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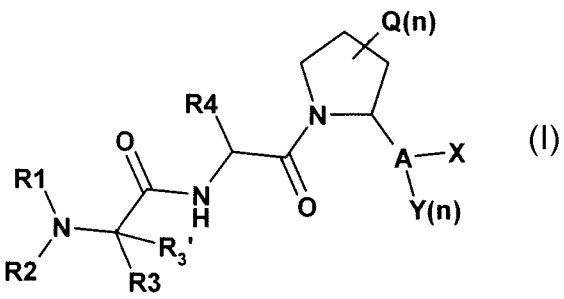
(54) Title: PYRROLYDINE DERIVATIVES AS IAP INHIBITORS



(I)

(57) Abstract: The present invention relates to novel IAP inhibitor compounds of: Formula (I).

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PYRROLYDINE DERIVATIVES AS IAP INHIBITORS

The present invention relates generally to novel compounds that inhibit the binding of the Smac protein to Inhibitor of Apoptosis Proteins (IAPs). More specifically, the present invention includes novel compounds, novel compositions, methods of their use and methods of their manufacture, where such compounds are generally pharmacologically useful as agents in therapies whose mechanism of action rely on the inhibition of the Smac/IAP interaction, and more particularly useful in therapies for the treatment of proliferative diseases, including cancer.

BACKGROUND

Programmed cell death plays a critical role in regulating cell number and in eliminating stressed or damaged cells from normal tissues. Indeed, the network of apoptotic signaling mechanisms inherent in most cell types provides a major barrier to the development and progression of human cancer. Since most commonly used radiation and chemo-therapies rely on activation of apoptotic pathways to kill cancer cells, tumor cells which are capable of evading programmed cell death often become resistant to treatment.

Apoptosis signaling networks are classified as either intrinsic when mediated by death receptor-ligand interactions or extrinsic when mediated by cellular stress and mitochondrial permeabilization. Both pathways ultimately converge on individual Caspases. Once activated, Caspases cleave a number of cell death-related substrates, effecting destruction of the cell.

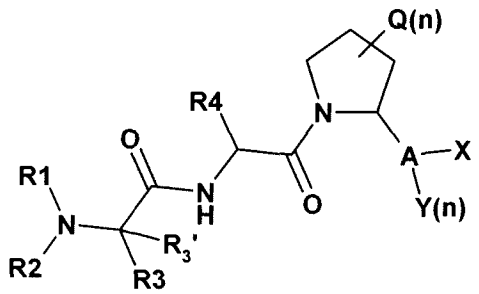
Tumor cells have devised a number of strategies to circumvent apoptosis. One recently reported molecular mechanism involves the overexpression of members of the IAP (Inhibitor of Apoptosis) protein family. IAPs sabotage apoptosis by directly interacting with and neutralizing Caspases. The prototype IAPs, XIAP and cIAP have three functional domains referred to as BIR 1, 2 & 3 domains. BIR3 domain interacts directly with Caspase 9 and inhibits its ability to bind and cleave its natural substrate, Procaspase 3.

It has been reported that a proapoptotic mitochondrial protein, Smac (also known as DIABLO), is capable of neutralizing XIAP and/or cIAP by binding to a peptide binding pocket

(Smac binding site) on the surface of BIR3 thereby precluding interaction between XIAP and/or cIAP and Caspase 9. Binding of peptides derived from Smac has also been reported to trigger autocatalytic polyubiquitination and subsequent proteosome-mediated degradation of CIAP1. The present invention relates to therapeutic molecules that bind to the Smac binding pocket thereby promoting apoptosis in rapidly dividing cells. Such therapeutic molecules are useful for the treatment of proliferative diseases, including cancer.

SUMMARY OF THE INVENTION

The present invention relates to novel compounds of formula I:



Formula I

and pharmaceutically acceptable salts thereof, wherein

R_1 is H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl or C_3-C_{10} cycloalkyl, which R_1 may be unsubstituted or substituted;

R_2 is H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_{10} cycloalkyl which R_2 may be unsubstituted or substituted;

R_1 and R_2 may be taken together to form a ring or het;

R_3 and R_3' are independently H, CF_3, C_2F_5, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, CH_2-Z or R_2 and R_3 taken together with the nitrogen atom to which they are attached form het, wherein alkyl, alkenyl, alkynyl or het ring may be unsubstituted or substituted;

Z is H, OH, F, Cl, CH_3, CH_2Cl, CH_2F or CH_2OH;

R_4 is $C_{0\text{-}10}$ alkyl, $C_{0\text{-}10}$ alkyl-$C_{3\text{-}10}$ cycloalkyl, $C_{0\text{-}10}$alkyl-$C_{6\text{-}10}$aryl, $C_{0\text{-}10}$alkyl-het, wherein any carbon may be replaced with a heteroatom or group from the list N, O, $S(O)_r$ and any atom may be unsubstituted or substituted;

A is a 6 membered heteroaryl ring or an 8-12 membered fused ring system that may include one 5-7 membered heterocyclic ring containing 1, 2, or 3 heteroring atoms selected from N, O and S, which any position of the rings is unsubstituted or substituted with one or more Q's;

r is 0, 1, or 2;

Q and Y are independently H, F, Cl, Br, I, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, aryl C_1-C_{10} alkoxy, OH, O-C_1-C_{10}-alkyl, $(CH_2)_{0-6}$-C_3-C_7 cycloalkyl, aryl, aryl C_1-C_{10} alkyl, O-$(CH_2)_{0-6}$ aryl, $(CH_2)_{1-6}$het, het, O-$(CH_2)_{1-6}$het, -OR_{11}, C(O)R_{11}, -C(O)N(R_{11})(R_{12}), N(R_{11})(R_{12}),SR_{11}, S(O)R_{11},S$(O)_2$ R_{11}, S$(O)_2$-N(R_{11})(R_{12}), or NR_{11}-S$(O)_2$-(R_{12}), wherein alkyl, cycloalkyl and aryl are unsubstituted or substituted, independent Q's may be joined to form a 5-10 membered ring;

X is aryl, C_3-C_{10} cycloalkyl, or het, substituted or unsubstituted, in which substituents on aryl, C_3-C_{10} cycloalkyl and het are alkyl, halo, lower alkoxy, NR_5R_6, CN, NO_2 or SR_5;

R_5 and R_6 are independently H, F, Cl, Br, I, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, aryl C_1-C_{10} alkoxy, OH, O-C_1-C_{10}-alkyl, $(CH_2)_{0-6}$-C_3-C_7 cycloalkyl, aryl, aryl C_1-C_{10} alkyl, O-$(CH_2)_{0-6}$ aryl, $(CH_2)_{1-6}$het, het, O-$(CH_2)_{1-6}$het, -OR_{11}, C(O)R_{11}, -C(O)N(R_{11})(R_{12}), N(R_{11})(R_{12}),SR_{11}, S(O)R_{11},S$(O)_2$ R_{11}, S$(O)_2$-N(R_{11})(R_{12}), or NR_{11}-S$(O)_2$-(R_{12});

each n is independently 0, 1, 2, 3, 4, 5, 6 or 7;

het is a 5-7 membered monocyclic heterocyclic ring containing 1-4 heteroring atoms selected from N,O and S or an 8-12 membered fused ring system that includes one 5-7 membered heterocyclic ring containing 1, 2, or 3 heteroring atoms selected from N, O and S, which het is unsubstituted or substituted;

R_{11} and R_{12} are independently H, C_1-C_{10} alkyl, $(CH_2)_{0-6}$-C_3-C_7cycloalkyl, $(CH_2)_{0-6}$-$(CH)_{0-1}$(aryl)$_{1-2}$,C(O)-C_1-C_{10}alkyl, -C(O)-$(CH_2)_{0-6}$-C_3-C_7cycloalkyl, -C(O)-O-$(CH_2)_{0-6}$-aryl, -C(O)-$(CH_2)_{0-6}$-O-fluorenyl, C(O)-NH-$(CH_2)_{0-6}$-aryl, C(O)-$(CH_2)_{0-6}$-aryl, C(O)-$(CH_2)_{0-6}$-het, -C(S)-C_1-C_{10}alkyl, -C(S)-$(CH_2)_{0-6}$-C_3-C_7cycloalkyl, -C(S)-O-$(CH_2)_{0-6}$-aryl, -C(S)-$(CH_2)_{0-6}$-O-fluorenyl, C(S)-NH-$(CH_2)_{0-6}$-aryl, -C(S)-$(CH_2)_{0-6}$-aryl or C(S)-$(CH_2)_{0-6}$-het, C(O)R_{11}, C(O)N$R_{11}R_{12}$, C(O)OR_{11}, S(O)nR_{11}, S$(O)_m$N$R_{11}R_{12}$, m = 1 or 2, C(S)R_{11}, C(S)N$R_{11}R_{12}$, C(S)OR_{11}, wherein alkyl, cycloalkyl and aryl are unsubstituted or substituted; or R_{11} and R_{12} together with the nitrogen atom form het;

wherein the alkyl substituents of R_{11} and R_{12} may be unsubstituted or substituted by one or more substituents selected from C_1-C_{10}alkyl, halogen, OH, O-C_1-C_6alkyl, -S-C_1-C_6alkyl, CF_3 or N$R_{11}R_{12}$;

substituted cycloalkyl substituents of R_{11} and R_{12} are substituted by one or more substituents selected from a C_2-C_{10} alkene; C_1-C_6alkyl; halogen; OH; O-C_1-C_6alkyl; S-C_1-C_6alkyl,CF_3; or $NR_{11}R_{12}$ and

substituted het or substituted aryl of R_{11} and R_{12} are substituted by one or more substituents selected from halogen, hydroxy, C_1-C_4 alkyl, C_1-C_4 alkoxy, nitro, CN O-C(O)-C_1-C_4alkyl and C(O)-O-C_1-C_4-alkyl;

wherein the substituents on R_1, R_2, R_3, R_4, Q, and A and X groups are independently halo, hydroxy, lower alkyl, lower alkenyl, lower alkynyl, lower alkanoyl, lower alkoxy, aryl, aryl lower alkyl, amino, amino lower alkyl, diloweralkylamino, lower alkanoyl, amino lower alkoxy, nitro, cyano, cyano lower alkyl, carboxy, lower carbalkoxy, lower alkanoyl, aryloyl, lower arylalkanoyl, carbamoyl, N-mono- or N,N-dilower alkyl carbamoyl, lower alkyl carbamic acid ester, amidino, guanidine, ureido, mercapto, sulfo, lower alkylthio, sulfoamino, sulfonamide, benzosulfonamide, sulfonate, sulfanyl lower alkyl, aryl sulfonamide, halogen substituted aryl sulfonate, lower alkylsulfinyl, arylsulfinyl; aryl-lower alkylsulfinyl, lower alkylarylsulfinyl, lower alkylsulfonyl, arylsulfonyl, aryl-lower alkylsulfonyl, lower aryl alkyl lower alkylarylsulfonyl, halogen-lower alkylmercapto, halogen-lower alkylsulfonyl, phosphono (-P(=O)$(OH)_2$), hydroxy-lower alkoxy phosphoryl or di-lower alkoxyphosphoryl, $(R_9)NC(O)$-$NR_{10}R_{13}$, lower alkyl carbamic acid ester or carbamates or $-NR_8R_{14}$, wherein R_8 and R_{14} can be the same or different and are independently H or lower alkyl, or R_8 and R_{14} together with the N atom form a 3- to 8-membered heterocyclic ring containing a nitrogen heteroring atoms and may optionally contain one or two additional heteroring atoms selected from nitrogen, oxygen and sulfur, which heterocyclic ring may be unsubstituted or substituted with lower alkyl, halo, lower alkenyl, lower alkynyl, hydroxy, lower alkoxy, nitro, amino, lower alkyl, amino, diloweralkyl amino, cyano, carboxy, lower carbalkoxy, formyl, lower alkanoyl, oxo, carbarmoyl, N-lower or N, N-dilower alkyl carbamoyl, mercapto, or lower alkylthio, and

R_9, R_{10}, and R_{13} are independently hydrogen, lower alkyl, halogen substituted lower alkyl, aryl, aryl lower alkyl, halogen substituted aryl, halogen substituted aryl lower alkyl.

The present invention also relates to pharmaceutical compositions comprising therapeutically effective amounts of compounds of Formula I, as defined hereinabove, or a pharmaceutically acceptable salt thereof, and a pharmaceutical carrier therefor. In another embodiment, the present invention is directed to a method of treating a mammal, especially human, afflicted with a proliferative disease, especially those dependent on the binding of the smac protein to Inhibitor of Apoptosis Proteins (IAPs), such as cancer, which method

comprises administering to said mammal in need of treatment an anti-proloferative effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof. The present invention is also directed to the manufacture of compounds of Formula I for use in the treatment of said diseases.

DETAILED DESCRIPTION OF THE PRESENT INVENTION

As used herein, the term "Aryl" is defined as an aromatic radical having 6 to 14 ring carbon atoms, and no ring heteroatoms. The aryl group may be monocyclic or fused bicyclic or tricyclic. It may be unsubstituted or substituted by one or more, preferably one or two, substituents, wherein the substituents are as described herein. As defined herein, the aryl moiety may be completely aromatic regardless of whether it is monocyclic or bicyclic. However, if it contains more than one ring, as defined herein, the term aryl includes moieties wherein at least one ring is completely aromatic while the other ring(s) may be partially unsaturated or saturated or completely aromatic. Preferred "aryl" is phenyl or naphthyl. The most preferred aryl is phenyl.

"Het" as used herein, refers to heteroaryl and heterocyclic compounds containing at least one S, O or N ring heteroatom. More specifically, "Het" is a 5-7 membered heterocyclic ring containing 1- 4 heteroatoms selected from N, O and S, or an 8-12 membered fused ring system including at least one 5-7 membered heterocyclic ring containing 1, 2 or 3 heteroatoms selected from N, O, and S. Examples of het, as used herein, include unsubstituted and substituted pyrrolidyl, tetrahydrofuryl, tetrahydrothiofuryl, piperidyl, piperazyl, purinyl, tetrahydropyranyl, morpholino, 1,3-diazapanyl, 1,4-diazapanyl, 1,4-oxazepanyl, 1,4-oxathiapanyl, furyl, thienyl, pyrryl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, oxadiazolyl, imidazolyl, pyrrolidyl, pyrrolidinyl, thiazolyl, oxazolyl, pyridyl, pyrazolyl, pyrazinyl, pyrimidinyl, isoxazolyl, pyrazinyl, quinolyl, isoquinolyl, pyridopyrazinyl, pyrrolopyridyl, furopyridyl, indolyl, benzofuryl, benzothiofuryl, benzoindolyl, benzothienyl, pyrazolyl, piperidyl, piperazinyl, indolinyl, morpholinyl, benzoxazolyl, pyrroloquinolyl, pyrrolo[2,3-b]pyridinyl, benzotriazolyl, oxobenzo-oxazolyl, benco[1,3]dioxolyl, benxzoimidazolyl, quinolinyl, indanyl and the like. Heteroaryls are within the scope of the definition of het. Examples of heteroaryls are pyridyl, pyrimidinyl, quinolyl, thiazolyl and benzothiazolyl. The most preferred het are pyridyl, pyrimidinyl and thiazolyl. The het may be unsubstituted or substituted as described herein. It is preferred that it is unsubstituted or if substituted it is substituted on a carbon atom by halogen, especially fluorine or chlorine, hydroxy, C_1-C_4 alkyl, such as methyl and ethyl, C_1-C_4 alkoxy, especially methoxy and ethoxy, nitro, -O-C(O)-C_1-C_4alkyl or –C(O)-O-C_1-C_4alkyl, SCN or nitro or on a nitrogen atom by C_1-C_4

alkyl, especially methyl or ethyl, -O-C(O)-C_1-C_4alkyl or –C(O)-O-C_1-C_4alkyl, such as carbomethoxy or carboethoxy.

When two substituents together with a commonly bound nitrogen are het, it is understood that the resulting heterocyclic ring is a nitrogen-containing ring, such as aziridine, azetidine, azole, piperidine, piperazine, morphiline, pyrrole, pyrazole, thiazole, oxazole, pyridine, pyrimidine, isoxazole, and the like, wherein such het may be unsubstituted or substituted as defined hereinabove.

Halogen is fluorine, chlorine, bromine or iodine, especially fluorine and chlorine.

Unless otherwise specified "alkyl", either above or in combination, includes straight or branched chain alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, n-pentyl and branched pentyl, n-hexyl and branched hexyl, and the like.

A "cycloalkyl" group means C_3 to C_{10} cycloalkyl having 3 to 10 ring carbon atoms and may be, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl, cyclononyl and the like. The cycloalkyl group may be monocyclic or fused bicyclic. It is preferred that it is monocyclic. Moreover, the preferred cycloalkyl group is cyclopentyl or cyclohexyl. Most preferably, cycloalkyl is cyclohexyl. The cycloalkyl group may be fully saturated or partially unsaturated, although it is preferred that it is fully saturated. As defined herein, it excludes aryl groups. The cycloalkyl groups may be unsubstituted or substituted with any of the substituents defined below, preferably halo, hydroxy or C_1-C_6 alkyl such as methyl.

Substituents that facilitate transport of the molecule across a cell membrane are known to those of skill in the medicinal chemistry arts (see, for example, Gangewar S., Pauletti G. M.,Wang B., Siahaan T. J., Stella V. J., Borchardt R. T., *Drug Discovery Today*, vol. 2. p148-155 (1997) and Bundgaard H. and Moss J., *Pharmaceutical Research*, vol. 7, p 885 (1990)). Generally, such substituents are lipophillic substituents. Such lipophillic substituents include a C_6-C_{30} alkyl which is saturated, monounsaturated, polyunsaturated, including methylene-interrupted polyene, phenyl, phenyl which is substituted by one or two C_1-C_8 alkyl groups, C_5-C_9 cycloalkyl, C_5-C_9 cycloalkyl which is substituted by one or two C_1-C_8 alkyl groups, -X_1-phenyl, -X_1-phenyl which is substituted in the phenyl ring by one or two

C_1-C_8 alkyl groups, X_1-C_5-C_9 cycloalkyl or X_1-C_5-C_9 cycloalkyl which is substituted by one or two C_1-C_8 alkyl groups; where X_1 is C_1-C_{24} alkyl which is saturated, monounsaturated or polyunsaturated and straight or branched chain.

Unsubstituted is intended to mean that hydrogen is the only substituent.

