt werden aus Alkyl, Alkenyl, Alkinyl, Halogen, Cyano, Carbonyl, -Cn, Aryl, Arylalkyl, Arylalkenyl, Arylalkinyl, Cycloalkyl, Alkoxy, Alkoxyalkyl, Aryloxy, Aryloxyalkyl, Heterocyclus, Heteroaryl, Heteroarylalkyl, $-OR_2$, $-NR_5R_5$', $-CF_3$, $-SO_2R_6$ $-OC(O)R_5$, $-SO_2NR_6R_6$', $-(CH_2)_mR_8$ und R_9;

R_6 und R_6' für jedes Vorkommen jeweils unabhängig voneinander ausgewählt werden aus Wasserstoff, Alkyl, Alkenyl, Alkinyl, Alkylthioalkyl, Alkoxyalkyl, Aryl, Arylalkyl, Heterocyclus, Heteroaryl, Heteroarylalkyl, Heterocycloalkyl und Cycloalkyl, wobei R_6 und R_6' für jedes Vorkommen optional mit 1 bis 3 Substituenten substituiert sein können, die ausgewählt werden aus Halogen, OR_2, Alkoxy, Heterocycloalkyl, $-NR_5C(O)NR_5R_5$', $-C(O)NR_5R_5$', $-NR_5C(O)R_5$', -CN, $-NR_5SO_2R_5$', $-OC(O)R_5$, $-SO_2NR_5R_5$', $-SOR_7$, -COOH und $-C(O)OR_7$ oder R_6 und R_6' zusammengenommen cyclisiert werden können, um $-(CH_2)_qX(CH_2)_s-$ zu bilden;

R_7 für jedes Vorkommen unabhängig ausgewählt wird aus C_1- bis C_6-Alkyl, Aryl und Heteroaryl, wobei R_7 optional mit $-(CH_2)_wOH$ substituiert sein kann;

R_8 ausgewählt wird aus Alkoxy, Alkoxycarbonyl, $-C(O)NR_6R_6$', $-NR_5R_5$', $-C(O)R_6$, $-NR_5C(O)NR_5R_5$' und -N-Heteroaryl;

R_9 ausgewählt wird aus Heterocycloalkyl, Heteroaryl, -CN, $-(CH_2)_pN(R_6)C(O)R_6$', $-(CH_2)_pCN$, $-(CH_2)_pN(R_6)C(O)OR_6$', $-(CH_2)_pN(R_6)C(O)NR_6R_6$', $-(CH_2)_pN(R_6)SO_2R_6$, $-(CH_2)_pC(O)NR_6R_6$', $-(CH_2)_pC(O)OR_6$, $-(CH_2)_pOC(O)OR_6$, $-(CH_2)_pOC(O)R_6$, $-(CH_2)_pOC(O)NR_6R_6$', $-(CH_2)_pN(R_6)SO_2NR_6R_6$', $-(CH_2)_pOR_6$, $-(CH_2)_pOC(O)N(R_6)(CH_2)_mOH$, $-(CH_2)_pSOR_6$ und $-(CH_2)_pOCH_2C(O)N(R_6)(CH_2)_mOH$;

X ausgewählt wird aus $-CR_5R_5$'-, -O-, -S-, -SO-, $-SO_2$-, $-NC(O)OR_7$-, $-NC(O)NR_5$- und $-NR_5$-;

Z Stickstoff ist;

m eine ganze Zahl zwischen 1 und 6 ist;

n eine ganze Zahl von 1 bis 6 ist;

p eine ganze Zahl von 0 bis 5 ist;

w eine ganze Zahl zwischen 0 und 5 ist und

q und s jeweils unabhängig eine ganze Zahl zwischen 1 und 3 sind,

mit der Maßgabe, dass R_5, R_5', R_6 oder R_6' nicht Wasserstoff sein können, wenn eines von ihnen mit einer Carbonylgruppe oder Sulfongruppe verbunden ist.

2. Verbindung nach Anspruch 1, wobei, wenn Ra oder Rb R_9 sind, R_6 ein Heterocyclus oder Alkyl ist, optional substituiert mit Hydroxyl oder Halogen.

3. Verbindung nach Anspruch 2, wobei R_9 $(CH_2)_pC(O)OR_6$, $(CH_2)_pOC(O)R_6$ oder $(CH_2)_pOC(O)N(R_6)(CH_2)_mOH$ ist.

4. Verbindung nach Anspruch 1, wobei, wenn Ra oder Rb R_9 sind, R_6 und R_6' unabhängig voneinander Wasserstoff, Alkyl oder Cycloalkyl sind, wobei das Alkyl oder Cycloalkyl optional mit $-C(O)OR_7$ oder $-C(O)NR_5R_5$' substituiert ist oder R_6 und R_6' zusammengenommen cyclisiert werden können, um $-(CH_2)_qX(CH_2)_s-$ zu bilden.