Except as described herein, any of the above defined aryl, het, alkyl, alkenyl, alkynyl, or cycloalkyl, may be unsubstituted or independently substituted by up to four, preferably one, two or three substituents, selected from the group consisting of: halo (such as Cl or Br); hydroxy; lower alkyl (such as C_1-C_3 alkyl); lower alkyl which may be substituted with any of the substituents defined herein; lower alkenyl; lower alkynyl; lower alkanoyl; lower alkoxy (such as methoxy); aryl (such as phenyl or naphthyl); substituted aryl (such as fluoro phenyl or methoxy phenyl); aryl lower alkyl such as benzyl, amino, mono or di-lower alkyl (such as dimethylamino); lower alkanoyl amino acetylamino; amino lower alkoxy (such as ethoxyamine); nitro; cyano; cyano lower alkyl; carboxy; lower carbalkoxy (such as methoxy carbonyl; n-propoxy carbonyl or iso-propoxy carbonyl), lower aryloyl, such as benzoyl; carbamoyl; N-mono- or N,N di-lower alkyl carbamoyl; lower alkyl carbamic acid ester; amidino; guanidine; ureido; mercapto; sulfo; lower alkylthio; sulfoamino; sulfonamide; benzosulfonamide; sulfonate; sulfanyl lower alkyl (such as methyl sulfanyl); sulfoamino; aryl sulfonamide; halogen substituted or unsubstituted aryl sulfonate (such as chloro-phenyl sulfonate); lower alkylsulfinyl; arylsulfinyl; aryl-lower alkylsulfinyl; lower alkylarylsulfinyl; lower alkanesulfonyl; arylsulfonyl; aryl-lower alkylsulfonyl; lower aryl alkyl; lower alkylarylsulfonyl; halogen-lower alkylmercapto; halogen-lower alkylsulfonyl; such as trifluoromethane sulfonyl; phosphono(-P(=O)$(OH)_2$); hydroxy-lower alkoxy phosphoryl or di-lower alkoxyphosphoryl; urea and substituted urea of the formula (R_9) N C(O) N(R_{10}), (R_{13}) wherein R_9, R_{10} and R_{13} are as defined herein(such as urea or 3-trifluoro-methyl-phenyl urea); alkyl carbamic acid ester or carbamates (such as ethyl-N-phenyl-carbamate) or $-NR_8R_{14}$, wherein R_8 and R_{14} can be the same or different and are independently H; lower alkyl (e.g. methyl, ethyl or propyl); or R_8 and R_{14} together with the N atom form a 3- to 8-membered heterocyclic ring containing a nitrogen heteroring atom and optionally one or two additional heteroring atoms selected from the group consisting of nitrogen, oxygen and sulfur (e.g. piperazinyl, pyrazinyl, lower alkyl-piperazinyl, pyridyl, indolyl, thiophenyl, thiazolyl, benzothiophenyl, pyrrolidinyl, piperidino or imidazolinyl) where the heterocyclic ring may be substituted with any of the substituents defined hereinabove.

Preferably the above mentioned alkyl, cycloalkyl, and aryl groups are independently unsubstituted or are substituted by lower alkyl, aryl, aryl lower alkyl, carboxy, lower carbalkoxy and especially halogen, -OH, -SH, $-OCH_3$, $-SCH_3$, -CN, -SCN or nitro.

As defined herein the term "lower alkyl", when used alone or in combination refers to alkyl containing 1-6 carbon atoms. The alkyl group may be branched or straight-chained, and is as defined hereinabove.

The term "lower alkenyl" refers to a alkenyl group which contains 2-6 carbon atoms. An alkenyl group is a hydrocarbyl group containing at least one carbon-carbon double bond. As defined herein, it may be unsubstituted or substituted with the substituents described herein. The carbon-carbon double bonds may be between any two carbon atoms of the alkenyl group. It is preferred that it contains 1 or 2 carbon-carbon double bonds and more preferably one carbon-carbon double bond. The alkenyl group may be straight chained or branched. Examples include ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 2-methyl-1-propenyl, 1, 3-butadienyl, and the like. The preferred alkenyl group is ethenyl.

The term "lower alkynyl", as used herein, refers to an alkynyl group containing 2-6 carbon atoms. An alkynyl group is a hydrocarbyl group containing at least one carbon-carbon triple bond. The carbon-carbon triple bond may be between any two carbon atom of the alkynyl group. It is preferred that the alkynyl group contains 1 or 2 carbon-carbon triple bonds and more preferably one carbon-carbon triple bond. The alkynyl group may be straight chained or branched. Examples include ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl and the like. The preferred alkynyl group is ethynyl.

As used herein, the term "aryl alkyl" refers to a aryl group connected to the main chain by a bridging alkylene group. Examples include benzyl, phenethyl, naphthylmethyl, and the like. The preferred aryl alkyl is benzyl. Similarly, cyano alkyl group refers to a cyano group connected to the main chain by a bridging alkylene group.

The term "alkyl aryl" on the other hand, refers to an alkyl group bridged to the main chain through a phenylene group. Examples include methylphenyl, ethylphenyl, and the like.

As used herein, the term lower alkanoyl refers to a lower alkyl chain in which one of the carbon atoms is replaced by a C=O group. The C=O group may be present at one of the ends of the substituent or in the middle of the moiety. Examples include formyl, acetyl, 2-propanoyl, 1-propanoyl and the like.

The term "alkoxy" refers to an alkyl group as defined herein, connected to the main chain by an oxygen atom. Examples include methoxy, ethoxy, and the like.

The term "lower thioalkyl" refers to an alkyl group, as defined herein, connected to the main chain by a sulfur atom. Examples include thiomethyl (or mercapto methyl), thioethyl (mercapto ethyl) and the like.

The term "lower carbalkoxy" or synonym thereto refers to an alkoxycarbonyl group, where the attachment to the main chain is through the aryl group (C(O)). Examples include methoxy carbonyl, ethoxy carbonyl, and the like.

It is to be understood that the terminology C(O) refers to a –C=O group, whether it be ketone, aldehydre or acid or acid derivative. Similarly, S(O) refers to a –S=O group.

As used herein, the term S(O)r refers to the number of oxygen atoms bonded to the sulfur atom. When r = 2, then S(O)r = SO_2; when r is 1, then S(O)r is SO; and when r = O, then S(O)r is S.

The term "C_o", as used herein, as part of a definition of alkyl, as e.g., C_{0-10}, refers to zero carbon atoms. Thus, "C_0-C_{10} aryl alkyl" means that the aryl group is bonded directly to the main chain (C_o) or that there is a C_1-C_{10} alkylene group bridging the main chain to an aryl group.

The term "$(CH_2)_{0-6}$" as part of definition of a larger group, e.g., $(CH_2)_{0-6}$ C_3-C_7 cycloalkyl, refers to a group that is not present $(CH_2)_0$, or to a group that contains 1-6 carbon atoms $(CH_2)_{1-6}$.

The term $(CH_2)_{0-6}$-$(CH)_{0-1}$,$(aryl)_{1-2}$, in the definition of R_{11} and R_{12}, is intended to mean one of the following $(CH_2)_{1-6}$-aryl, aryl, -$CH(aryl)_2$ or $(CH_2)_{1-6}$ (CH) $(aryl)_2$.

As used herein, the variable n refers to number of substitutents on the pyrrolidinyl (tetrahydropyrrolyl) ring. The term "n" is defined as 0-7 and it determines the number of Q substituents on the pyrrolidinyl (tetrahydro-pyrrolyl) ring. Q can only be present at the 2, 3, 4, or 5 positions of the pyrrolidinyl ring, i.e., at the carbon atoms of the pyrrolidinyl ring. Except for carbon number 2 that can allow for one substitution, each of other carbon atoms are saturated and each of them may have two substituents thereon. When n is 7, then each of the carbon atoms are bonded with Q as defined herein. Each Q may be the same or different. However, when n is 6, then one of the seven possible substituents is H, and the other five are Q, which can be the same or different. Further, when n is 5, then two of the possible substitutents are H, and the other five are independently Q, as defined herein. When n is 4, then three of the seven possible substituents are H, and the remainder are Q independently as defined herein. Where n is 3, then four of the seven possible substituents are H, and the other three are Q as defined herein. When n is 2, then two of the seven possible substituent are Q, and the remainder are H. When n is 1, then only one of the seven possible substituent is Q, and the remainder are H. Finally, when n is 0, all seven of the substituents are H.

It is to be understood that each of the Q substituents may be the same or they may be different.

Any asymmetric carbon atom may be present in the (R)-, (S)- or (R,S)-configuration, preferably in the (R)- or (S)-configuration. Substituents at a ring at atoms with saturated bonds or substituents on carbon-carbon double bonds may, if possible, be present in cis- (= Z-) or trans (= E-) form. The compounds may thus be present as mixtures of isomers or preferably as pure isomers, preferably as enantiomermally pure diastereomers or pure enantiomers.

Preferred Embodiments

The preferred R_1 group is H and C_1-C_4 alkyl especially methyl. R_1 may be unsubstituted or substituted and is most preferably unsubstituted. The most preferred values of R_1 is H, methyl and ethyl, and especially methyl or ethyl and most especially methyl.

R_2 is preferably H or C_1-C_4 alkyl, especially methyl. R_2 may be unsubstituted or substituted. It is most preferably unsubstituted. It is preferred that R_2 is hydrogen.

R_3 and R_3' are, independently, preferably H or C_1-C_4 alkyl especially hydrogen, methyl, or ethyl and most especially methyl or ethyl, and most especially methyl, which may be unsubstituted or substituted. R_3 may be unsubstituted or substituted as defined herein. It is preferred that it is unsubstituted methyl or H. In a most preferred embodiment one of R_3 and R_3' is H and the other is methyl.

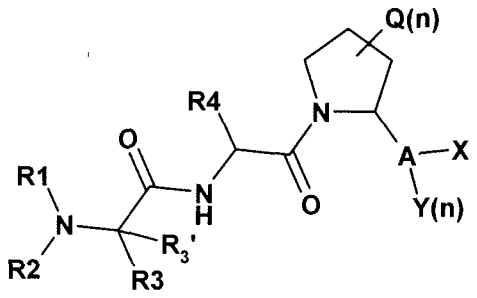
R_4 is preferably C_5-C_7 cycloalkyl, especially cyclohexyl, or C_1-C_4 alkyl, especially isopropyl . R_4 may be substituted or unsubstituted.

Q is preferably H.

A is a 6-membered heteroaryl or an 8-12 membered fused ring system that may include one 5-7 membered heterocyclic ring containing 1, 2, or 3 heteroring atoms selected from N, O and S. A may be unsubstituted or substituted in any position with one or more Q's. Preferably A is pyridyl, pyrimidinyl, indolyl, benzothiazolyl, or quinolinyl. A may be unsubstituted or substituted. It is preferred that A is unsubstituted or substituted with lower alkyl such as methyl, or halo.

X is aryl, C_3-C_{10} cycloalkyl, or het. Preferably X is quinolinyl, isoquinolyl, benzothiazolyl, pyridinyl, indolyl, benzoimidazolyl, naphthyl, benzo[1,3]dioxolyl, benzofurnayl, naphthyridine, pyrrolo[2,3b]pyridinyl, indanzolyl, benzotriazolyl, indazolyl, 2-oxobenzo-oxazolyl, or phenyl. X may be unsubstituted or substituted in any position with one or more Y. Prefereably Y is halo especially F or Cl, lower alkyl, especially methyl, ethyl, t- butyl or isopropyl, said lower alkyl may be substituted such as trifluoromethyl, lower alkoxy such as methoxy, lower alkyl amino such as dimethyl amino.

Another embodiment of the compound of Formula I wherein:



Formula I

or pharmaceutically acceptable salts thereof, wherein

R_1 is H, C_1-C_4 alkyl, which R_1 may be unsubstituted or substituted;

R_2 is H, C_1-C_4 alkyl, which R_2 may be unsubstituted or substituted;

R_3 and R_3' are independently H, or C_1-C_4 alkyl;

R_4 is C_5-C_7 cycloalkyl, especially cyclohexyl, or C_1-C_4 alkyl, especially isopropyl;

A is a 6 membered heteroaryl ring or an 8-12 membered fused ring system that may include one 5-7 membered heterocyclic ring containing 1, 2, or 3 heteroring atoms selected from N, O and S, which any position of the rings is unsubstituted or substituted with one or more Q's;

Q and Y are independently H, F, Cl, Br, I, C_1-C_{10} alkyl, C_1-C_{10} alkoxy;

X is aryl, C_3-C_{10} cycloalkyl, or het, which may be substituted or unsubstituted.

A preferred embodiment is the compound of Formula I, or pharmaceutically acceptable salts thereof, wherein

R_1 is H, or methyl;

R_2 is H, or methyl;

one of R_3 and R_3' a is H and the other is methyl;

R_4 is cyclohexyl, or isopropyl;

A is pyridyl, pyrimidinyl, indolyl, benzothiazolyl, or quinolinyl which may be unsubstituted or substituted with lower alkyl such as methyl, or halo;

Q and Y are independently H, F or Cl, lower alkyl, especially methyl, ethyl, t- butyl or isopropyl, said lower alkyl may be substituted such as trifluoromethyl, lower alkoxy such as methoxy, lower alkyl amino such as dimethyl amino; and

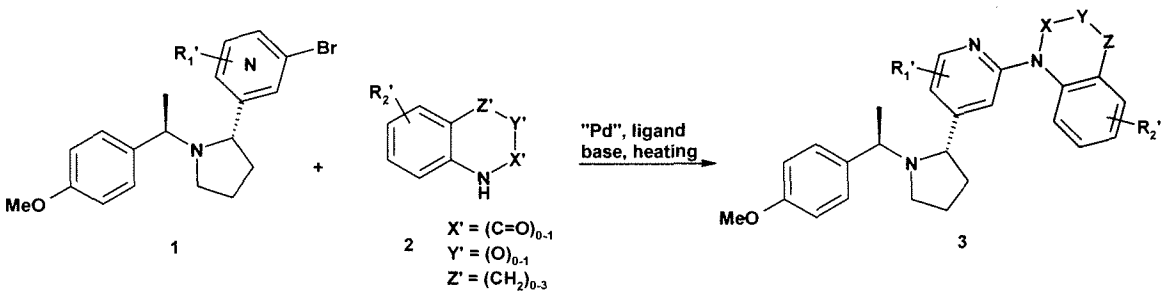
X is quinolinyl, isoquinolyl, benzothiazolyl, pyridinyl, indolyl, benzoimidazolyl, naphthyl, benzo[1,3]dioxolyl, benzofurnayl, naphthyridine, pyrrolo[2,3b]pyridinyl, indanzolyl,

benzotriazolyl, indazolyl, 2-oxobenzo-oxazolyl, or phenyl, which may be substituted or unsubstituted.

General Procedure

The active compounds of this invention may be prepared as described in the following reaction schemes. Unless otherwise indicated, R_1, R_2 in the reaction schemes and discussion that follow, are as defined above.

Scheme A

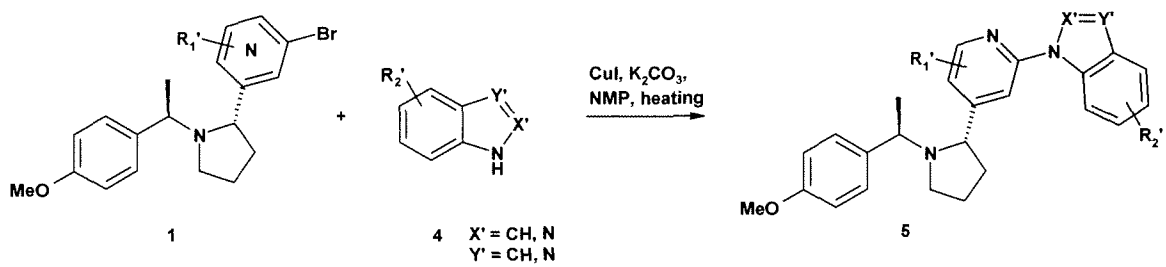


1 2 3

X' = $(C=O)_{0-1}$
Y' = $(O)_{0-1}$
Z' = $(CH_2)_{0-3}$

Scheme A illustrates a method for preparing compounds of the formula **3** by reacting a compound of the formula **1** (Int. Pat. Appl. WO2005097791A1), wherein R_1' is either fluorine or methyl, nitrogen could be in any position of the ring, with an excess compound of formula **2**. The reaction is run in the presence of a palladium catalyst such as $Pd_2(dba)_3$, a ligand such as 2-(dicyclohexylphosphino)-biphenyl and a base such as potassium tert-butoxide in toluene at a rang of temperature of 70°C to 100°C, but preferably at around 80°C. The reaction is typically run for a period of 3 hour up to 15 hours but preferably between 3 and 5 hours.

Scheme B

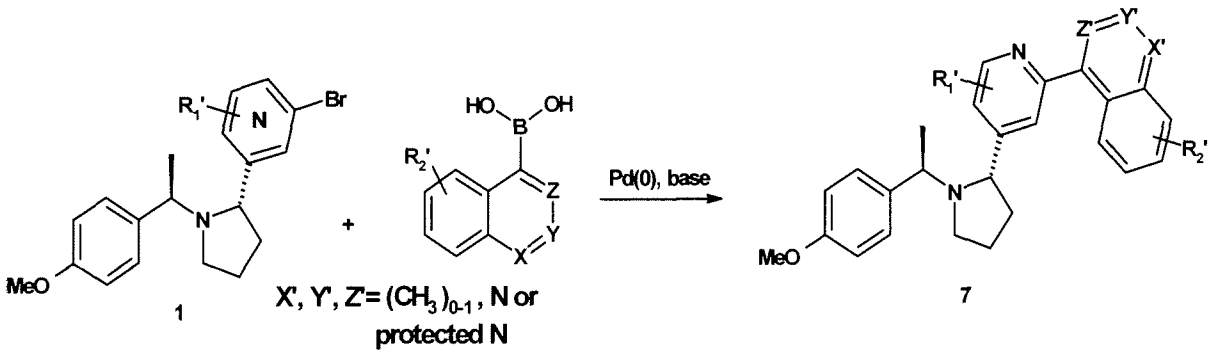


1 4 5

X' = CH, N
Y' = CH, N

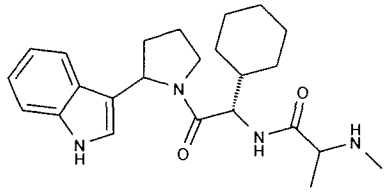
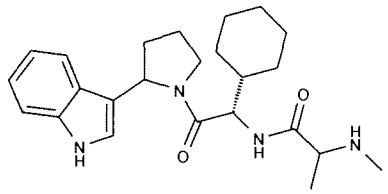
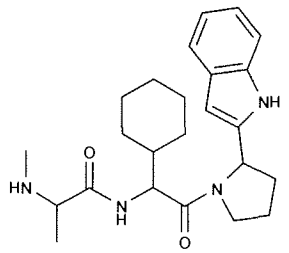
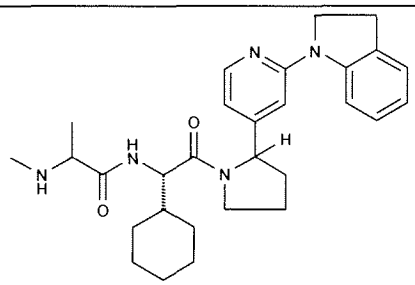
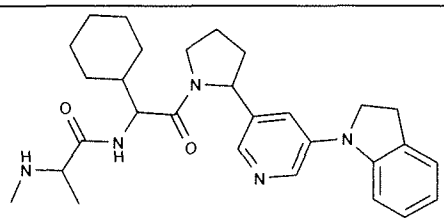
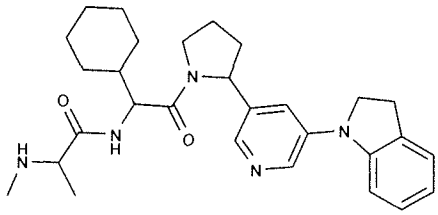
Scheme B illustrates a method for preparing compounds of the formula **5** by reacting a compound of the formula **1** (Int. Pat. Appl. WO2005097791A1), wherein R'_1 is either fluorine or methyl, nitrogen could be in any position of the ring, with a compound of formula **4**. The reaction typically run in the presence of a base such as potassium carbonate or cesium carbonate. CuI was employed as catalyst in the reaction. The solvent used may be NMP. The temperature of the reaction may vary from 180°C to 220°C for a period of 25 min to 60 min in a microwave reaction stove, preferably around 30 min.

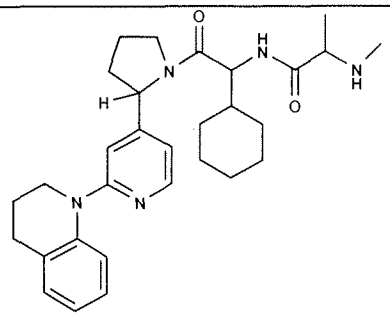
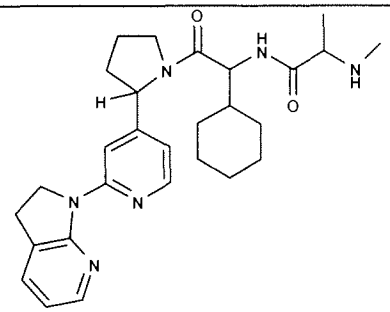
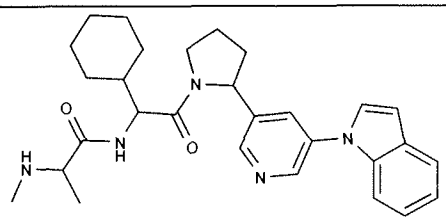
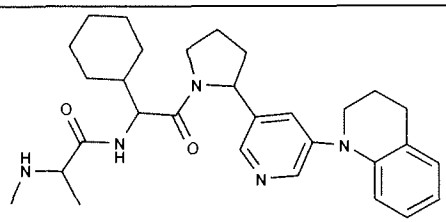
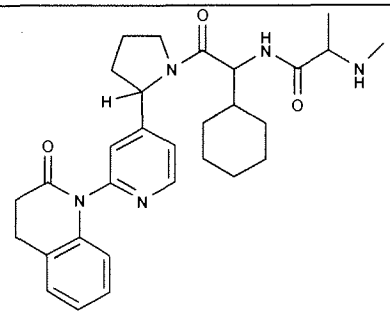
Scheme C

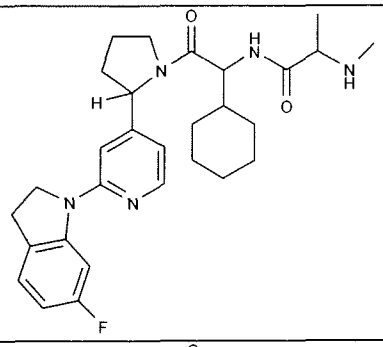
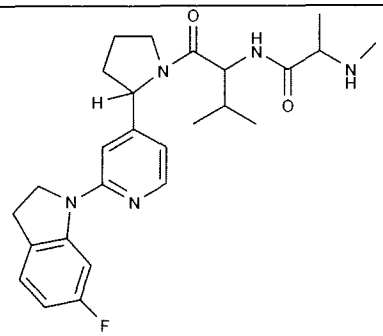
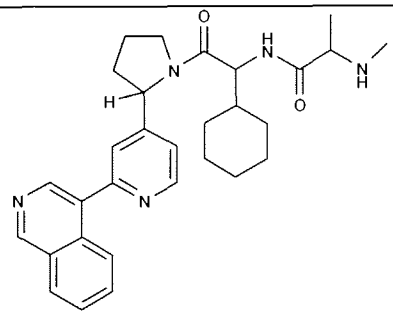
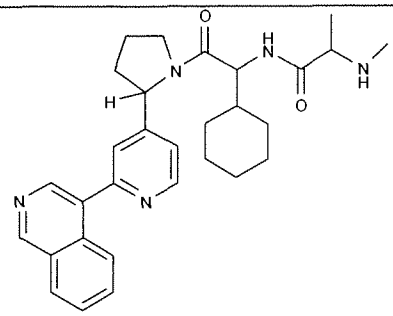


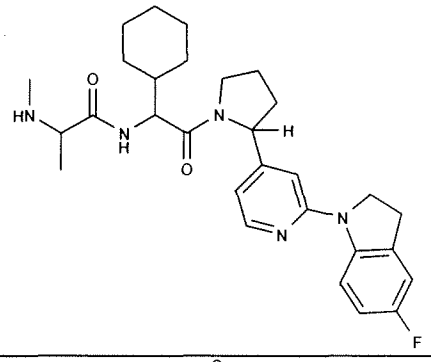
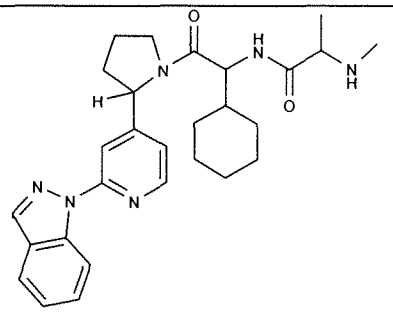
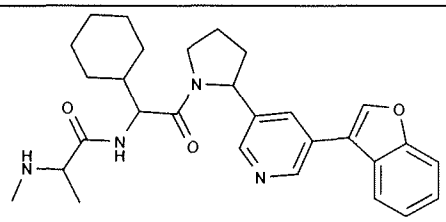
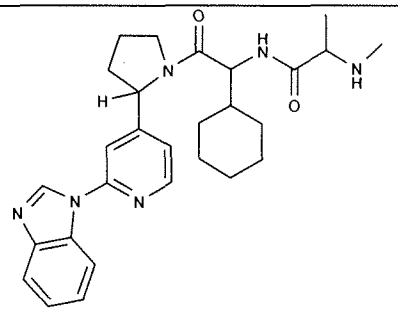
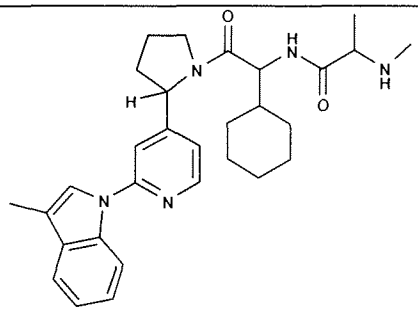
Scheme C illustrates a method of Suzuki coupling for preparing compounds of the formula **7** by reacting a compound of the formula **1** (Int. Pat. Appl. WO2005097791A1), wherein R'_1 is either fluorine or methyl, nitrogen could be in any position of the ring, with a compound of formula **6**. The reaction typically run in the presence of Pd(0) such as $Pd(Ph)_4$ and base such as sodium carbonate, and in a solvent mixture of toluene, ethanol and water. The temperature of the reaction typically is 80°C. Alternatively, compounds of formula **1** may be transformed to boronic acid/ester and couple to heterocyclic bromides similar to formula **6**.

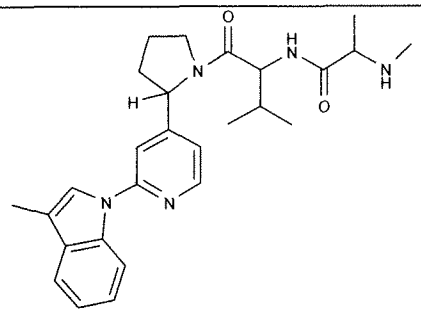
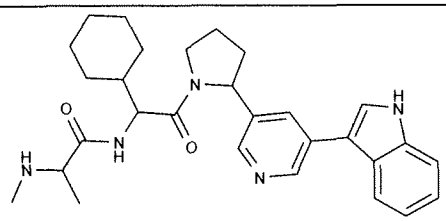
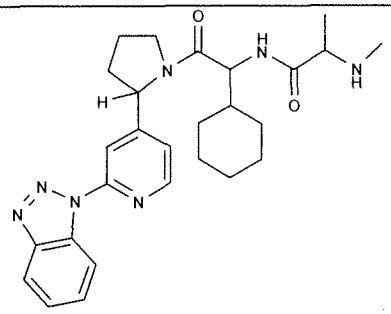
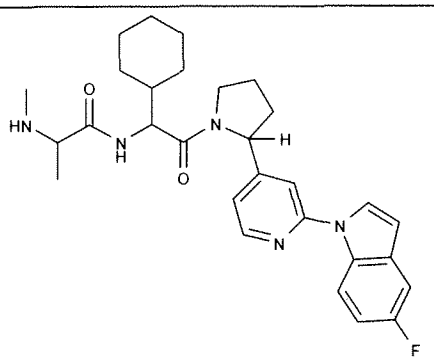
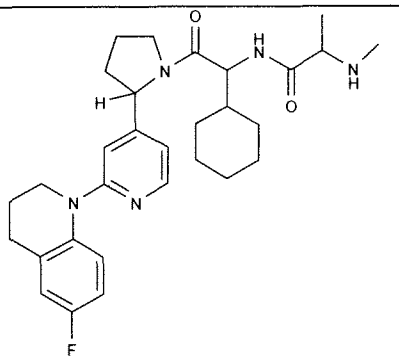
Table I

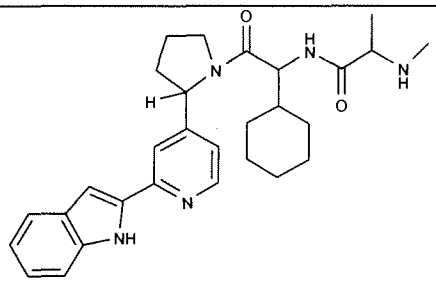
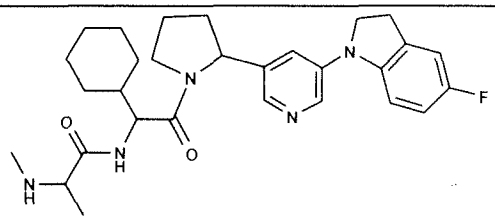
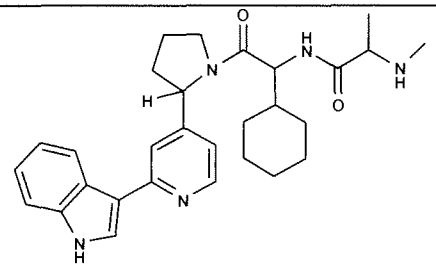
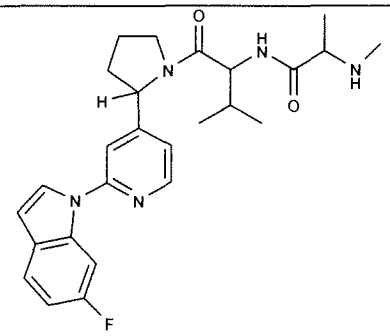
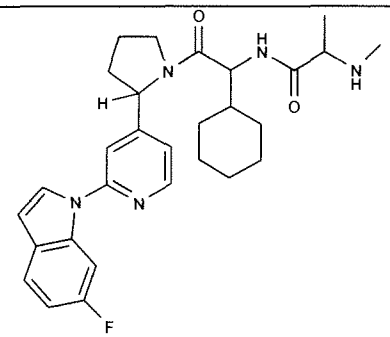
	Example	Name	MS ESI $(M+H)^+$
	1	*N*-{1-Cyclohexyl-2-[2-(1*H*-indol-3-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methyl amino-propionamide	411.56
	2	*N*-{1-Cyclohexyl-2-[2-(1*H*-indol-3-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methyl amino-propionamide	411.56
	3	*N*-{1-Cyclohexyl-2-[2-(1*H*-indol-2-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methy lamino-propionamide	411.56
	4	*N*-(1-Cyclohexyl-2-{2-[2-(2,3-dihydro-indol-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methyl amino-propionamide	490.67
	5	*N*-(1-Cyclohexyl-2-{2-[5-(2,3-dihydro-indol-1-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	490.67
	6	*N*-(1-Cyclohexyl-2-{2-[5-(2,3-dihydro-indol-1-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	490.67

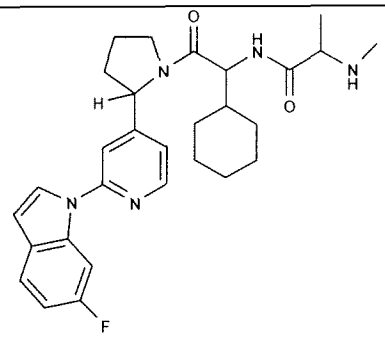
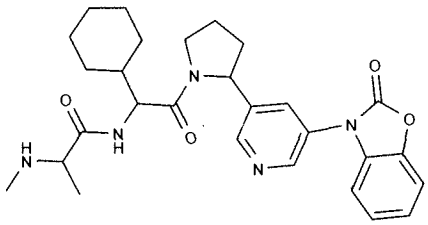
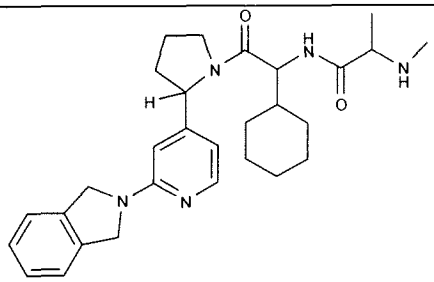
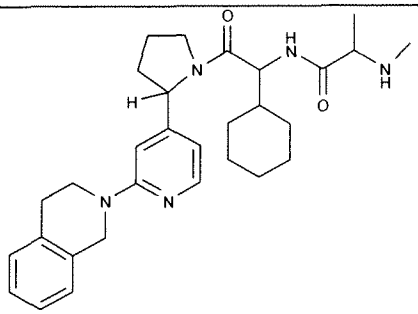
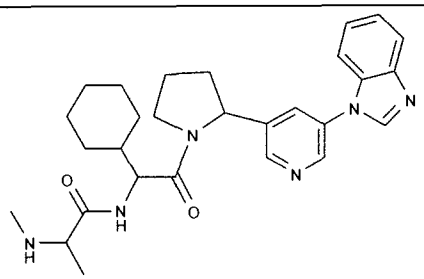
	Example	Name	MS ESI $(M+H)^+$
	7	*N*-(1-Cyclohexyl-2-{2-[2-(3,4-dihydro-2*H*-quinolin-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	504.69
	8	*N*-(1-Cyclohexyl-2-{2-[2-(2,3-dihydro-pyrrolo[2,3-*b*]pyridin-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	491.65
	9	*N*-{1-Cyclohexyl-2-[2-(5-indol-1-yl-pyridin-3-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide	488.65
	10	*N*-(1-Cyclohexyl-2-{2-[5-(3,4-dihydro-2*H*-quinolin-1-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	504.69
	11	*N*-(1-Cyclohexyl-2-oxo-2-{2-[2-(2-oxo-3,4-dihydro-2*H*-quinolin-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-ethyl)-2-methylamino-propionamide	518.68

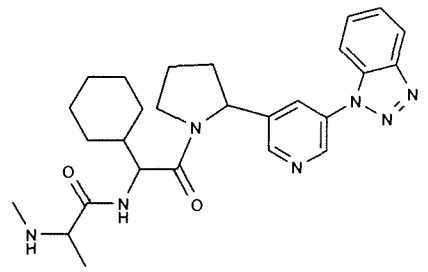
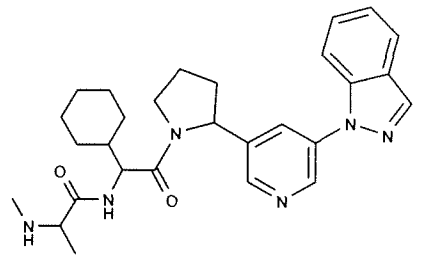
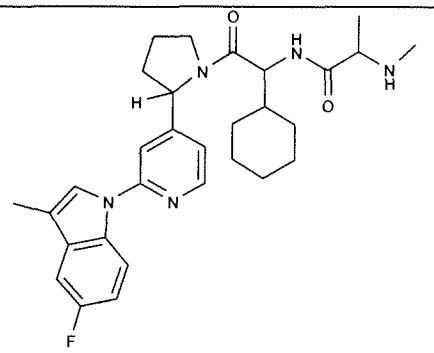
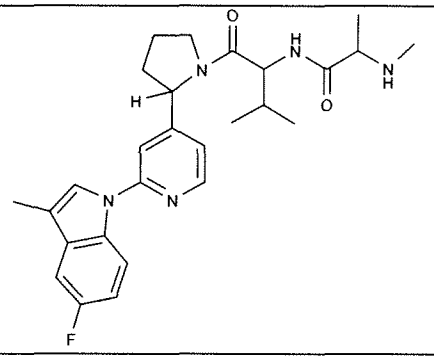
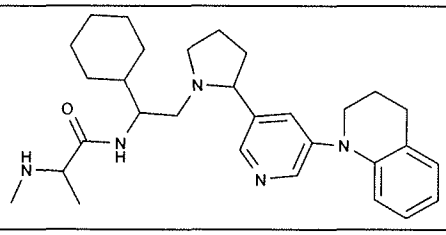
	Example	Name	MS ESI $(M+H)^+$
	12	*N*-(1-Cyclohexyl-2-{2-[2-(6-fluoro-2,3-dihydro-indol-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	508.66
	13	*N*-(1-{2-[2-(6-Fluoro-2,3-dihydro-indol-1-yl)-pyridin-4-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-2-methylamino-propionamide	468.59
	14	*N*-{1-Cyclohexyl-2-[2-(2-isoquinolin-4-yl-pyridin-4-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide	500.66
	15	*N*-{1-Cyclohexyl-2-[2-(2-isoquinolin-4-yl-pyridin-4-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide	500.66