5. Verbindung nach Anspruch 4, wobei R_9 $-(CH_2)_pN(R_6)C(O)OR_6$', $-(CH_2)_pN(R_6)C(O)NR_6R_6$' oder $(CH_2)_pOC(O)NR_6R_6$' ist, wobei R_6 und R_6' unabhängig voneinander Wasserstoff oder Alkyl sind, wobei das Alkyl optional mit $-C(O)NR_5R_5$' substituiert ist, wobei R_5 und R_5' unabhängig voneinander Wasserstoff oder Alkyl sind.

6. Pharmazeutische Zusammensetzung, die eine Verbindung nach einem der Ansprüche 1 bis 5 und einen pharmazeutisch verträglichen Träger dafür umfasst.

7. Pharmazeutische Zusammensetzung nach Anspruch 6, die ferner mindestens ein zusätzliches therapeutisches Mittel umfasst, das ausgewählt wird aus anderen Verbindungen der Formel 1, Nebenschilddrüsenhormon, Bisphosphonaten, Östrogen, Testosteron, selektiven Östrogenrezeptormodulatoren, selektiven Androgenrezeptormodulatoren, Progestinrezeptoragonisten, Antidiabetesmittel, Antihypertonika, entzündungshemmenden Mitteln, Antiosteoporosemitteln, Antifettleibigkeitsmitteln, Herzglykosiden, Cholesterinspiegelsenkungsmitteln und Schilddrüsenmimetika.

8. Verbindung nach einem der Ansprüche 1 bis 5 zur Verwendung zur Erhöhung des Niveaus des endogenen Wachstumshormons.

9. Verbindung nach einem der Ansprüche 1 bis 5 zur Verwendung bei der Behandlung oder Verzögerung der Progression oder des Beginns von Folgendem: HIV-Auszehrungssyndrom, Muskelatrophie, Lipodistrophie, kritische Langzeiterkrankung, Osteoporose, Sarkopenie, Gebrechlichkeit oder ARFD bei älteren Menschen, Fettleibigkeit, Nierenkrankheit, Anorexie, Schlafstörungen, Depressionen, Syndrom X, Diabetes, kongestive Herzinsuffizienz, Herzmyopathie, Herzdysfunktion assoziiert mit Klappenerkrankungen und Kachexie.

10. Verbindung zur Verwendung nach Anspruch 9, wobei die Verwendung die gleichzeitige oder sequentielle Verabreichung einer therapeutisch wirksamen Menge mindestens eines zusätzlichen therapeutischen Mittels umfasst, das ausgewählt wird aus anderen Verbindungen der Formel I, Nebenschilddrüsenhormon, Bisphosphonaten, Östrogen, Testosteron, selektiven Östrogenrezeptormodulatoren, selektiven Androgenrezeptormodulatoren, Progestinrezeptoragonisten, Antidiabetesmitteln, Antihypertonika, entzündungshemmenden Mitteln, Antiosteoporosemitteln, Antifettleibigkeitsmitteln, Herzglykosiden, Cholesterinspiegelsenkungsmitteln und S childdrüsenmimetika.

11. Verbindung nach einem der Ansprüche 1 bis 5 zur Verwendung zur Stimulierung der Wundheilung und/oder des Immunsystems.

12. Verbindung nach einem der Ansprüche 1 bis 5 zur Verwendung bei der Erhöhung der Muskelmasse und/oder der Muskelkraft oder der Aufrechterhaltung der Muskelkraft und der Muskelfunktion bei älteren Menschen, der Erhöhung der mageren Körpermasse oder zur Verbesserung der kognitiven Funktion oder zur Verbesserung der Immunantwort auf Impfungen oder zur Beschleunigung der Erholung von Hüftfrakturen.

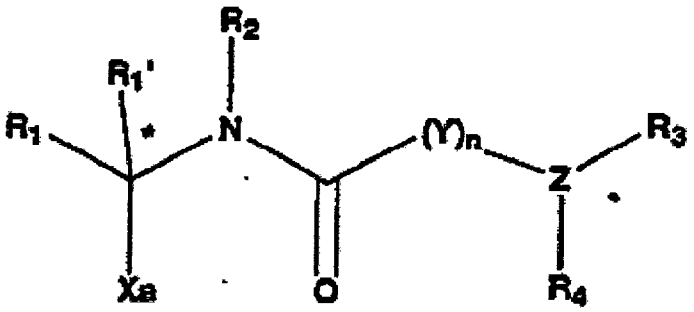
13. Pharmazeutische Zusammensetzung nach Anspruch 6, die ferner mindestens ein Nahrungsergänzungsmittel umfasst.