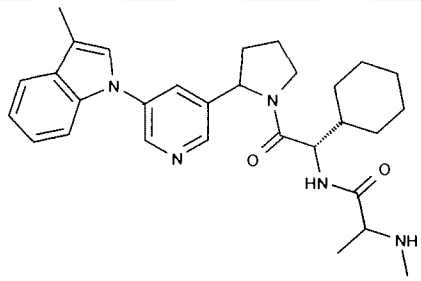
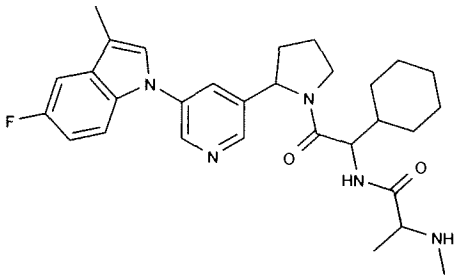
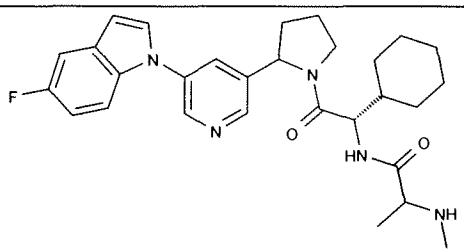
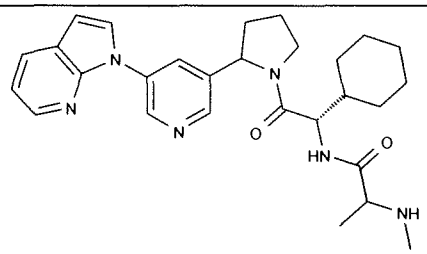
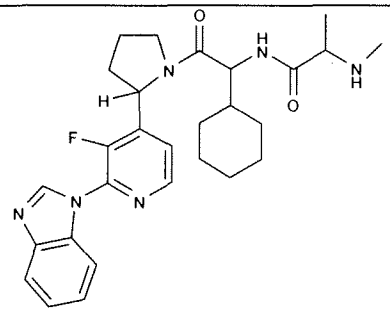
	Example	Name	MS ESI $(M+H)^+$
	16	*N*-(1-Cyclohexyl-2-{2-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	508.66
	17	*N*-{1-Cyclohexyl-2-[2-(2-indazol-1-yl-pyridin-4-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide	489.64
	18	*N*-{2-[2-(5-Benzofuran-3-yl-pyridin-3-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethyl}-2-methylamino-propionamide	489.64
	19	*N*-{2-[2-(2-Benzoimidazol-1-yl-pyridin-4-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethyl}-2-methylamino-propionamide	489.64
	20	*N*-(1-Cyclohexyl-2-{2-[2-(3-methyl-indol-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	502.68

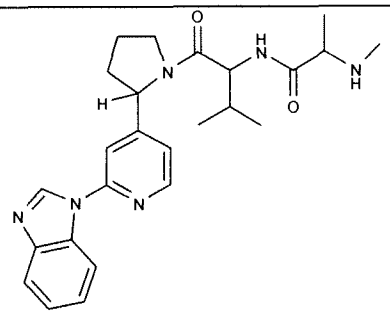
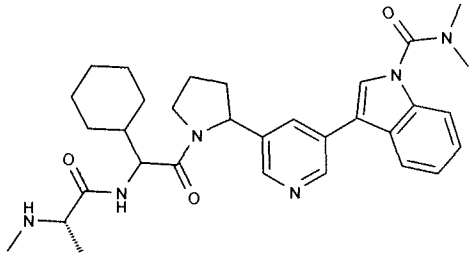
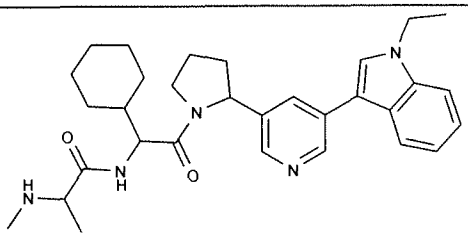
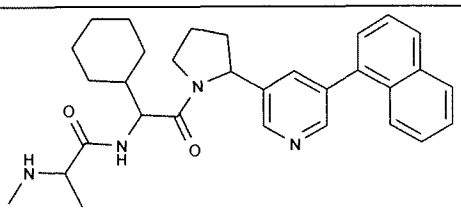
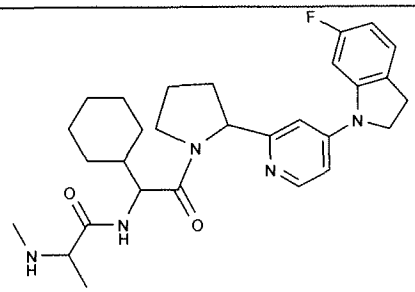
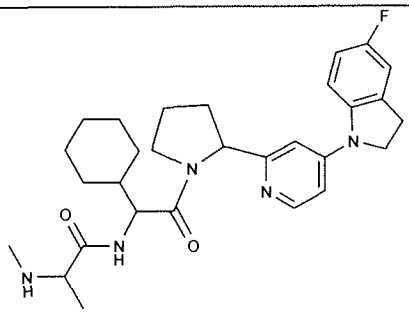
	Example	Name	MS ESI $(M+H)^+$
	21	2-Methylamino-*N*-(2-methyl-1-{2-[2-(3-methyl-indol-1-yl)-pyridin-4-yl]-pyrrolidine-1-carbonyl}-propyl)-propionamide	462.61
	22	*N*-(1-Cyclohexyl-2-{2-[5-(1*H*-indol-3-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	488.65
	23	*N*-{2-[2-(2-Benzotriazol-1-yl-pyridin-4-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethyl}-2-methylamino-propionamide	490.63
	24	*N*-(1-Cyclohexyl-2-{2-[2-(5-fluoro-indol-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	506.64
	25	*N*-(1-Cyclohexyl-2-{2-[2-(6-fluoro-3,4-dihydro-2*H*-quinolin-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	522.68

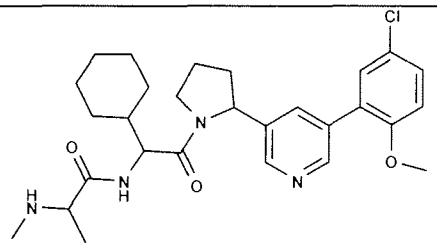
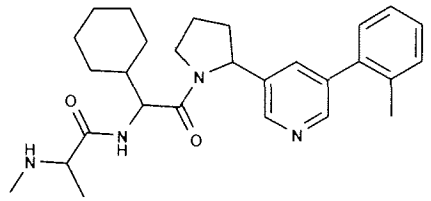
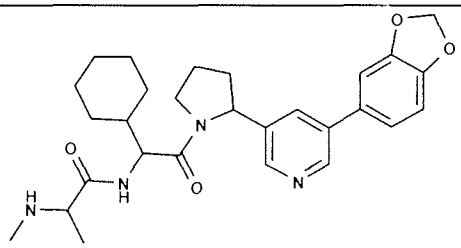
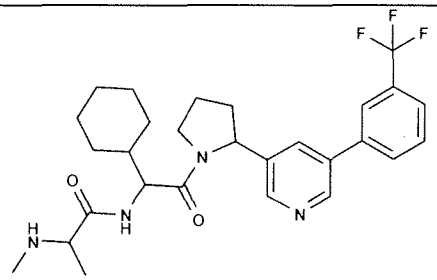
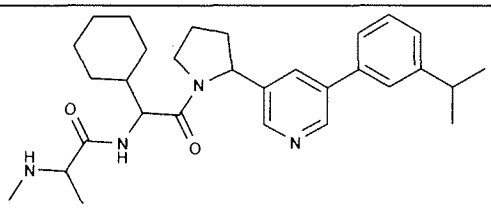
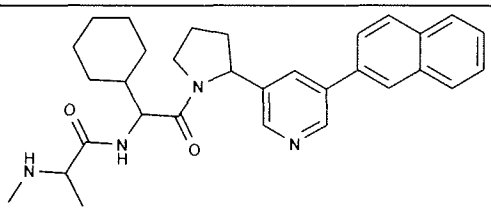
	Example	Name	MS ESI $(M+H)^+$
	26	*N*-(1-Cyclohexyl-2-{2-[2-(1*H*-indol-2-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	488.65
	27	*N*-(1-Cyclohexyl-2-{2-[5-(5-fluoro-2,3-dihydro-indol-1-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	508.66
	28	*N*-(1-Cyclohexyl-2-{2-[2-(1*H*-indol-3-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	488.65
	29	*N*-(1-{2-[2-(6-Fluoro-indol-1-yl)-pyridin-4-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-2-methylamino-propionamide	466.58
	30	*N*-(1-Cyclohexyl-2-{-2-[2-(6-fluoro-indol-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	506.64

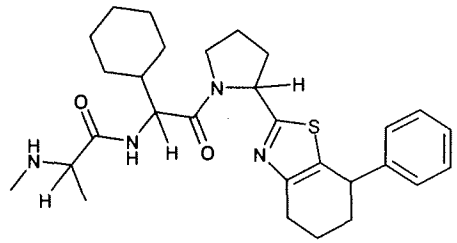
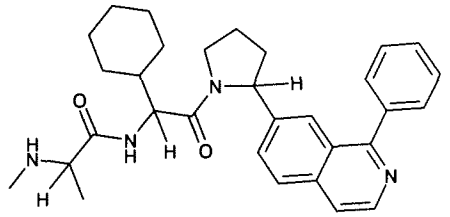
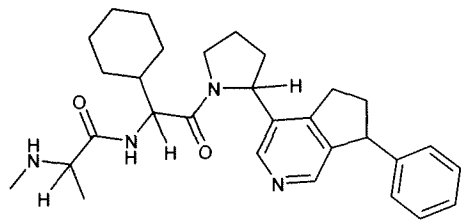
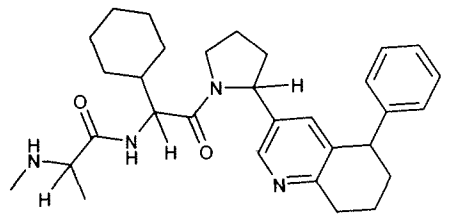
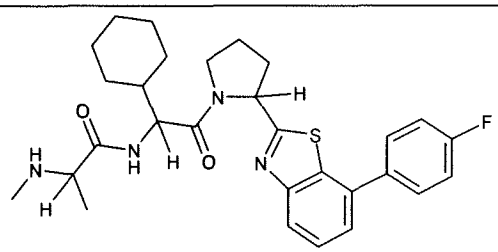
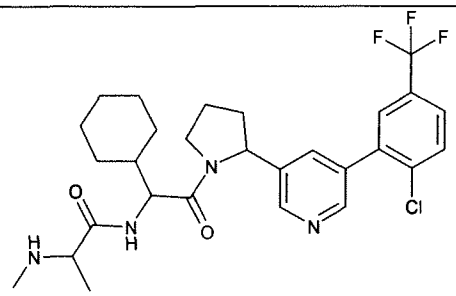
	Example	Name	MS ESI $(M+H)^+$
	31	*N*-(1-Cyclohexyl-2-{2-[2-(6-fluoro-indol-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	506.64
	32	*N*-(1-Cyclohexyl-2-oxo-2-{2-[5-(2-oxo-benzooxazol-3-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-ethyl)-2-methylamino-propionamide	506.62
	33	*N*-(1-Cyclohexyl-2-{2-[2-(1,3-dihydro-isoindol-2-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	490.67
	34	*N*-(1-Cyclohexyl-2-{2-[2-(3,4-dihydro-1*H*-isoquinolin-2-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	504.69
	35	*N*-{2-[2-(5-Benzoimidazol-1-yl-pyridin-3-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethyl}-2-methylamino-propionamide	489.64

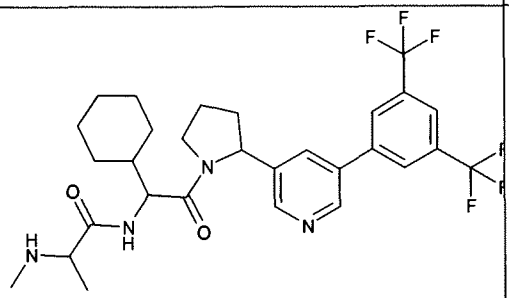
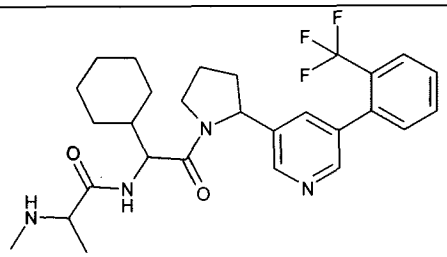
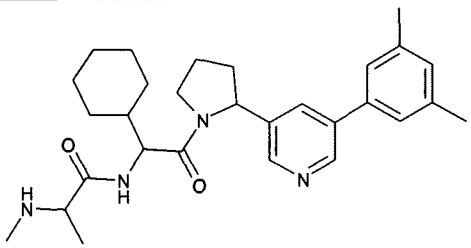
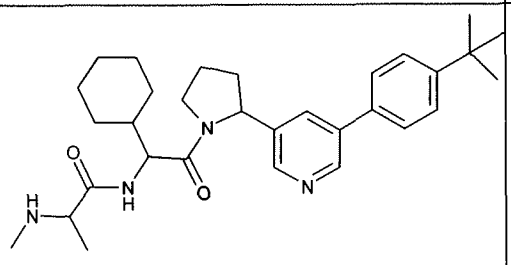
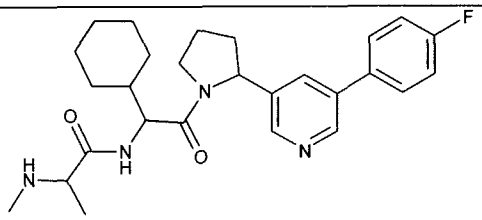
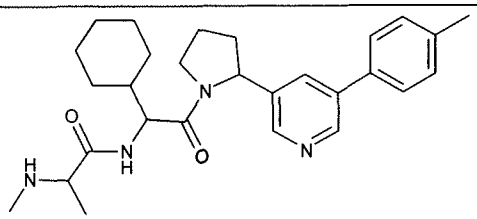
	Example	Name	MS ESI $(M+H)^+$
	36	*N*-{2-[2-(5-Benzotriazol-1-yl-pyridin-3-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethyl}-2-methylamino-propionamide	490.63
	37	*N*-{1-Cyclohexyl-2-[2-(5-indazol-1-yl-pyridin-3-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide	489.64
	38	*N*-(1-Cyclohexyl-2-{2-[2-(5-fluoro-3-methyl-indol-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	520.67
	39	*N*-(1-{2-[2-(5-Fluoro-3-methyl-indol-1-yl)-pyridin-4-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-2-methylamino-propionamide	480.6
	40	*N*-(1-Cyclohexyl-2-{2-[5-(3,4-dihydro-2*H*-quinolin-1-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-ethyl)-2-methylamino-propionamide	490.71

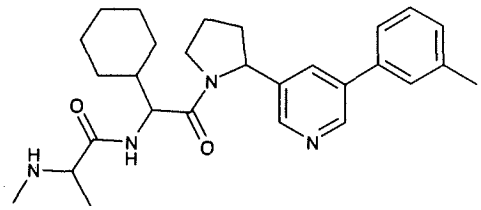
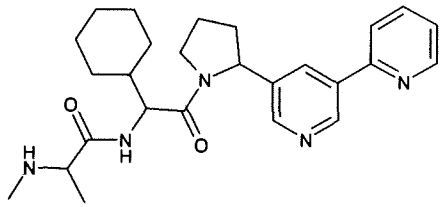
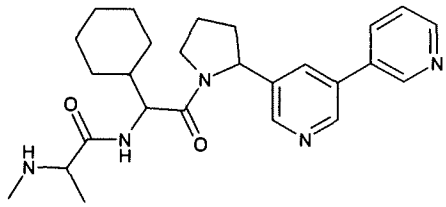
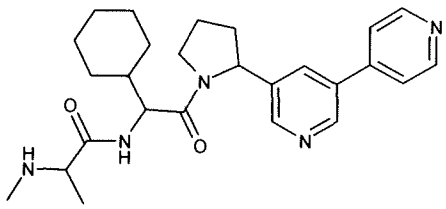
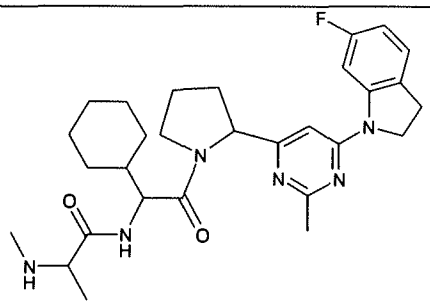
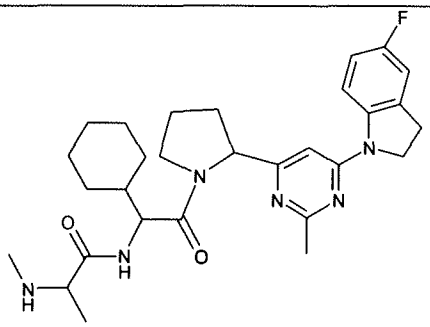
	Example	Name	MS ESI $(M+H)^+$
	41	*N*-(1-Cyclohexyl-2-{2-[5-(3-methyl-indol-1-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	502.68
	42	*N*-(1-Cyclohexyl-2-{2-[5-(5-fluoro-3-methyl-indol-1-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	520.67
	43	*N*-(1-Cyclohexyl-2-{2-[5-(5-fluoro-indol-1-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	506.64
	44	*N*-{1-Cyclohexyl-2-oxo-2-[2-(5-pyrrolo[2,3-*b*]pyridin-1-yl-pyridin-3-yl)-pyrrolidin-1-yl]-ethyl}-2-methylamino-propionamide	489.64
	45	*N*-{2-[2-(2-Benzoimidazol-1-yl-3-fluoro-pyridin-4-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethyl}-2-methylamino-propionamide	507.63

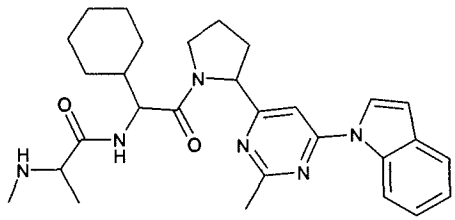
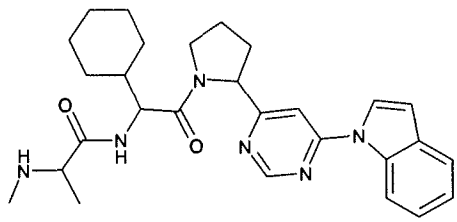
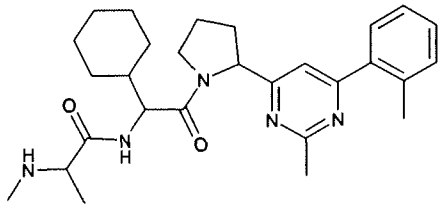
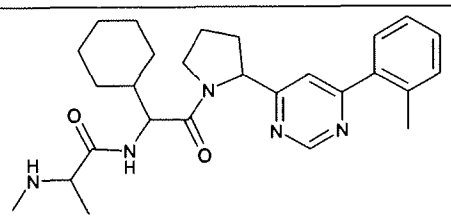
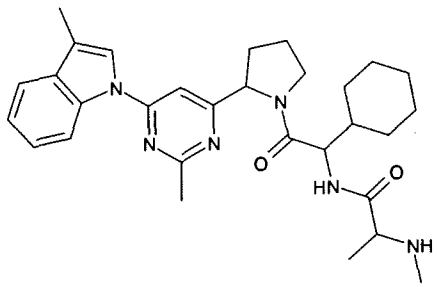
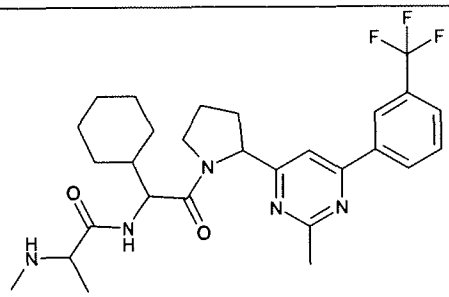
	Example	Name	MS ESI $(M+H)^+$
	46	*N*-{1-[2-(2-Benzoimidazol-1-yl-pyridin-4-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-2-methylamino-propionamide	449.57
	47	3-(5-{1-[2-Cyclohexyl-2-(2-methylamino-propionylamino)-acetyl]-pyrrolidin-2-yl}-pyridin-3-yl)-indole-1-carboxylic acid dimethylamide	559.73
	48	*N*-(1-Cyclohexyl-2-{2-[5-(1-ethyl-1*H*-indol-3-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	516.7
	49	*N*-{1-Cyclohexyl-2-[2-(5-naphthalen-1-yl-pyridin-3-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide	499.67
	50	*N*-(1-Cyclohexyl-2-{2-[4-(6-fluoro-2,3-dihydro-indol-1-yl)-pyridin-2-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	508.66
	51	*N*-(1-Cyclohexyl-2-{2-[4-(5-fluoro-2,3-dihydro-indol-1-yl)-pyridin-2-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	508.66

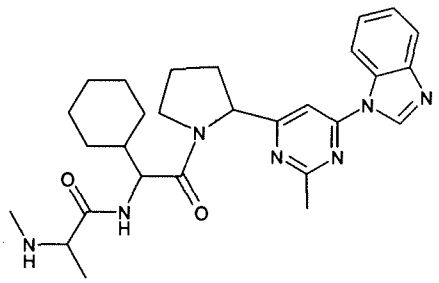
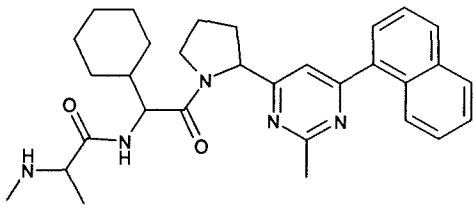
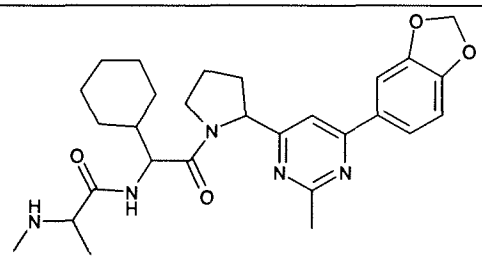
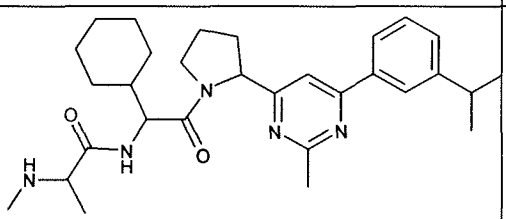
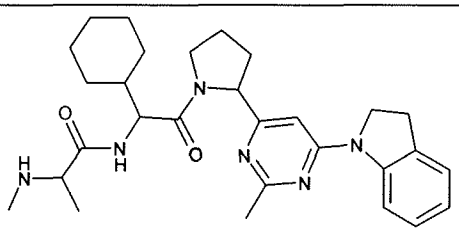
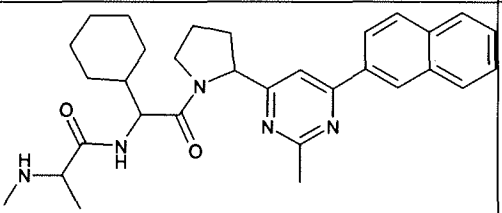
	Example	Name	MS ESI $(M+H)^+$
	52	*N*-(2-{2-[5-(5-Chloro-2-methoxy-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-1-cyclohexyl-2-oxo-ethyl)-2-methylamino-propionamide	514.09
	53	*N*-{1-Cyclohexyl-2-oxo-2-[2-(5-o-tolyl-pyridin-3-yl)-pyrrolidin-1-yl]-ethyl}-2-methylamino-propionamide	463.64
	54	*N*-{2-[2-(5-Benzo[1,3]dioxol-5-yl-pyridin-3-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethyl}-2-methylamino-propionamide	493.62
	55	*N*-(1-Cyclohexyl-2-oxo-2-{2-[5-(3-trifluoromethyl-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-ethyl)-2-methylamino-propionamide	517.61
	56	*N*-(1-Cyclohexyl-2-{2-[5-(3-isopropyl-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	491.69
	57	*N*-{1-Cyclohexyl-2-[2-(5-naphthalen-2-yl-pyridin-3-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide	499.67

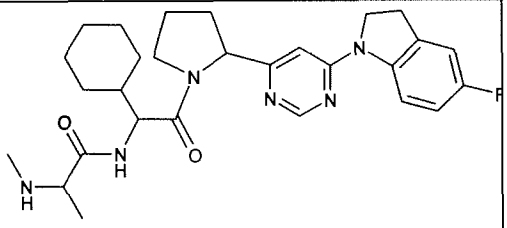
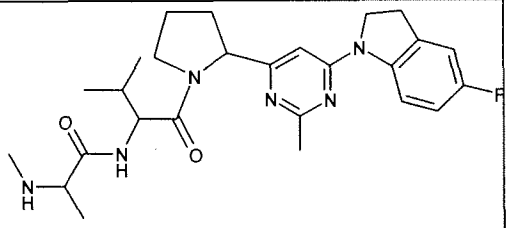
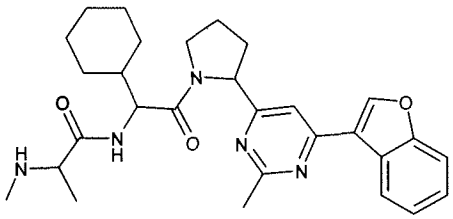
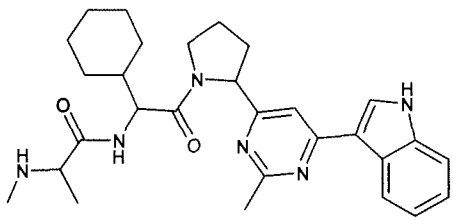
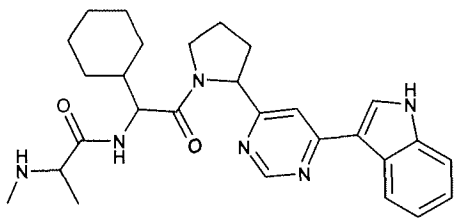
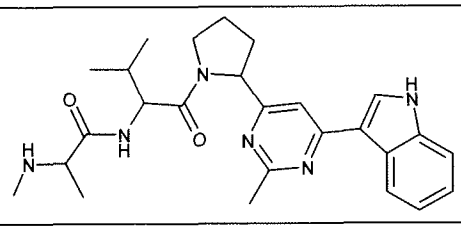
	Example	Name	MS ESI $(M+H)^+$
	58	*N*-{1-Cyclohexyl-2-oxo-2-[2-(7-phenyl-4,5,6,7-tetrahydro-benzothiazol-2-yl)-pyrrolidin-1-yl]-ethyl}-2-methylamino-propionamide	509.73
	59	*N*-{1-Cyclohexyl-2-oxo-2-[2-(1-phenyl-isoquinolin-7-yl)-pyrrolidin-1-yl]-ethyl}-2-methylamino-propionamide	499.67
	60	*N*-{1-Cyclohexyl-2-oxo-2-[2-(7-phenyl-6,7-dihydro-5*H*-[2]pyrindin-4-yl)-pyrrolidin-1-yl]-ethyl}-2-methylamino-propionamide	489.68
	61	*N*-{1-Cyclohexyl-2-oxo-2-[2-(5-phenyl-5,6,7,8-tetrahydro-quinolin-3-yl)-pyrrolidin-1-yl]-ethyl}-2-methylamino-propionamide	503.71
	62	*N*-(1-Cyclohexyl-2-{2-[7-(4-fluoro-phenyl)-benzothiazol-2-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	523.69
	63	*N*-(2-{2-[2-Chloro-5-(3-trifluoromethyl-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-1-cyclohexyl-2-oxo-ethyl)-2-methylamino-propionamide	551.24

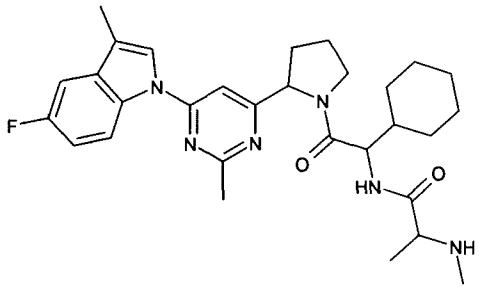
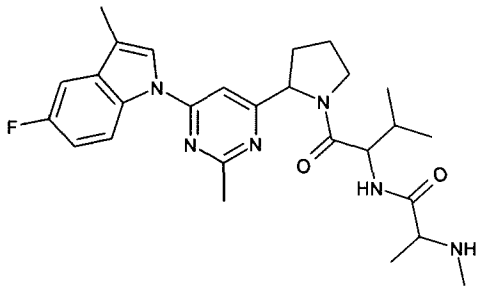
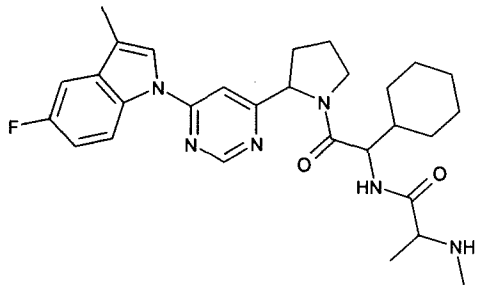
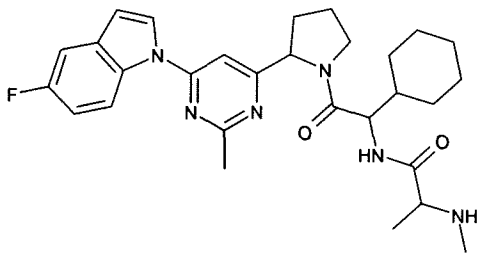
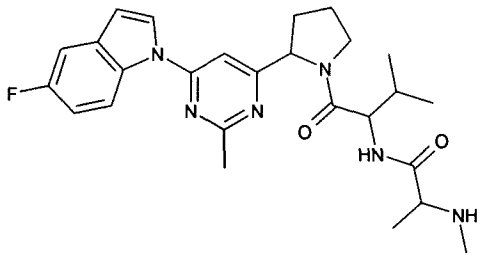
	Example	Name	MS ESI $(M+H)^+$
	64	N-(2-{2-[5-(3,5-Bis-trifluoromethyl-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-1-cyclohexyl-2-oxo-ethyl)-2-methylamino-propionamide	585.27
	65	*N*-(1-Cyclohexyl-2-oxo-2-{2-[5-(2-trifluoromethyl-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-ethyl)-2-methylamino-propionamide	517.28
	66	*N*-(1-Cyclohexyl-2-{2-[5-(3,5-dimethyl-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	477.32
	67	*N*-(2-{2-[5-(4-tert-Butyl-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-1-cyclohexyl-2-oxo-ethyl)-2-methylamino-propionamide	505.35
	68	*N*-(1-Cyclohexyl-2-{2-[5-(4-fluoro-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	467.28
	69	*N*-{1-Cyclohexyl-2-oxo-2-[2-(5-*p*-tolyl-pyridin-3-yl)-pyrrolidin-1-yl]-ethyl}-2-methylamino-propionamide	463.31

	Example	Name	MS ESI $(M+H)^+$
	70	*N*-{1-Cyclohexyl-2-oxo-2-[2-(5-*m*-tolyl-pyridin-3-yl)-pyrrolidin-1-yl]-ethyl}-2-methylamino-propionamide	463.31
	71	*N*-[2-(2-[2,3']Bipyridinyl-5'-yl-pyrrolidin-1-yl)-1-cyclohexyl-2-oxo-ethyl]-2-methylamino-propionamide	450.29
	72	*N*-[2-(2-[3,3']Bipyridinyl-5-yl-pyrrolidin-1-yl)-1-cyclohexyl-2-oxo-ethyl]-2-methylamino-propionamide	450.29
	73	*N*-[2-(2-[3,4']Bipyridinyl-5-yl-pyrrolidin-1-yl)-1-cyclohexyl-2-oxo-ethyl]-2-methylamino-propionamide	450.29
	74	*N*-(1-Cyclohexyl-2-{2-[6-(6-fluoro-2,3-dihydro-indol-1-yl)-2-methyl-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	523.32
	75	*N*-(1-Cyclohexyl-2-{2-[6-(5-fluoro-2,3-dihydro-indol-1-yl)-2-methyl-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	523.32

	Example	Name	MS ESI $(M+H)^+$
	76	N-{1-Cyclohexyl-2-[2-(6-indol-1-yl-2-methyl-pyrimidin-4-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide	503.21
	77	*N*-{1-Cyclohexyl-2-[2-(6-indol-1-yl-pyrimidin-4-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide	489.3
	78	*N*-{1-Cyclohexyl-2-[2-(2-methyl-6-*o*-tolyl-pyrimidin-4-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide	478.32
	79	*N*-{1-Cyclohexyl-2-oxo-2-[2-(6-*o*-tolyl-pyrimidin-4-yl)-pyrrolidin-1-yl]-ethyl}-2-methylamino-propionamide	464.3
	80	*N*-(1-Cyclohexyl-2-{2-[2-methyl-6-(3-methyl-indol-1-yl)-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	517.33
	81	*N*-(1-Cyclohexyl-2-{2-[2-methyl-6-(3-trifluoromethyl-phenyl)-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	532.29

	Example	Name	MS ESI $(M+H)^+$
	82	*N*-{2-[2-(6-Benzoimidazol-1-yl-2-methyl-pyrimidin-4-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethyl}-2-methylamino-propionamide	504.31
	83	*N*-{1-Cyclohexyl-2-[2-(2-methyl-6-naphthalen-1-yl-pyrimidin-4-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide	514.32
	84	*N*-{2-[2-(6-Benzo[1,3]dioxol-5-yl-2-methyl-pyrimidin-4-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethyl}-2-methylamino-propionamide	508.29
	85	*N*-(1-Cyclohexyl-2-{2-[6-(3-isopropyl-phenyl)-2-methyl-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	506.35
	86	*N*-(1-Cyclohexyl-2-{2-[6-(2,3-dihydro-indol-1-yl)-2-methyl-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	505.33
	87	*N*-{1-Cyclohexyl-2-[2-(2-methyl-6-naphthalen-2-yl-pyrimidin-4-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide	504.32

	Example	Name	MS ESI $(M+H)^+$
	88	*N*-(1-Cyclohexyl-2-{2-[6-(5-fluoro-2,3-dihydro-indol-1-yl)-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	509.3
	89	*N*-(1-{2-[6-(5-Fluoro-2,3-dihydro-indol-1-yl)-2-methyl-pyrimidin-4-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-2-methylamino-propionamide	483.29
	90	*N*-{2-[2-(6-Benzofuran-3-yl-2-methyl-pyrimidin-4-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethyl}-2-methylamino-propionamide	504.3
	91	*N*-(1-Cyclohexyl-2-{2-[6-(1*H*-indol-3-yl)-2-methyl-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	503.31
	92	*N*-(1-Cyclohexyl-2-{2-[6-(1*H*-indol-3-yl)-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	489.3
	93	*N*-(1-{2-[6-(1*H*-Indol-3-yl)-2-methyl-pyrimidin-4-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-2-methylamino-propionamide	463.28

	Example	Name	MS ESI $(M+H)^+$
	94	*N*-(1-Cyclohexyl-2-{2-[6-(5-fluoro-3-methyl-indol-1-yl)-2-methyl-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	535.32
	95	*N*-(1-{2-[6-(5-Fluoro-3-methyl-indol-1-yl)-2-methyl-pyrimidin-4-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-2-methylamino-propionamide	495.29
	96	*N*-(1-Cyclohexyl-2-{2-[6-(5-fluoro-3-methyl-indol-1-yl)-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	521.3
	97	*N*-(1-Cyclohexyl-2-{2-[6-(5-fluoro-indol-1-yl)-2-methyl-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	521.3
	98	*N*-(1-{2-[6-(5-Fluoro-indol-1-yl)-2-methyl-pyrimidin-4-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-2-methylamino-propionamide	481.27