14. Verbindung nach einem der Ansprüche 1 bis 5 zur Herstellung einer pharmazeutischen Zusammensetzung zur Erhöhung des Niveaus des endogenen Wachstumshormons; zur Erhöhung der Muskelmasse und/oder der Muskelkraft oder zur Aufrechterhaltung der Muskelkraft und -funktion bei älteren Menschen, zur Erhöhung der mageren Körpermasse oder zur Verbesserung der kognitiven Funktion oder zur Verbesserung der Immunantwort auf Impfungen oder zur Beschleunigung der Erholung von Hüftfrakturen; zur Stimulierung der Wundheilung und/oder des Immunsystems; zur Behandlung oder Verzögerung der Progression oder des Beginns von Folgendem: HIV-Auszehrungssyndrom, Muskelatrophie, Lipodistrophie, kritische Langzeiterkrankung, Osteoporose, Sarkopenie, Gebrechlichkeit oder ARFD bei älteren Menschen, Fettleibigkeit, Nierenkrankheit, Anorexie, Schlafstörungen, Depressionen, Syndrom X, Diabetes, kongestive Herzinsuffizienz, Herzmyopathie, Herzdysfunktion assoziiert mit Klappenerkrankungen und Kachexie.

15. Verwendung nach Anspruch 14, wobei die Verwendung die gleichzeitige oder sequentielle Verabreichung einer therapeutisch wirksamen Menge mindestens eines zusätzlichen therapeutischen Mittels umfasst, das ausgewählt wird aus anderen Verbindungen der Formel I, Nebenschilddrüsenhormon, Bisphosphonaten, Östrogen, Testosteron, selektiven Östrogenrezeptormodulatoren, selektiven Androgenrezeptormodulatoren, Progestinrezeptoragonisten, Antidiabetesmittel, Antihypertonika, entzündungshemmenden Mitteln, Antiosteoporosemitteln, Antifettleibigkeitsmitteln, Herzglykosiden, Cholesterinspiegelsenkungsmitteln und Schilddrüsenmimetika.

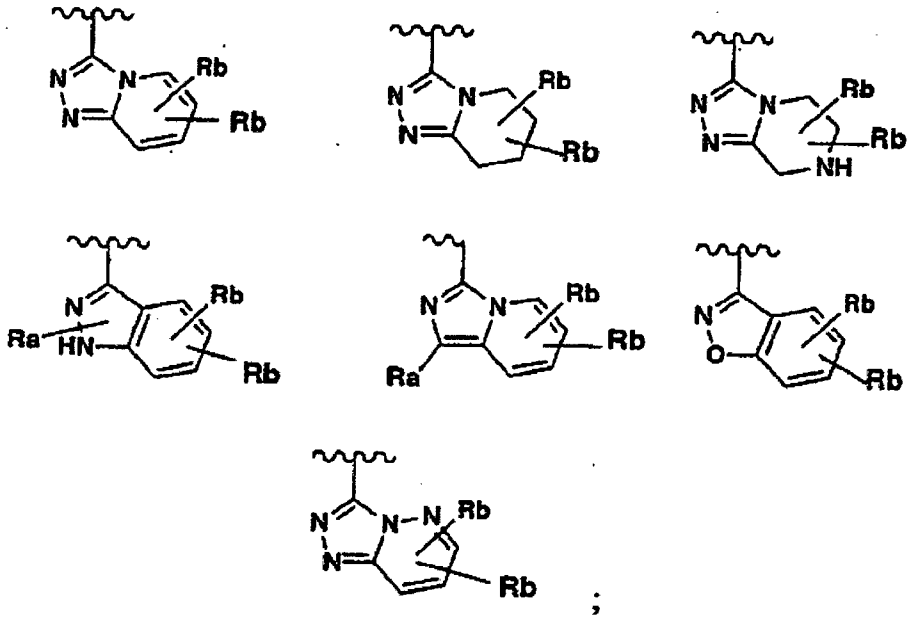
Revendications

1. Composé de la formule I:



I

dans lequel Xa présente la structure:



R_1 est un groupe fonctionnel substitué ou non substitué choisi parmi un alkyle, un aryle, un alcényle, un alcynyle, un arylalkyle, un cycloalkyle, un hétérocycle, un alcoxyalkyle, un arylalkyloxyalkyle, un aryloxyalkyle, un hétéroaryle, un cycloalkylalcoxyalkyle, un hétéroarylalcoxy, un hétéroarylalkyle et un hétérocycloalkyle;

R_2, R_3 et R_4 sont chacun indépendamment un groupe fonctionnel substitué ou non substitué choisi parmi un hydrogène, un alkyle, un aryle, un alcényle, un alcynyle, un arylalkyle, un cycloalkyle, un hétérocycle, un alcoxyalkyle, un arylalkyloxyalkyle, un aryloxyalkyle, un hétéroaryle, un cycloalkylalcoxyalkyle, un hétéroarylalkyle et un hétérocycloalkyle, ou R_3 et R_4 pris ensemble peuvent former un cycle cycloalkyle ou hétérocyclique de 3 à 8 membres, ou un ou plus de R_3 et R_4 peuvent être pris ensemble avec un ou plus de Y et Z pour former un cycle cycloalkyle ou hétérocyclique mono- ou bicyclique;

$R_{1'}$ est un groupe fonctionnel substitué ou non substitué choisi parmi un hydrogène, un alkyle, un cycloalkyle, un hétérocycle, un aryle et un hétéroaryle;

Y est un groupe de liaison choisi parmi un alkylène, un alcénylène, un alcynylène, un arylène et un hétéroarylène, ledit groupe de liaison peut optionnellement être substitué avec un ou plusieurs groupes fonctionnels choisis parmi un alkyle, un aryle, un cycloalkyle, un hétérocycle, un alcoxyalkyle, un hétéroaryle, un arylalkyle, un arylalkyloxyalkyle, un aryloxyalkyle, un cycloalkylalcoxyalkyle, un hétéroarylalkyle, - OR_5, $-OC(O)R_5$, $-CF_3$, $-OCF_3$, $-N(R_5)C(O)R_5$' et $-NR_5R_5$';

R_5 et R_5' pour chaque occurrence sont chacun indépendamment choisis parmi un hydrogène, un alkyle, un cycloalkyle, un hétérocycle et un aryle, dans lequel R_5 et R_5' pour chaque occurrence peuvent optionnellement être substitués avec un ou plusieurs Rb;

Ra et Rb pour chaque occurrence peuvent être absents ou sont chacun indépendamment choisis parmi un alkyle, un alcényle, un alcynyle, un halogène, un cyano, un carbonyle, -CN, un aryle, un arylalkyle, un arylal-

cényle, un arylalcynyle, un cycloalkyle, un alcoxy, un alcoxyalkyle, un aryloxy, un aryloxyalkyle, un hétérocycle, un hétéroaryle, un hétéroarylalkyle, $-OR_2$, $-NR_5R_5'$, $-CF_3$, $-SO_2R_6$, $-OC(O)R_5$, $-SO_2NR_6R_6'$, $-(CH_2)_mR_8$ et R_9;
R_6 et R_6' pour chaque occurrence sont chacun indépendamment choisis parmi un hydrogène, un alkyle, un alcényle, un alcynyle, un alkylthioalkyle, un alcoxyalkyle, un aryle, un arylalkyle, un hétérocycle, un hétéroaryle, un hétéroarylalkyle, un hétérocycloalkyle et un cycloalkyle, dans lequel R_6 et R_6' pour chaque occurrence peuvent optionnellement être substitués avec 1 à 3 substituants choisis parmi un halogène, OR_2, un alcoxy, un hétérocycloalkyle, $-NR_5C(O)NR_5R_5'$, $-C(O)NR_5R_5'$, $-NR_5C(O)R_5'$, - CN, $-NR_5SO_2R_5'$, $-OC(O)R_5$, $-SO_2NR_5R_5'$, $-SOR_7$, -COOH et $-C(O)OR_7$, ou R_6 et R_6' pris ensemble peuvent être cyclisés pour former $-(CH_2)_qX(CH_2)_s-$;
R_7 pour chaque occurrence est indépendamment choisi parmi un C_1 à C_6 alkyle, un aryle et un hétéroaryle, dans lequel R_7 peut optionnellement être substitué avec $-(CH_2)_wOH$;
R_8 est choisi parmi un alcoxy, un alcoxycarbonyle, $-C(O)NR_6R_6'$, $-NR_5R_5'$, -, $C(O)R_6$, $-NR_5C(O)NR_5R_5'$ et un -N-hétéroaryle;
R_9 est choisi parmi un hétérocycloalkyle, un hétéroaryle, -CN, $-(CH_2)_pN(R_6)C(O)R_6'$, $-(CH_2)_pCN$, $-(CH_2)_pN(R_6)C(O)OR_6'$, $-(CH_2)_pN(R_6)C(O)NR_6R_6'$, $-(CH_2)_pN(R_6)SO_2R_6$, $-(CH_2)_pC(O)NR_6R_6'$, $-(CH_2)_pC(O)OR_6$, $-(CH_2)_pOC(O)OR_6$, $-(CH_2)_pOC(O)R_6$, $-(CH_2)_pOC(O)NR_6R_6'$, $-(CH_2)_pN(R_6)SO_2NR_6R_6'$, $-(CH_2)_pOR_6$, $-(CH_2)_pOC(O)N(R_6)(CH_2)_mOH$, $-(CH_2)_pSOR_6$ et $-(CH_2)_pOCH_2C(O)N(R_6)(CH_2)_mOH$;
X est choisi parmi $-CR_5R_5'-$, -O-, -S-, -SO-, $-SO_2-$, $-NC(O)OR_7-$, $-NC(O)NR_5-$ et $-NR_5-$;
Z est un azote;
m est un nombre entier entre 1 et 6;
n est un nombre entier de 1 à 6;
p est un nombre entier de 0 à 5;
w est un nombre entier entre 0 et 5; et
q et s sont chacun indépendamment un nombre entier entre 1 et 3,
sous réserve que R_5, R_5', R_6 ou R_6' ne puisse pas être un hydrogène lorsque l'un ou l'autre est relié à un groupe carbonyle ou un groupe sulfone.

2. Composé selon la revendication 1, dans lequel lorsque Ra ou Rb sont R_9, R_6 est un hétérocycle ou un alkyle, optionnellement substitué avec un hydroxyle ou un halogène.