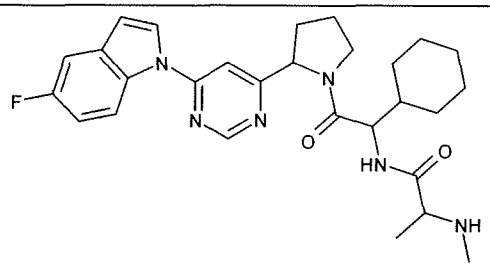
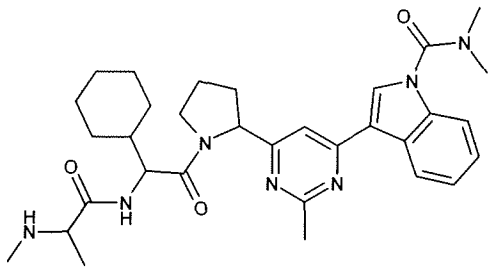
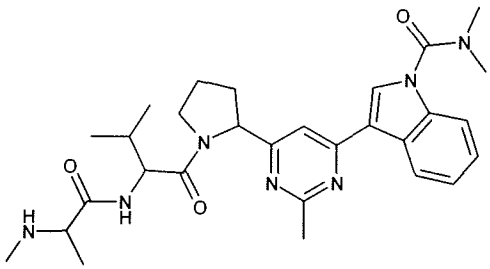
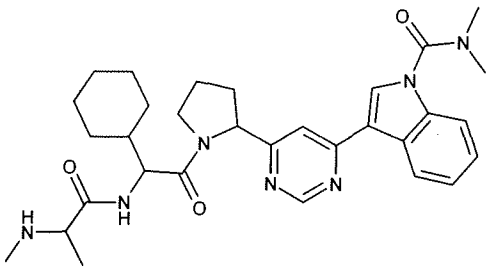
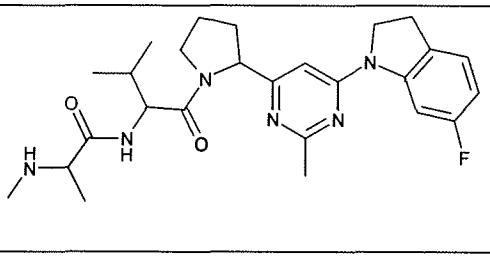
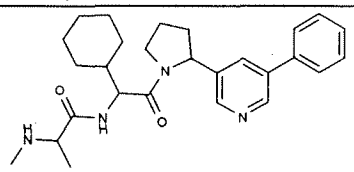
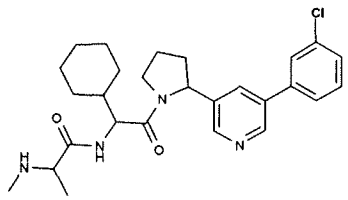
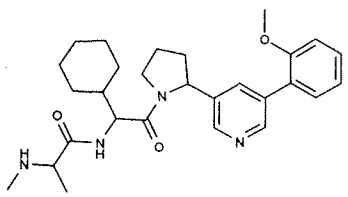
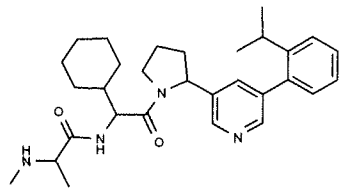
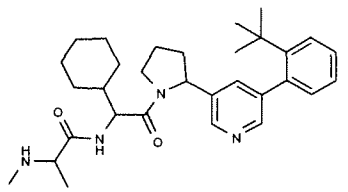
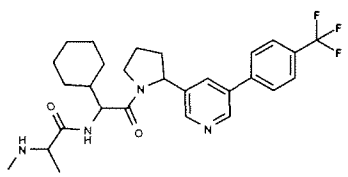
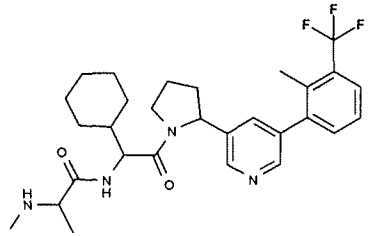
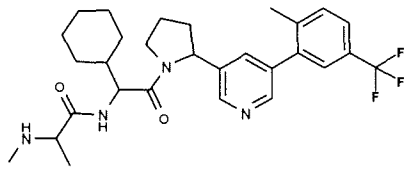
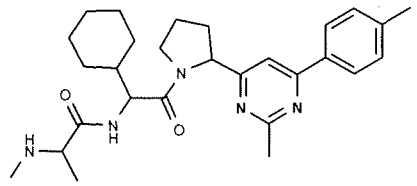
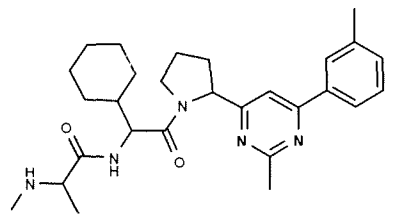
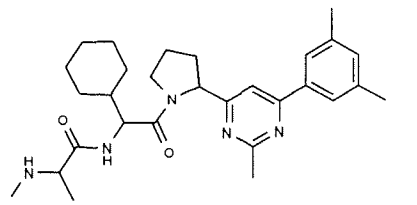
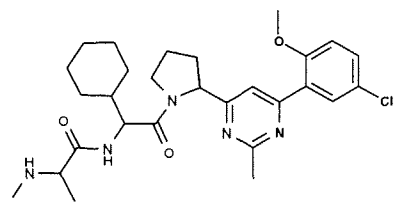
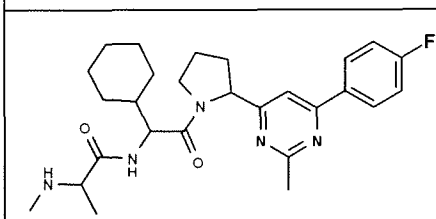
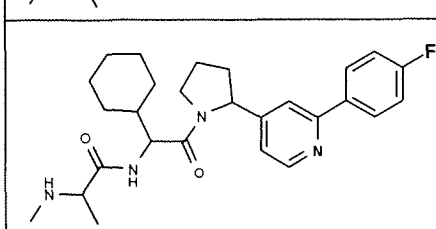
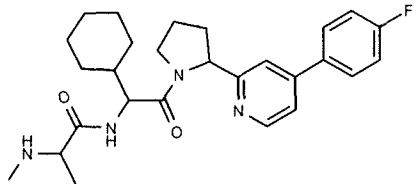
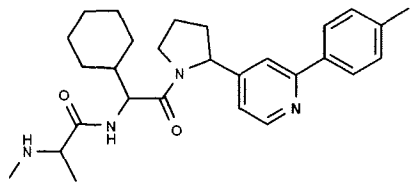
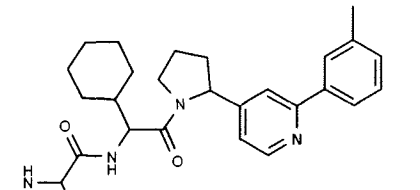
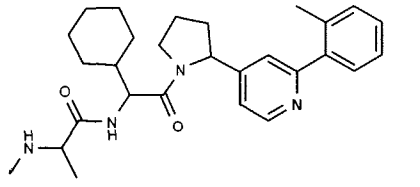
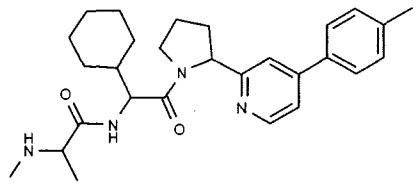
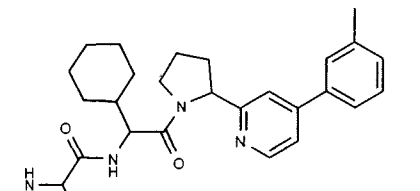
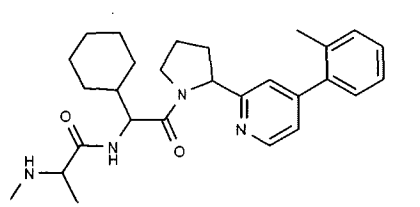
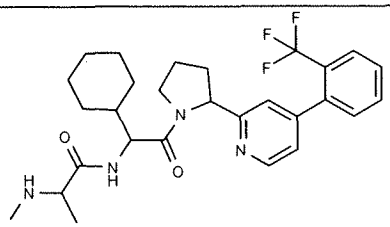
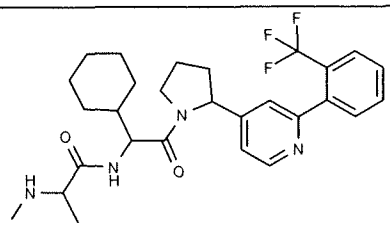
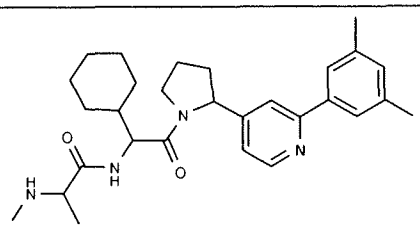
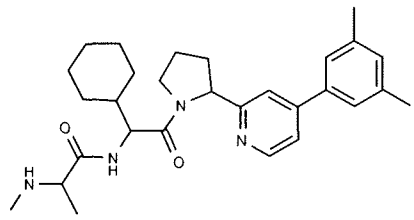
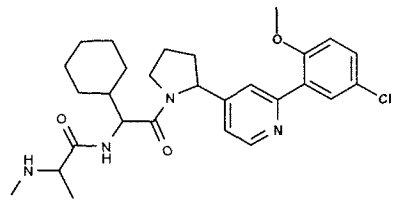
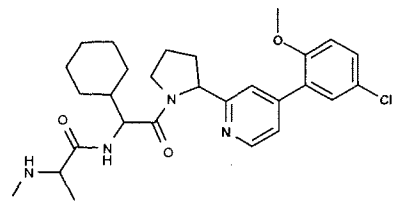
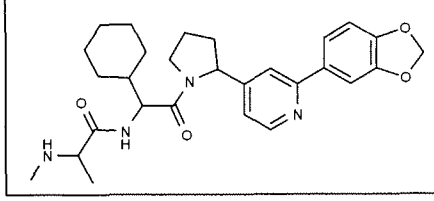
	Example	Name	MS ESI $(M+H)^+$
	99	*N*-(1-Cyclohexyl-2-{2-[6-(5-fluoro-indol-1-yl)-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	507.29
	100	3-(6-{1-[2-Cyclohexyl-2-(2-methylamino-propionylamino)-acetyl]-pyrrolidin-2-yl}-2-methyl-pyrimidin-4-yl)-indole-1-carboxylic acid dimethylamide	574.35
	101	3-(2-Methyl-6-{1-[3-methyl-2-(2-methylamino-propionylamino)-butyryl]-pyrrolidin-2-yl}-pyrimidin-4-yl)-indole-1-carboxylic acid dimethylamide	534.32
	102	3-(6-{1-[2-Cyclohexyl-2-(2-methylamino-propionylamino)-acetyl]-pyrrolidin-2-yl}-pyrimidin-4-yl)-indole-1-carboxylic acid dimethylamide	560.33
	103	*N*-(1-{2-[6-(6-Fluoro-2,3-dihydro-indol-1-yl)-2-methyl-pyrimidin-4-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-2-methylamino-propionamide	483.29

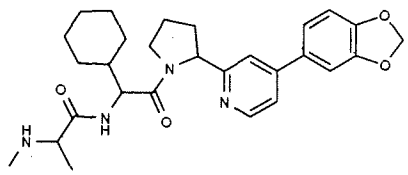
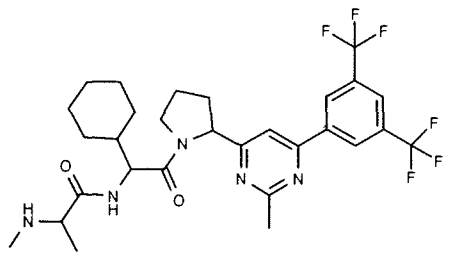
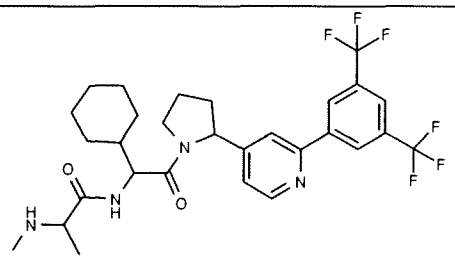
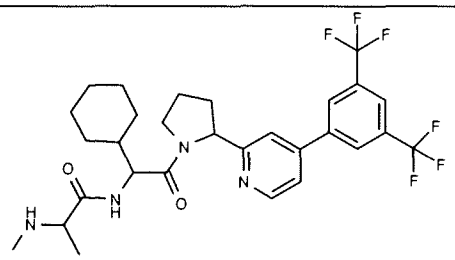
Table 2

structure	Example	name	MS ESI (M+H)+
	104	N-{1-Cyclohexyl-2-oxo-2-[2-(5-phenyl-pyridin-3-yl)-pyrrolidin-1-yl]-ethyl}-2-methylamino-propionamide	449.29
	105	N-(2-{2-[5-(3-Chloro-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-1-cyclohexyl-2-oxo-ethyl)-2-methylamino-propionamide	483.25
	106	N-(1-Cyclohexyl-2-{2-[5-(2-methoxy-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	479.3
	107	N-(1-Cyclohexyl-2-{2-[5-(2-isopropyl-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	491.34
	108	N-(2-{2-[5-(2-tert-Butyl-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-1-cyclohexyl-2-oxo-ethyl)-2-methylamino-propionamide	505.35
	109	N-(1-Cyclohexyl-2-oxo-2-{2-[5-(4-trifluoromethyl-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-ethyl)-2-methylamino-propionamide	517.28
	110	N-(1-Cyclohexyl-2-{2-[5-(2-methyl-3-trifluoromethyl-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	531.29

	111	N-(1-Cyclohexyl-2-{2-[5-(2-methyl-5-trifluoromethyl-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	531.29
	112	N-{1-Cyclohexyl-2-[2-(2-methyl-6-p-tolyl-pyrimidin-4-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide	478.32
	113	N-{1-Cyclohexyl-2-[2-(2-methyl-6-m-tolyl-pyrimidin-4-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide	478.32
	114	N-(1-Cyclohexyl-2-{2-[6-(3,5-dimethyl-phenyl)-2-methyl-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	492.33
	115	N-(2-{2-[6-(5-Chloro-2-methoxy-phenyl)-2-methyl-pyrimidin-4-yl]-pyrrolidin-1-yl}-1-cyclohexyl-2-oxo-ethyl)-2-methylamino-propionamide	528.27
	116	N-(1-Cyclohexyl-2-{2-[6-(4-fluoro-phenyl)-2-methyl-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	482.29
	117	N-(1-Cyclohexyl-2-{2-[2-(4-fluoro-phenyl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	467.28

	118	N-(1-Cyclohexyl-2-{2-[4-(4-fluoro-phenyl)-pyridin-2-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	467.28
	119	N-{1-Cyclohexyl-2-oxo-2-[2-(2-p-tolyl-pyridin-4-yl)-pyrrolidin-1-yl]-ethyl}-2-methylamino-propionamide	463.31
	120	N-{1-Cyclohexyl-2-oxo-2-[2-(2-m-tolyl-pyridin-4-yl)-pyrrolidin-1-yl]-ethyl}-2-methylamino-propionamide	463.31
	121	N-{1-Cyclohexyl-2-oxo-2-[2-(2-o-tolyl-pyridin-4-yl)-pyrrolidin-1-yl]-ethyl}-2-methylamino-propionamide	463.31
	122	N-{1-Cyclohexyl-2-oxo-2-[2-(4-p-tolyl-pyridin-2-yl)-pyrrolidin-1-yl]-ethyl}-2-methylamino-propionamide	463.31
	123	N-{1-Cyclohexyl-2-oxo-2-[2-(4-m-tolyl-pyridin-2-yl)-pyrrolidin-1-yl]-ethyl}-2-methylamino-propionamide	463.31
	124	N-{1-Cyclohexyl-2-oxo-2-[2-(4-o-tolyl-pyridin-2-yl)-pyrrolidin-1-yl]-ethyl}-2-methylamino-propionamide	463.31

	125	N-(1-Cyclohexyl-2-oxo-2-{2-[4-(2-trifluoromethyl-phenyl)-pyridin-2-yl]-pyrrolidin-1-yl}-ethyl)-2-methylamino-propionamide	517.28
	126	N-(1-Cyclohexyl-2-oxo-2-{2-[2-(2-trifluoromethyl-phenyl)-pyridin-4-yl]-pyrrolidin-1-yl}-ethyl)-2-methylamino-propionamide	517.28
	127	N-(1-Cyclohexyl-2-{2-[2-(3,5-dimethyl-phenyl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	477.32
	128	N-(1-Cyclohexyl-2-{2-[4-(3,5-dimethyl-phenyl)-pyridin-2-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide	477.32
	129	N-(2-{2-[2-(5-Chloro-2-methoxy-phenyl)-pyridin-4-yl]-pyrrolidin-1-yl}-1-cyclohexyl-2-oxo-ethyl)-2-methylamino-propionamide	513.26
	130	N-(2-{2-[4-(5-Chloro-2-methoxy-phenyl)-pyridin-2-yl]-pyrrolidin-1-yl}-1-cyclohexyl-2-oxo-ethyl)-2-methylamino-propionamide	513.26
	131	N-{2-[2-(2-Benzo[1,3]dioxol-5-yl-pyridin-4-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethyl}-2-methylamino-propionamide	493.28

	132	N-{2-[2-(4-Benzo[1,3]dioxol-5-yl-py ridin-2-yl)-pyrrolidin-1-yl]-1-cycl ohexyl-2-oxo-ethyl}-2-methylamino-p ropionamide	493.28
	133	N-(2-{2-[6-(3,5-Bis-trifluoromethyl -phenyl)-2-methyl-pyrimidin-4-yl]-p yrrolidin-1-yl}-1-cyclohexyl-2-oxo-ethyl)-2-methylamino-propionamide	600.28
	134	N-(2-{2-[2-(3,5-Bis-trifluoromethyl -phenyl)-pyridin-4-yl]-pyrrolidin-1 -yl}-1-cyclohexyl-2-oxo-ethyl)-2-me thylamino-propionamide	585.27
	135	N-(2-{2-[4-(3,5-Bis-trifluoromethyl -phenyl)-pyridin-2-yl]-pyrrolidin-1 -yl}-1-cyclohexyl-2-oxo-ethyl)-2-me thylamino-propionamide	585.27

The preferred stereochemistry of the compound of Examples 1-103 are:

(*S*)-*N*-{(*S*)-1-Cyclohexyl-2-[(*R*)-2-(1*H*-indol-3-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide;

(*S*)-*N*-{(*S*)-1-Cyclohexyl-2-[(*S*)-2-(1*H*-indol-3-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide;

(*S*)-*N*-{(*S*)-1-Cyclohexyl-2-[(*R*)-2-(1*H*-indol-2-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide;

(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[2-(2,3-dihydro-indol-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[5-(2,3-dihydro-indol-1-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;
(*S*)-*N*-((*R*)-1-Cyclohexyl-2-{(*S*)-2-[5-(2,3-dihydro-indol-1-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;
(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[2-(3,4-dihydro-2*H*-quinolin-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;
(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[2-(2,3-dihydro-pyrrolo[2,3-*b*]pyridin-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamidel;
(*S*)-*N*-{(*S*)-1-Cyclohexyl-2-[(*S*)-2-(5-indol-1-yl-pyridin-3-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide;
(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[5-(3,4-dihydro-2*H*-quinolin-1-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;
(*S*)-*N*-((*S*)-1-Cyclohexyl-2-oxo-2-{(*S*)-2-[2-(2-oxo-3,4-dihydro-2*H*-quinolin-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-ethyl)-2-methylamino-propionamide;
(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[2-(6-fluoro-2,3-dihydro-indol-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;
(*S*)-*N*-((*S*)-1-{(*S*)-2-[2-(6-Fluoro-2,3-dihydro-indol-1-yl)-pyridin-4-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-2-methylamino-propionamide;
(*S*)-*N*-{(*S*)-1-Cyclohexyl-2-[(*S*)-2-(2-isoquinolin-4-yl-pyridin-4-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide;
(*S*)-*N*-{(*S*)-1-Cyclohexyl-2-[(*R*)-2-(2-isoquinolin-4-yl-pyridin-4-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide;
(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;
(*S*)-*N*-{(*S*)-1-Cyclohexyl-2-[(*S*)-2-(2-indazol-1-yl-pyridin-4-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide;
(*S*)-*N*-{(*S*)-2-[(*S*)-2-(5-Benzofuran-3-yl-pyridin-3-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethyl}-2-methylamino-propionamide;
(*S*)-*N*-{(*S*)-2-[(*S*)-2-(2-Benzoimidazol-1-yl-pyridin-4-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethyl}-2-methylamino-propionamide;
(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[2-(3-methyl-indol-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;
(*S*)-2-Methylamino-*N*-((*S*)-2-methyl-1-{(*S*)-2-[2-(3-methyl-indol-1-yl)-pyridin-4-yl]-pyrrolidine-1-carbonyl}-propyl)-propionamide;

(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[5-(1*H*-indol-3-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

(*S*)-*N*-{(*S*)-2-[(*S*)-2-(2-Benzotriazol-1-yl-pyridin-4-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethyl}-2-methylamino-propionamide;

(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[2-(5-fluoro-indol-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[2-(6-fluoro-3,4-dihydro-2*H*-quinolin-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[2-(1*H*-indol-2-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[5-(5-fluoro-2,3-dihydro-indol-1-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[2-(1*H*-indol-3-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

(*S*)-*N*-((*S*)-1-{(*S*)-2-[2-(6-Fluoro-indol-1-yl)-pyridin-4-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-2-methylamino-propionamide;

(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*R*)-2-[2-(6-fluoro-indol-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[2-(6-fluoro-indol-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

(*S*)-*N*-((*S*)-1-Cyclohexyl-2-oxo-2-{(*S*)-2-[5-(2-oxo-benzooxazol-3-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-ethyl)-2-methylamino-propionamide;

(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[2-(1,3-dihydro-isoindol-2-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[2-(3,4-dihydro-1*H*-isoquinolin-2-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

(*S*)-*N*-{(*S*)-2-[(*S*)-2-(5-Benzoimidazol-1-yl-pyridin-3-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethyl}-2-methylamino-propionamide;

(*S*)-*N*-{(*S*)-2-[(*S*)-2-(5-Benzotriazol-1-yl-pyridin-3-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethyl}-2-methylamino-propionamide;

(*S*)-*N*-{(*S*)-1-Cyclohexyl-2-[(*S*)-2-(5-indazol-1-yl-pyridin-3-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide;

(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[2-(5-fluoro-3-methyl-indol-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

(*S*)-*N*-((*S*)-1-{(*S*)-2-[2-(5-Fluoro-3-methyl-indol-1-yl)-pyridin-4-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-2-methylamino-propionamide;
(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[5-(3,4-dihydro-2*H*-quinolin-1-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-ethyl)-2-methylamino-propionamide;
(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[5-(3-methyl-indol-1-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;
(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[5-(5-fluoro-3-methyl-indol-1-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;
(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[5-(5-fluoro-indol-1-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;
(*S*)-*N*-{(*S*)-1-Cyclohexyl-2-oxo-2-[(*S*)-2-(5-pyrrolo[2,3-*b*]pyridin-1-yl-pyridin-3-yl)-pyrrolidin-1-yl]-ethyl}-2-methylamino-propionamide;
(*S*)-*N*-{(*S*)-2-[(*S*)-2-(2-Benzoimidazol-1-yl-3-fluoro-pyridin-4-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethyl}-2-methylamino-propionamide;
(*S*)-*N*-{(*S*)-1-[(*S*)-2-(2-Benzoimidazol-1-yl-pyridin-4-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-2-methylamino-propionamide;
3-(5-{(*S*)-1-[(*S*)-2-Cyclohexyl-2-((*S*)-2-methylamino-propionylamino)-acetyl]-pyrrolidin-2-yl}-pyridin-3-yl)-indole-1-carboxylic acid dimethylamide;
(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[5-(1-ethyl-1*H*-indol-3-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;
(*S*)-*N*-{(*S*)-1-Cyclohexyl-2-[(*S*)-2-(5-naphthalen-1-yl-pyridin-3-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide;
(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[4-(6-fluoro-2,3-dihydro-indol-1-yl)-pyridin-2-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;
(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[4-(5-fluoro-2,3-dihydro-indol-1-yl)-pyridin-2-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;
(*S*)-*N*-((*S*)-2-{(*S*)-2-[5-(5-Chloro-2-methoxy-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-1-cyclohexyl-2-oxo-ethyl)-2-methylamino-propionamide;
(*S*)-*N*-{(*S*)-1-Cyclohexyl-2-oxo-2-[(*S*)-2-(5-o-tolyl-pyridin-3-yl)-pyrrolidin-1-yl]-ethyl}-2-methylamino-propionamide;
(*S*)-*N*-{(*S*)-2-[(*S*)-2-(5-Benzo[1,3]dioxol-5-yl-pyridin-3-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethyl}-2-methylamino-propionamide;
(*S*)-*N*-((*S*)-1-Cyclohexyl-2-oxo-2-{(*S*)-2-[5-(3-trifluoromethyl-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-ethyl)-2-methylamino-propionamide;

(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[5-(3-isopropyl-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

(*S*)-*N*-{(*S*)-1-Cyclohexyl-2-[(*S*)-2-(5-naphthalen-2-yl-pyridin-3-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide;

(*S*)-*N*-{(*S*)-1-Cyclohexyl-2-oxo-2-[(*S*)-2-(7-phenyl-4,5,6,7-tetrahydro-benzothiazol-2-yl)-pyrrolidin-1-yl]-ethyl}-2-methylamino-propionamide;

(*S*)-*N*-{(*S*)-1-Cyclohexyl-2-oxo-2-[(*S*)-2-(1-phenyl-isoquinolin-7-yl)-pyrrolidin-1-yl]-ethyl}-2-methylamino-propionamide;

(*S*)-*N*-{(*S*)-1-Cyclohexyl-2-oxo-2-[(*S*)-2-(7-phenyl-6,7-dihydro-5*H*-[2]pyrindin-4-yl)-pyrrolidin-1-yl]-ethyl}-2-methylamino-propionamide;

(*S*)-*N*-{(*S*)-1-Cyclohexyl-2-oxo-2-[(*S*)-2-(5-phenyl-5,6,7,8-tetrahydro-quinolin-3-yl)-pyrrolidin-1-yl]-ethyl}-2-methylamino-propionamide;

(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[7-(4-fluoro-phenyl)-benzothiazol-2-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

(*S*)-*N*-((*S*)-2-{(*S*)-2-[2-Chloro-5-(3-trifluoromethyl-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-1-cyclohexyl-2-oxo-ethyl)-2-methylamino-propionamide;

(S)-N-((S)-2-{(S)-2-[5-(3,5-Bis-trifluoromethyl-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-1-cyclohexyl-2-oxo-ethyl)-2-methylamino-propionamide;

(*S*)-*N*-((*S*)-1-Cyclohexyl-2-oxo-2-{(*S*)-2-[5-(2-trifluoromethyl-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-ethyl)-2-methylamino-propionamide;

(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[5-(3,5-dimethyl-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

(*S*)-*N*-((*S*)-2-{(*S*)-2-[5-(4-tert-Butyl-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-1-cyclohexyl-2-oxo-ethyl)-2-methylamino-propionamide;

(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[5-(4-fluoro-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

(*S*)-*N*-{(*S*)-1-Cyclohexyl-2-oxo-2-[(*S*)-2-(5-*p*-tolyl-pyridin-3-yl)-pyrrolidin-1-yl]-ethyl}-2-methylamino-propionamide;

(*S*)-*N*-{(*S*)-1-Cyclohexyl-2-oxo-2-[(*S*)-2-(5-*m*-tolyl-pyridin-3-yl)-pyrrolidin-1-yl]-ethyl}-2-methylamino-propionamide;

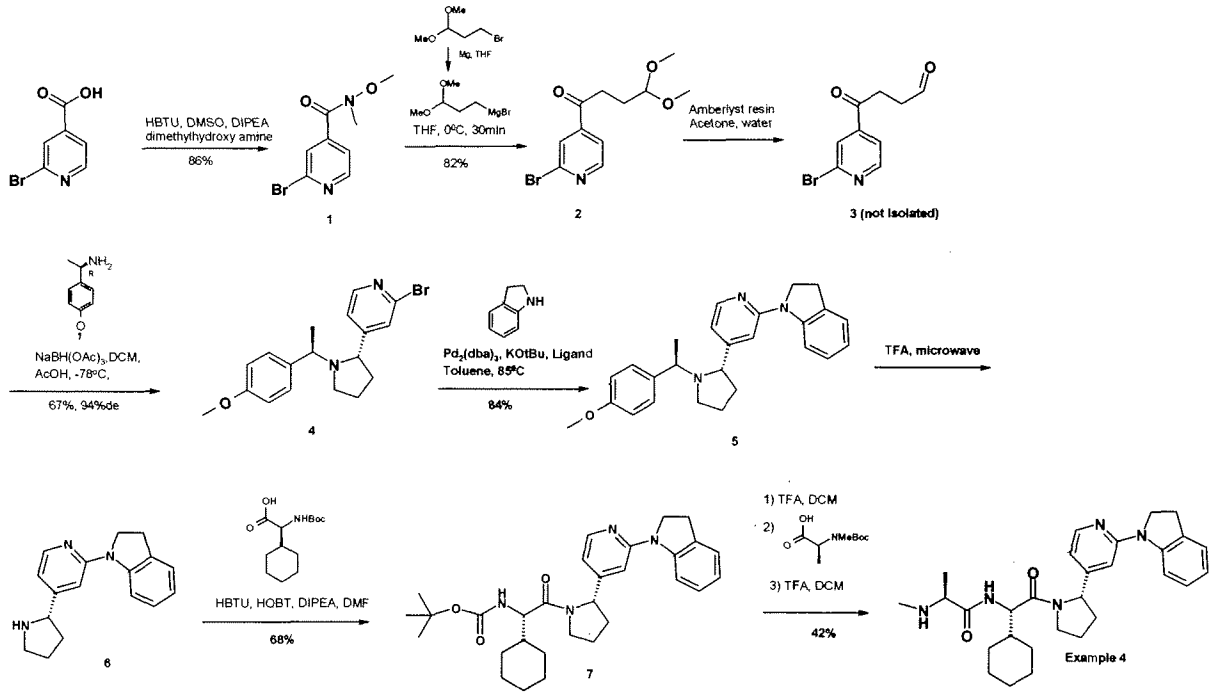
(*S*)-*N*-[(*S*)-2-((*S*)-2-[2,3']Bipyridinyl-5'-yl-pyrrolidin-1-yl)-1-cyclohexyl-2-oxo-ethyl]-2-methylamino-propionamide;

(*S*)-*N*-[(*S*)-2-((*S*)-2-[3,3']Bipyridinyl-5-yl-pyrrolidin-1-yl)-1-cyclohexyl-2-oxo-ethyl]-2-methylamino-propionamide;

(*S*)-*N*-[(*S*)-2-((*S*)-2-[3,4']Bipyridinyl-5-yl-pyrrolidin-1-yl)-1-cyclohexyl-2-oxo-ethyl]-2-methylamino-propionamide;
(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[6-(6-fluoro-2,3-dihydro-indol-1-yl)-2-methyl-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;
(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[6-(5-fluoro-2,3-dihydro-indol-1-yl)-2-methyl-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;
(*S*)-N-{(*S*)-1-Cyclohexyl-2-[(*S*)-2-(6-indol-1-yl-2-methyl-pyrimidin-4-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide;
(*S*)-*N*-{(*S*)-1-Cyclohexyl-2-[(*S*)-2-(6-indol-1-yl-pyrimidin-4-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide;
(*S*)-*N*-{(*S*)-1-Cyclohexyl-2-[(*S*)-2-(2-methyl-6-*o*-tolyl-pyrimidin-4-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide;
(*S*)-*N*-{(*S*)-1-Cyclohexyl-2-oxo-2-[(*S*)-2-(6-*o*-tolyl-pyrimidin-4-yl)-pyrrolidin-1-yl]-ethyl}-2-methylamino-propionamide;
(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[2-methyl-6-(3-methyl-indol-1-yl)-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;
(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[2-methyl-6-(3-trifluoromethyl-phenyl)-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;
(*S*)-*N*-{(*S*)-2-[(*S*)-2-(6-Benzoimidazol-1-yl-2-methyl-pyrimidin-4-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethyl}-2-methylamino-propionamide;
(*S*)-*N*-{(*S*)-1-Cyclohexyl-2-[(*S*)-2-(2-methyl-6-naphthalen-1-yl-pyrimidin-4-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide;
(*S*)-*N*-{(*S*)-2-[(*S*)-2-(6-Benzo[1,3]dioxol-5-yl-2-methyl-pyrimidin-4-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethyl}-2-methylamino-propionamide;
(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[6-(3-isopropyl-phenyl)-2-methyl-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;
(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[6-(2,3-dihydro-indol-1-yl)-2-methyl-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;
(*S*)-*N*-{(*S*)-1-Cyclohexyl-2-[(*S*)-2-(2-methyl-6-naphthalen-2-yl-pyrimidin-4-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide;
(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[6-(5-fluoro-2,3-dihydro-indol-1-yl)-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;
(*S*)-*N*-((*S*)-1-{(*S*)-2-[6-(5-Fluoro-2,3-dihydro-indol-1-yl)-2-methyl-pyrimidin-4-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-2-methylamino-propionamide;

(*S*)-*N*-{(*S*)-2-[(*S*)-2-(6-Benzofuran-3-yl-2-methyl-pyrimidin-4-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethyl}-2-methylamino-propionamide;
(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[6-(1*H*-indol-3-yl)-2-methyl-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;
(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[6-(1*H*-indol-3-yl)-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;
(*S*)-*N*-((*S*)-1-{(*S*)-2-[6-(1*H*-Indol-3-yl)-2-methyl-pyrimidin-4-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-2-methylamino-propionamide;
(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[6-(5-fluoro-3-methyl-indol-1-yl)-2-methyl-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;
(*S*)-*N*-((*S*)-1-{(*S*)-2-[6-(5-Fluoro-3-methyl-indol-1-yl)-2-methyl-pyrimidin-4-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-2-methylamino-propionamide;
(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[6-(5-fluoro-3-methyl-indol-1-yl)-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;
(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[6-(5-fluoro-indol-1-yl)-2-methyl-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;
(*S*)-*N*-((*S*)-1-{(*S*)-2-[6-(5-Fluoro-indol-1-yl)-2-methyl-pyrimidin-4-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-2-methylamino-propionamide;
(*S*)-*N*-((*S*)-1-Cyclohexyl-2-{(*S*)-2-[6-(5-fluoro-indol-1-yl)-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;
3-(6-{(*S*)-1-[(*S*)-2-Cyclohexyl-2-((*S*)-2-methylamino-propionylamino)-acetyl]-pyrrolidin-2-yl}-2-methyl-pyrimidin-4-yl)-indole-1-carboxylic acid dimethylamide;
3-(2-Methyl-6-{(*S*)-1-[(*S*)-3-methyl-2-((*S*)-2-methylamino-propionylamino)-butyryl]-pyrrolidin-2-yl}-pyrimidin-4-yl)-indole-1-carboxylic acid dimethylamide;
3-(6-{(*S*)-1-[(*S*)-2-Cyclohexyl-2-((*S*)-2-methylamino-propionylamino)-acetyl]-pyrrolidin-2-yl}-pyrimidin-4-yl)-indole-1-carboxylic acid dimethylamide;
(*S*)-*N*-((*S*)-1-{(S)-2-[6-(6-Fluoro-2,3-dihydro-indol-1-yl)-2-methyl-pyrimidin-4-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-2-methylamino-propionamide.

Preparation of Example 4 (S)-N-((S)-Cyclohexyl-2-{(S)-2-{2-[2,3-dihydro-indol-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-pyrrolidin-1-yl)-2-oxo-ethyl)-2-methylamino-propionamide.



2-Bromo-N-methoxy-N-methyl-isonicotinamide (1)

To a solution of 2-bromo-pyridine-4-carboxylic acid (11.83 g, 58.56 mmol) in DMSO (100 mL) are added HOBt (9.49 g, 70.30 mmol) and HBTU (26.70 g, 70.30 mmol). The mixture is stirred at room temperature for 20 min, then N,O-dimethylhydroxylamine HCl (6.28 g, 64.41 mmol) and diisopropylethylamine (22.72 g, 175.68 mmol) are added to the mixture. After stirring at room temperature for 3h, the reaction mixture is diluted with water and extracted with EtOAc. The combined organic layers are washed with water, sat. $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated down. The crude product is purified by flash chromatography on silica gel (EtOAc/Hexane: 10% ~ 40%) to give 2-Bromo-N-methoxy-N-methyl-isonicotinamide (12.4 g, 86%) as a white solid. M/Z=245.0

1-(2-Bromo-pyridin-4-yl)-4,4-dimethyoxy-butane-1-one (2)

To a suspension of Mg (3.67 g, 153.01 mmol) in THF (40 mL) is added cat. Iodine, followed by a solution of 3-bromo-1,1-dimethoxy-propane (21.47 g, 117.30 mmol) in THF (40 mL). The mixture is stirred at room temperature for 2 h. Then the fresh prepared Grignard reagent is cooled down in an ice bath, and added to a solution of 2-bromo-N-methoxy-N-methyl-isonicotinamide (12.50 g, 51.00 mmol) in THF (50 mL) at 0°C. The mixture is

warmed up to room temperature and stirred at this temperature for 2 h. Then the reaction mixture is cooled in an ice bath, sat. NH_4Cl and water are added and the mixture is extracted with EtOAc. The combined organic layers are washed with brine, dried over Na_2SO_4, filtered and concentrated down. The crude product is purified by flash chromatography on silica gel (EtOAc/Hexane: 10%) to give 1-(2-Bromo-pyridin-4-yl)-4,4-dimethyoxy-butane-1-one (12.1 g, 82%) as a pale yellow oil. M/Z=288.14

2-Bromo-4-{(S)-1-[(R)-1-(4-methoxy-phenyl)-ethyl]-pyrrolidin-2-yl}-pyridine (4)

To a solution of 1-(2-Bromo-pyridin-4-yl)-4,4-dimethyoxy-butane-1-one (1.34 g, 4.65 mmol) in acetone (15 mL) is added Amberlyst resin 15 (1 g) and water (0.5 mL). After mechanical shaking for 3 h at room temperature, the mixture is filtered. The resin beads are washed with acetone and dichloromethane. The filtrate is concentrated down to give 4-(2-bromo-pyridin-4-yl)-4-oxo-butylaldehyde (**3**), which is used in next step without further purification.