3. Composé selon la revendication 2, dans lequel R_9 est $(CH_2)_pC(O)OR_6$, $(CH_2)_pOC(O)R_6$ ou $(CH_2)_pOC(O)N(R_6)(CH_2)_mOH$.

4. Composé selon la revendication 1, dans lequel lorsque Ra ou Rb sont R_9, R_6 et R_6' sont indépendamment un hydrogène, un alkyle ou un cycloalkyle, où l'alkyle ou le cycloalkyle est optionnellement substitué avec $-C(O)OR_7$ ou $-C(O)NR_5R_5'$, ou R_6 et R_6' pris ensemble peuvent être cyclisés pour former $-(CH_2)_qX(CH_2)_s-$.

5. Composé selon la revendication 4, dans lequel R_9 est $-(CH_2)_pN(R_6)C(O)OR_6'$, $-(CH_2)_pN(R_6)C(O)NR_6R_6'$ ou $(CH_2)_pOC(O)NR_6R_6'$, où R_6 et R_6' sont indépendamment un hydrogène ou un alkyle, où l'alkyle est optionnellement substitué avec $-C(O)NR_5R_5'$, où R_5 et R_5' sont indépendamment un hydrogène ou un alkyle.

6. Composition pharmaceutique comprenant un composé selon l'une quelconque des revendications 1 à 5 et un véhicule pharmaceutiquement acceptable pour celui-ci.

7. Composition pharmaceutique selon la revendication 6 comprenant en outre au moins un agent thérapeutique supplémentaire choisi parmi d'autres composés de la formule I, une hormone parathyroïde, des bisphosphonates, un oestrogène, la testostérone, des modulateurs sélectifs de récepteur d'oestrogène, des modulateurs sélectifs de récepteur d'androgène, des agonistes de récepteur de progestine, des agents antidiabétiques, des agents antihypertenseurs, des agents anti-inflammatoires, des agents anti-ostéoporose, des agents anti-obésité, des glycosides cardiaques, des agents abaissant le cholestérol et des mimétiques de thyroïde.

8. Composé selon l'une quelconque des revendications 1 à 5 pour une utilisation pour l'augmentation des niveaux d'hormone de croissance endogène.

9. Composé selon l'une quelconque des revendications 1 à 5 pour une utilisation dans le traitement ou le retardement de la progression ou de l'apparition de: syndrome cachectique du VIH, atrophie musculaire, lipodystrophie, maladie critique à long terme, ostéoporose, sarcopénie, fragilité ou ARFD chez les personnes âgées, obésité, maladie rénale, anorexie, troubles du sommeil, dépression, syndrome X, diabète, insuffisance cardiaque congestive, myopathie

cardiaque, dysfonctionnement cardiaque associé à une maladie valvulaire et une cachexie.

10. Composé selon la revendication 9, dans lequel l'utilisation comprend l'administration, simultanément ou séquentiellement, d'une quantité thérapeutiquement efficace d'au moins un agent thérapeutique supplémentaire choisi parmi d'autres composés de la formule I, une hormone parathyroïde, des bisphosphonates, un oestrogène, la testostérone, des modulateurs sélectifs de récepteur d'oestrogène, des modulateurs sélectifs de récepteur d'androgène, des agonistes de récepteur de progestine, des agents antidiabétiques, des agents antihypertenseurs, des agents anti-inflammatoires, des agents anti-ostéoporose, des agents anti-obésité, des glycosides cardiaques, des agents abaissant le cholestérol et des mimétiques de thyroïde.

11. Composé selon l'une quelconque des revendications 1 à 5 pour une utilisation pour la stimulation de la cicatrisation et/ou du système immunitaire.

12. Composé selon l'une quelconque des revendications 1 à 5 pour une utilisation pour l'augmentation de la masse et/ou de la force musculaires ou le maintien de la force et de la fonction musculaires chez les personnes âgées, l'augmentation de la masse corporelle maigre ou pour l'amélioration de la fonction cognitive ou pour l'amélioration de la réponse immunitaire à une vaccination ou pour l'accélération de la récupération d'une fracture de la hanche.

13. Composition pharmaceutique selon la revendication 6 comprenant en outre au moins un complément nutritionnel.

14. Composé selon l'une quelconque des revendications 1 à 5 pour la préparation d'une composition pharmaceutique pour l'augmentation des niveaux d'hormone de croissance endogène; pour l'augmentation de la masse et/ou de la force musculaires ou le maintien de la force et de la fonction musculaires chez les personnes âgées, l'augmentation de la masse corporelle maigre ou pour l'amélioration de la fonction cognitive ou pour l'amélioration de la réponse immunitaire à une vaccination ou pour l'accélération de la récupération d'une fracture de la hanche; pour la stimulation de la cicatrisation et/ou du système immunitaire; pour le traitement ou le retardement de la progression ou de l'apparition de: syndrome cachectique du VIH, atrophie musculaire, lipodystrophie, maladie critique à long terme, ostéoporose, sarcopénie, fragilité ou ARFD chez les personnes âgées, obésité, maladie rénale, anorexie, troubles du sommeil, dépression, syndrome X, diabète, insuffisance cardiaque congestive, myopathie cardiaque, dysfonctionnement cardiaque associé à une maladie valvulaire et une cachexie.

15. Utilisation selon la revendication 14, où l'utilisation comprend l'administration, simultanément ou séquentiellement, d'une quantité thérapeutiquement efficace d'au moins un agent thérapeutique supplémentaire choisi parmi d'autres composés de la formule I, une hormone parathyroïde, des bisphosphonates, un oestrogène, la testostérone, des modulateurs sélectifs de récepteur d'oestrogène, des modulateurs sélectifs de récepteur d'androgène, des agonistes de récepteur de progestine, des agents antidiabétiques, des agents antihypertenseurs, des agents anti-inflammatoires, des agents anti-ostéoporose, des agents anti-obésité, des glycosides cardiaques, des agents abaissant le cholestérol et des mimétiques de thyroïde.

REFERENCES CITED IN THE DESCRIPTION

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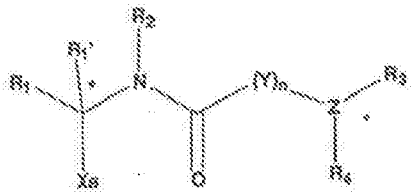
EP 2570414

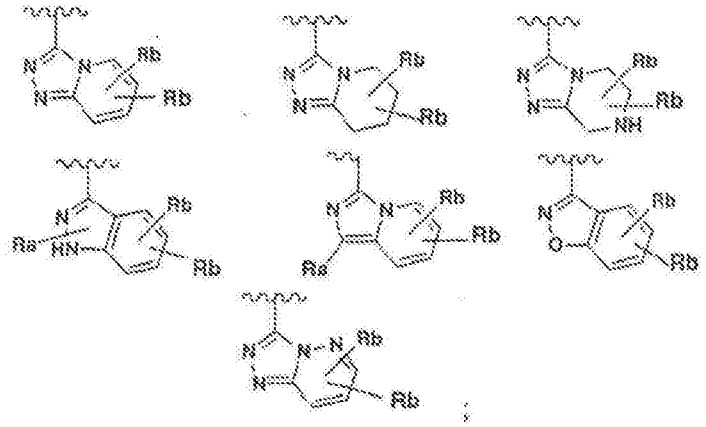
SZABADALMI IGÉNYPONTOK

1. A képlet I szerinti vegyület



I

ahol Xa szerkezete



;

R_1 szubsztituált vagy szubsztituálatlan funkcionális csoport, amely ki van választva a következőkből álló csoportból: alkil, aril, alkenil, alkinil, arilalkil, cikloalkil, heterociklus, alkoxialkil, arilalkiloxialkil, ariloxialkil, heteroaril, cikloalkilalkoxialkil, heteroarilalkoxi, heteroarilalkil és heterocikloalkil;

R_2, R_3 és R_4 mindegyik függetlenül szubsztituált vagy szubsztituálatlan funkcionális csoport, amely ki van választva a következőkből álló csoportból: hidrogén, alkil, aril, alkenil, alkinil, arilalkil, cikloalkil, heterociklus, alkoxialkil, arilalkiloxialkil, ariloxialkil, heteroaril, cikloalkilalkoxialkil, heteroarilalkil és heterocikloalkil, vagy R_3 és R_4 együtt véve 3-8 tagú cikloalkil vagy heterociklusos gyűrűt tud alkotni, vagy egy vagy több R_3 és R_4 együtt lehet véve egy vagy több Y-al és Z-vel, hogy mono- vagy biciklikus cikloalkil vagy heterociklusos gyűrűt tudjon alkotni;

R_1' szubsztituált vagy szubsztituálatlan funkcionális csoport, amely ki van választva a következőkből álló csoportból: hidrogén, alkil, cikloalkil, heterociklus, aril és heteroaril;

Y összekötő csoport, amely ki van választva a következőkből álló csoportból: alkilén, alkenylén, alkinilén, arilén és heteroarilén, az összekötő csoport opcionálisan szubsztituálható lehet egy vagy több funkcionális csoporttal, amely ki van választva a következőkből álló csoportból: alkil, aril, cikloalkil, heterociklus, alkoxialkil, heteroaril, arilalkil, arilalkiloxialkil, ariloxialkil, cikloalkilalkoxialkil, heteroarilalkil, $-OR_5$, $-OC(O)R_5$, $-CF_3$, $-OCF_3$, $-N(R_5)C(O)R_5'$ és $-NR_5R_5'$;

R_5 és R_5' mindegyik előfordulásban mindegyik függetlenül ki van választva a következőkből álló csoportból: hidrogén, alkil, cikloalkil, heterociklus és aril, ahol R_5 és R_5' mindegyik előfordulásban opcionálisan szubsztituálható lehet egy vagy több Rb-vel;

Ra és Rb mindegyik előfordulásban hiányozhat vagy mindegyik

függetlenül ki van választva a következőkből álló csoportból:

alkil, alkenil, alkinil, halogén, ciano, karbonil, -CN, aril, arilalkil, arilalkenil, arilalkinil, cikloalkil, alkoxi, alkoxialkil, ariloxi, ariloxialkil, heterociklus, heteroaril, heteroarilalkil, $-OR_2$, $-NR_3R_3'$, $-CF_3$, $-SO_2R_6$, $-OC(O)R_3$, $-SO_2NR_6R_6'$, $-(CH_2)_mR_9$ és R_6;

R_6 és R_6' mindegyik előfordulásban mindegyik függetlenül ki van választva a következőkből álló csoportból: hidrogén, alkil, alkenil, alkinil, alkilhioalkil, alkoxialkil, aril, arilalkil, heterociklus, heteroaril, heteroarilalkil, heterocikloalkil és cikloalkil, ahol R_6 és R_6' mindegyik előfordulásban opcionálisan szubsztituálható lehet 1-3 szubsztituenssel, amely ki van választva a következőkből álló csoportból: halogén, OR_2, alkoxi, heterocikloalkil, $-NR_3C(O)NR_3R_3'$, $-C(O)NR_3R_3'$, $-NR_3C(O)R_3'$, -CN, $-NR_3SO_2R_3'$, $-OC(O)R_3$, $-SO_2NR_3R_3'$, $-SOR_3$, -COOH és $-C(O)OR_3$, vagy R_6 és R_6' együtt véve lehet ciklizált, hogy a következőt alkossa: $-(CH_2)_qX(CH_2)_s-$;

R_7 mindegyik előfordulásban függetlenül ki van választva a következőkből álló csoportból: C_1-től C_6-ig alkil, aril és heteroaril, ahol R_7 opcionálisan szubsztituálható lehet $-(CH_2)_nOH$-val;

R_8 ki van választva a következőkből álló csoportból: alkoxi, alkoxikarbonil, $-C(O)NR_6R_6'$, $-NR_3R_3'$, $-C(O)R_6$, $-NR_3C(O)NR_3R_3'$ és -N-heteroaril;

R_9 ki van választva a következőkből álló csoportból: heterocikloalkil, heteroaril, -CN, $-(CH_2)_pN(R_6)C(O)R_6'$, $-(CH_2)_pCN$, $-(CH_2)_pN(R_6)C(O)OR_6'$, $-(CH_2)_pN(R_6)C(O)NR_6R_6'$, $-(CH_2)_pN(R_6)SO_2R_6$, $-(CH_2)_pC(O)NR_6R_6'$, $-(CH_2)_pC(O)OR_6$, $-(CH_2)_pOC(O)OR_6$, $-(CH_2)_pOC(O)R_6$, $-(CH_2)_pOC(O)NR_6R_6'$, $-(CH_2)_pN(R_6)SO_2NR_6R_6'$, $-(CH_2)_pOR_6$, $-(CH_2)_pOC(O)N(R_6)(CH_2)_mOH$, $-(CH_2)_pSOR_6$ és $-(CH_2)_pOCH_2C(O)N(R_6)(CH_2)_mOH$;

X ki van választva a következőkből álló csoportból: $-CR_3R_3'-$, -O-, -S-, -SO-, $-SO_2-$, $-NC(O)OR_6-$, $-NC(O)NR_6-$ és $-NR_6-$;

Z nitrogén;

m egész 1 és 6 között;

n egész 1-től 6-ig;

p egész 0-tól 5-ig;

w egész 0 és 5 között; és

q és s mindegyik függetlenül egész 1 és 3 között,

feltéve, hogy R_3, R_3', R_6 vagy R_6' nem lehet hidrogén, ha bármelyik kapcsolódik karbonil csoporthoz vagy szulfon csoporthoz.

2. Az 1. igénypontban definiált vegyület, ahol, ha Ra vagy Rb R_9, R_8 heterociklus vagy alkil, opcionálisan szubsztituálva van hidroxillal vagy halogénnel.

3. A 2. igénypontban definiált vegyület, ahol R_9 $(CH_2)_pC(O)OR_6$, $(CH_2)_pOC(O)R_6$, vagy $(CH_2)_pOC(O)N(R_6)(CH_2)_mOH$.

4. Az 1. igénypontban definiált vegyület, ahol , ha Ra vagy Rb R_6, R_6 és R_6' függetlenül hidrogén, alkil, vagy cikloalkil, ahol az alkil vagy cikloalkil opcionálisan szubsztituálva van a következővel: -

$C(O)OR_7$ vagy $-C(O)NR_5R_5'$, vagy R_6 és R_6' együtt véve lehet ciklizálva, hogy a következőt alkossa: $-(CH_2)_nX(CH_2)_n-$.

5. A 4. igénypontban definiált vegyület, ahol R_9 $-(CH_2)_nN(R_6)C(O)OR_6'$, $-(CH_2)_nN(R_6)C(O)NR_6R_6'$, vagy $(CH_2)_nOC(O)NR_6R_6'$, ahol R_6 és R_6' függetlenül hidrogén vagy alkil, ahol az alkil opcionálisan szubsztituálva van a következővel: $-C(O)NR_5R_5'$, ahol R_5 és R_5' függetlenül hidrogén vagy alkil.

6. Gyógyszerészeti kompozíció, amely tartalmazza az 1-5. igénypontok bármelyike szerinti vegyületet és gyógyszerészetileg elfogadható hordozóanyagot arra.

7. A 6. igénypont szerinti gyógyszerészeti kompozíció, amely továbbá tartalmaz legalább egy további terápiás szert, amely ki van választva a következőkből álló csoportból: más, képlet I szerinti vegyületek, paratiroid hormon, biszfoszfonátok, ösztrogén, tesztoszteron, szelektív ösztrogén receptor modulátorok, szelektív androgén receptor modulátorok, progesztin receptor agonisták, diabéteszellenes szerek, hipertenzió ellenes szerek, gyulladásellenes szerek, oszteoporozis ellenes szerek, elhízottságellenes szerek, szív glikozidok, koleszterin csökkentő szerek és tiroid mimetikumok.

8. Az 1-5. igénypontok bármelyike szerinti vegyület felhasználásra endogén növekedési hormon szintjeinek növelésére.

9. Az 1-5. igénypontok bármelyike szerinti vegyület felhasználásra a következők kezelésére vagy előrehaladásának vagy kitörésének késleltetésére: HIV elsorvadási szindróma, izomatrófia, lipodisztrófia, kritikus hosszú távú betegség, oszteoporozis, szarkopénia, gyengeség vagy ARFD idősekben, elhízottság, vesebetegség, anorexia, alvászavarok, depresszió, Szindróma X, diabétesz, kongestív szívelégtelenség, szívmyopathia, szívdiszfunkció, amely szívbillentyűbetegséggel kapcsolatos és cachexia.

10. A 9. igénypont szerinti vegyület felhasználásra, ahol a felhasználás tartalmazza legalább egy további terápiás szer terápiásan hatásos mennyiségének adagolását, egyidőben vagy egymás után, amely ki van választva a következőkből álló csoportból: képlet I szerinti más vegyületek, paratiroid hormon, biszfoszfonátok, ösztrogén, tesztoszteron, szelektív ösztrogén receptor modulátorok, szelektív androgén receptor modulátorok, progesztin receptor agonisták, diabéteszellenes szerek, hipertenzió ellenes szerek, gyulladásellenes szerek, oszteoporosis ellenes szerek, elhízottságellenes szerek, szívglikozidok, koleszterin csökkentő szerek és tiroid mimetikumok.

11. Az 1-5. igénypontok bármelyike szerinti vegyület felhasználásra sebgyógyulás és/vagy az immunrendszer stimulálására.

12. Az 1-5. igénypontok bármelyike szerinti vegyület felhasználásra izomtömeg és/vagy erő növelésére vagy izomerő és funkció megtartására idősekben, sovány testtömeg növelésére vagy kognitív funkció javítására, vagy vakcináció immunválaszának javítására, vagy csípőfraktúra gyógyulásának gyorsítására.

13. A 6. igénypont szerinti gyógyszerészeti kompozíció, amely továbbá tartalmaz legalább egy táplálék kiegészítőt.

14. Az 1-5. igénypontok bármelyike szerinti vegyület gyógyszerészeti kompozíció előállítására, amely a következőkre szolgál: endogén növekedési hormon szintjeinek növelésére; izomtömeg és/vagy erő növelésére vagy izomerő és funkció megtartására idősekben, sovány testtömeg növelésére, vagy kognitív

funkció javítására, vagy vakcináció immunválaszának javítására, vagy csípőfraktúra gyógyulásának gyorsítására; sebgyógyulás és/vagy immunrendszer stimulására; a következők kezelésére vagy előrehaladásának vagy kitörésének késleltetésére: HIV elsorvadási szindróma, izomatrófia, lipodisztrófia, kritikus hosszú távú betegség, oszteoporozis, szarkopenia, gyengeség vagy ARFD idősekben, elhízottság, vesebetegség, anorexia, alvászavarok, depresszió, Szindróma X, diabétesz, kongestiv szívelégtelenség, szívmyopathia, szívdiszfunkció, amely szívbillentyűbetegséggel kapcsolatos és cachexia.

15. A 14. igénypont szerinti felhasználás, ahol a felhasználás tartalmazza legalább egy további terápiás szer terápiásan hatásos mennyiségének adagolását, egyidőben vagy egymás után, amely ki van választva a következőkből álló csoportból: képlet I szerinti más vegyületek, paratiroid hormon, bisfoszfonátok, ösztrogén, tesztoszteron, szelektív ösztrogén receptor modulátorok, szelektív androgén receptor modulátorok, progesztin receptor agonisták, diabéteszellenes szerek, hipertenzió ellenes szerek, gyulladásellenes szerek, oszteoporosis ellenes szerek, elhízottságellenes szerek, szívglikozidok, koleszterin csökkentő szerek és tiroid mimetikumok.