A solution of 4-(2-bromo-pyridin-4-yl)-4-oxo-butylaldehyde in dichloromethane (50 mL) is cooled to -78°C, then sodium triethoxyborohydride (2.96 g, 13.95 mmol) and acetic acid (0.5 mL) are added. After the mixture was stirred at this temperature for 30 min, R(+)-α-methylbenzylamine (0.67 g, 4.42 mmol) is added and the mixture was warmed up to room temperature overnight. Sat. $NaHCO_3$ is added to the mixture and the layers are separated. The aqueous layer is extracted with dichloromethane and the combined organic layers are washed with brine, dried over Na_2SO_4, filtered and concentrated down. The crude product is purified by flash chromatography on silica gel (EtOAc/Hexane: 5% ~ 20%) to give 2-Bromo-4-{(S)-1-[(R)-1-(4-methoxy-phenyl)-ethyl]-pyrrolidin-2-yl}-pyridine as a white solid (1.12 g, 67%). M/Z=361.28

1-(4-{(S)-1-[(R)-1-(4-Methoxy-phenyl)-ethyl]-pyrrolidin-2-yl}-pyridin-2-yl)-2,3-dihydro-1H-indole (5)

To a solution of 2-Bromo-4-{(S)-1-[(R)-1-(4-methoxy-phenyl)-ethyl]-pyrrolidin-2-yl}-pyridine (0.15 g, 0.41 mmol) in toluene (30 mL) are added indoline (0.10 g, 0.83 mmol), 2-(dicyclohexylphosphino)-biphenyl (14 mg, 0.04 mmol), $Pd_2(dba)_3$ (19 mg, 0.02 mmol) and potassium tert-butoxide (0.11 g, 1.04 mmol). The reaction mixture is stirred at 85°C for 3 h and cooled to room temperature. Water and EtOAc are added to the mixture. The layers are separated and the aqueous layer is extracted with EtOAc. The combined organic layers are washed with brine, dried over Na_2SO_4, filtered and concentrated down. The crude product is purified by flash chromatography on silica gel (EtOAc/Hexane: 5% ~ 25%) to give (1-(4-{(S)-

1-[(R)-1-(4-Methoxy-phenyl)-ethyl]-pyrrolidin-2-yl}-pyridin-2-yl)-2,3-dihydro-1H-indole (140 mg, 84%) as an oil. M/Z=400.2 [M+1]

((S)-1-Cyclohexyl-2-{(S)-2-[2-(2,3-dihydro-indol-1-yl)-pridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-carbamic acid tert-butyl ester (7)

A solution of (1-(4-{(S)-1-[(R)-1-(4-Methoxy-phenyl)-ethyl]-pyrrolidin-2-yl}-pyridin-2-yl)-2,3-dihydro-1H-indole (140 mg, 0.35 mmol) in TFA (10 mL) is heated in microwave at 100°C for 30 min and concentrated down to give crude 1-((S)-4-pyrrolidin-2-yl-pyridin-2-yl)-2,3-dihydro-1H-indole (**6**), which is used in next step without further purification.

A solution of (S)-tert-butoxycarbonylamino-cyclohexyl-acetic acid (99 mg, 0.39 mmol), HOBt (57 mg, 0.42 mmol) and HBTU(160 mg, 0.42 mmol) in DMF (10 mL) is stirred at room temperature for 30 min. Then a solution of 1-((S)-4-pyrrolidin-2-yl-pyridin-2-yl)-2,3-dihydro-1H-indole (6) in DMF (10 mL) is added, followed by diisopropylamine (226 mg, 1.75 mmol). After stirring at room temperature for 2 h, the reaction mixture is diluted with water and extracted with EtOAc. The combined organic layers are washed with water, sat. $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated down. The crude product is purified by flash chromatography on silica gel (EtOAc/Hexane: 5% ~ 40%) to give ((S)-1-Cyclohexyl-2-{(S)-2-[2-(2,3-dihydro-indol-1-yl)-pridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-carbamic acid tert-butyl ester as white solid (120 mg, 68%). M/Z=505.3 [M+1]

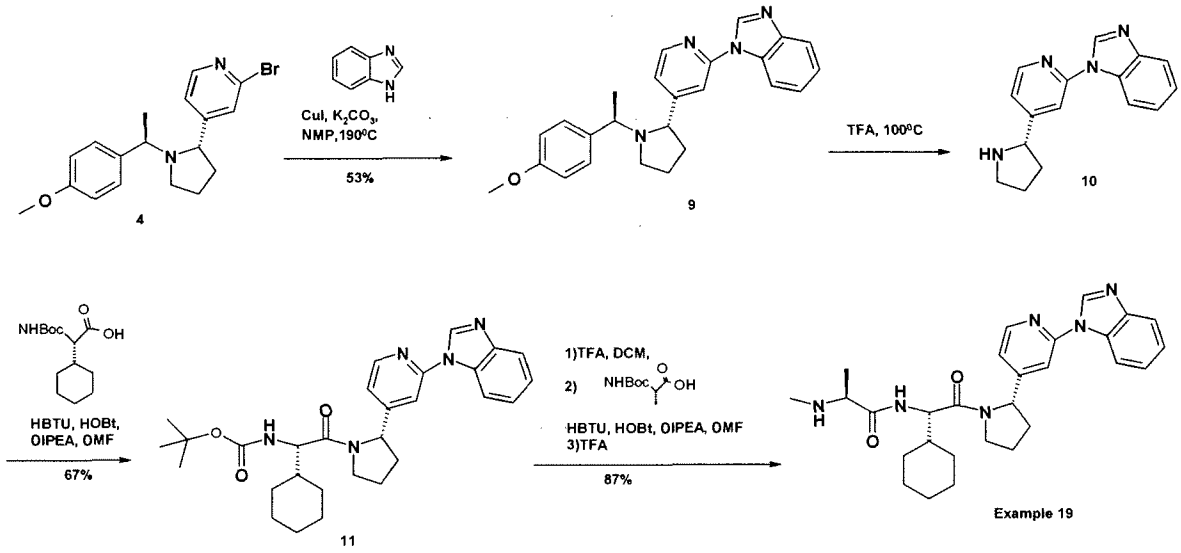
(S)-N-((S)-1-Cyclohexyl-2-{(S)-2-[2-(2,3-dihydro-indol-1-yl)-pridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide (Example 4)

A solution of ((S)-1-Cyclohexyl-2-{(S)-2-[2-(2,3-dihydro-indol-1-yl)-pridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-carbamic acid tert-butyl ester (120 mg, 0.24 mmol) in DCM (5 mL) is added TFA (6 mL). After stirring at room temperature for 1h, the reaction mixture is concentrated down to give crude (S)-2-Amino-2-cyclohexyl-1-{(S)-2-[2-(2,3-dihydro-indol-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-ethanone, which is used in next step without further purification.

A solution of Boc-N-methyl-L-α-alanine (53 mg, 0.26 mmol), HOBt (39 mg, 0.29 mmol) and HBTU (108 mg, 0.29 mmol) in DMF (10 mL) is stirred at room temperature for 30 min. Then a solution of (S)-2-Amino-2-cyclohexyl-1-{(S)-2-[2-(2,3-dihydro-indol-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-ethanone in DMF (10 mL) is added, followed by diisopropylethylamine (153 mg, 1.19 mmol). The mixture is stirs at room temperature for 2 h, then diluted with water

and extracted with EtOAc. The combined organic layers are washed with water, sat. $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated down. The crude product is dissolved in dichloromethane (5 mL). TFA (5 mL) is added. The resulting mixture is stirred at room temperature for 1h and concentrated down to give a crude product, which is purified by prep. reverse phase HPLC (Column: Waters Sunfire Prep C18 OBD 5 μM 30×100 mm; Gradient: AcCN/water with 0.1% TFA: 10% ~ 70%) to give (S)-N-((S)-1-Cyclohexyl-2-{(S)-2-[2-(2,3-dihydro-indol-1-yl)-pridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide (72 mg, 42%) as a TFA salt. M/Z=490.2 [M+1].

Preparation of Example 19 (S)-N-{(S)-2[(S)-2-(2-Benzoimidazol-1-yl-pridin-4-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide.



2-(4-{(S)-1-[(R)-1-(4-methoxy-phenyl)-ethyl]-pyrrolidin-2-yl}-pyridin-2-yl)-1H-benzomidazole (9)

To a solution of 2-Bromo-4-{(S)-1-[(R)-1-(4-methoxy-phenyl)-ethyl]-pyrrolidin-2-yl}-pyridine (0.15 g, 0.41 mmol) in NMP (1 mL) are added benzomidazole (98 mg, 0.83 mmol), copper(I) iodide (8 mg, 0.04 mmol) and potassium carbonate (143 mg, 1.04 mmol). The mixture is heated in microwave at 190°C for 30 min and cooled down. Water and EtOAc are added. The layers are separated and the organic layer is washed with water, brine, dried over Na_2SO_4, filtered and concentrated down. The crude product is purified by flash chromatography on silica gel (EtOAc/Hexane: 5% ~ 15%) to give 2-(4-{(S)-1-[(R)-1-(4-methoxy-phenyl)-ethyl]-pyrrolidin-2-yl}-pyridin-2-yl)-1H-benzomidazole as a yellow solid (88 mg, 53%). M/Z=399.2 [M+1]

{(S)-2-[(S)-2-(2-benzoimidazol-1-yl-pyridin-4-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethyl}-carbamic acid tert-butyl ester (11)

A solution of 2-(4-{(S)-1-[(R)-1-(4-methoxy-phenyl)-ethyl]-pyrrolidin-2-yl}-pyridin-2-yl)-1H-benzomidazole (88 mg, 0.21 mmol) in TFA (5 mL) is heated in microwave at 100°C for 30 min and concentrated down to give crude 1-((S)-4-pyrrolidin-2-yl-pyridine-2-yl)-1H-benzoimidazole (**10**), which is used in next step without further purification.

A solution of (S)-tert-butoxycarbonylamino-cyclohexyl-acetic acid (51 mg, 0.21 mmol), HOBt (31mg, 0.23 mmol) and HBTU (88 mg, 0.23 mmol) in DMF (5 mL) is stirred at room temperature for 30 min. Then a solution of -((S)-4-pyrrolidin-2-yl-pyridine-2-yl)-1H-benzoimidazole (**10**) in DMF (5 mL) is added, followed by diisopropylethylamine (135 mg, 1.05 mmol). After stirring at room temperature for 2 h, the reaction mixture is diluted with water and extracted with EtOAc. The combined organic layers are washed with water, sat. $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated down. The crude product is purified by flash chromatography on silica gel (EtOAc/Hexane: 5% ~ 40%) to give {(S)-2-[(S)-2-(2-benzoimidazol-1-yl-pyridin-4-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethyl}-carbamic acid tert-butyl ester (71 mg, 67%) as a white solid. M/Z=504.2 [M+1]

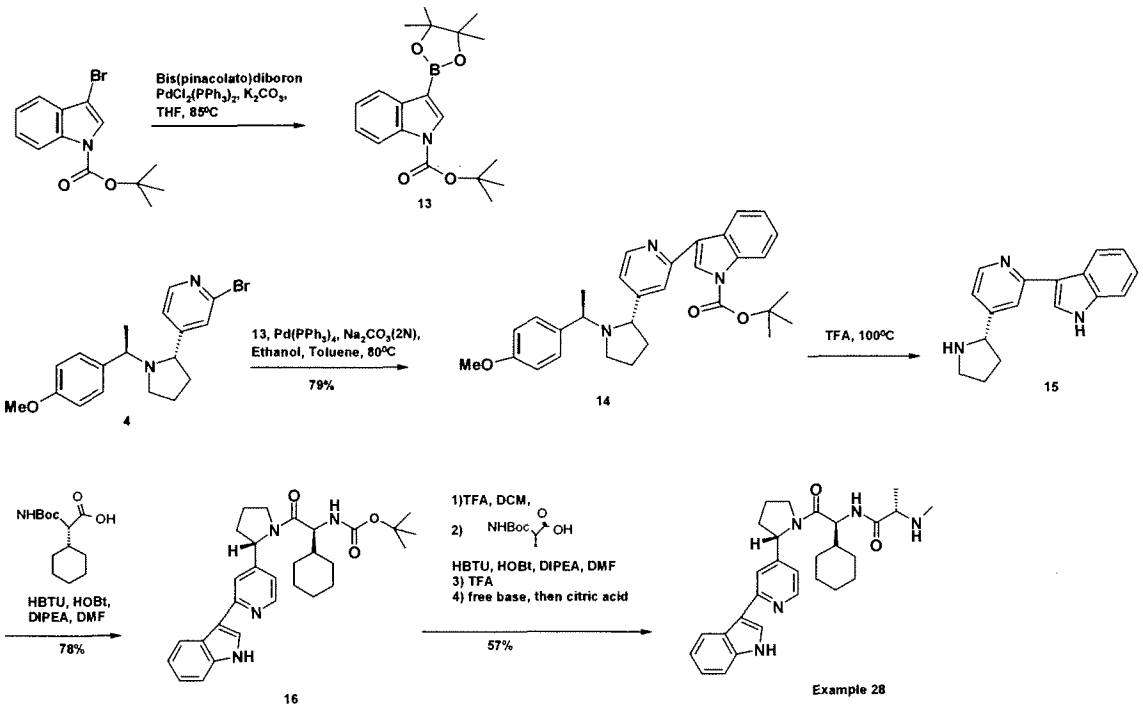
(S)-N-{(S)-2[(S)-2-(2-Benzoimidazol-1-yl-pridin-4-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide (Example 18)

A solution of {(S)-2-[(S)-2-(2-benzoimidazol-1-yl-pyridin-4-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethyl}-carbamic acid tert-butyl ester (70 mg, 0.14 mmol) in DCM (2 mL) is added TFA (2 mL). After stirring at room temperature for 1h, the reaction mixture is concentrated down to give crude (S)-2-Amino-1-[(S)-2-(2-benzoimidazol-1-yl-pyridin-4-yl)-pyrrolidin-1-yl]-2-cyclohexyl-ethanone, which is used in next step without further purification.

A solution of Boc-N-methyl-L-α-alanine (27 mg, 0.14 mmol), HOBt (21 mg, 0.15 mmol) and HBTU(58mg, 0.15 mmol) in DMF (5 mL) is stirred at room temperature for 30 min. Then a solution of (S)-2-Amino-1-[(S)-2-(2-benzoimidazol-1-yl-pyridin-4-yl)-pyrrolidin-1-yl]-2-cyclohexyl-ethanone in DMF (5 mL) is added, followed by diisopropylethylamine (90 mg, 0.69 mmol). After stirring at room temperature for 2 h, the reaction mixture is diluted with water and extracted with EtOAc. The combined organic layers are washed with water, sat. $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated down. The crude product is dissolved in dichloromethane (2 mL) and TFA (2 mL) is added. The resulting mixture is stirred at room temperature for 1h and concentrated down to give a crude product, which is

purified by prep. reverse phase HPLC (Column: Waters Sunfire Prep C18 OBD 5 uM 30×100 mm; Gradient: AcCN/water with 0.1% TFA: 10% ~ 70%) to give (S)-N-{(S)-2[(S)-2-(2-Benzoimidazol-1-yl-pridin-4-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide (87 mg, 87%) as a TFA salt. Mass M/Z=489.36 [M+1]).

Preparation of Example 28 (S)-N-((S)-1-Cyclohexyl-2-{(S)-2-[2-[2-(1H-indol-3-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide.



3-(4-{(S)-1-[(R)-1-(4-Methoxy-phenyl)-ethyl]-pyrrolidin-2-yl}-pyridin-2yl)-indole-1-carboxylic acid tert-butyl ester (14)

To a solution of 3-bromoindole-1-carboxylic acid tert-butyl ester (200 mg, 0.67 mmol) in THF(10 mL) are added bis(pinacolato)diboron (257 mg, 1.01 mmol), $PdCl_2(PPh_3)_2$ (23 mg, 0.03 mmol) and potassium carbonate (0.23 g, 2.36 mmol). The reaction mixture is stirred at 85°C overnight, cooled to room temperature, filtered through a celite pad and concentrated down to give crude 3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indole-1-carboxylic acid tert-butyl ester (**13**), which is used in next step without further purification.

To a solution of 2-Bromo-4-{(S)-1-[(R)-1-(4-methoxy-phenyl)-ethyl]-pyrrolidin-2-yl}-pyridine (160 mg, 0.44 mmol) in a mixture of toluene (9 mL) and ethanol (3 mL) are added 3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indole-1-carboxylic acid tert-butyl ester (228 mg, 0.66

mmol), $Pd(PPh_3)_4$ (51 mg, 0.04 mmol) and sodium carbonate (2N) (0.7 mL, 1.40 mmol). The reaction mixture is stirred at 85°C overnight, cooled to room temperature. Water and EtOAc are added to the mixture. The layers are separated and the aqueous layer is extracted with EtOAc. The combined organic layers are washed with brine, dried over Na_2SO_4, filtered and concentrated down. The crude product is purified by flash chromatography on silica gel (EtOAc/Hexane: 10% ~ 90%) to give 3-(4-{(S)-1-[(R)-1-(4-Methoxy-phenyl)-ethyl]-pyrrolidin-2-yl}-pyridin-2yl)-indole-1-carboxylic acid tert-butyl ester as a yellow solid (175 mg, 79%). M/Z=498.32 [M+1]

((S)-1-Cyclohexyl-2-{(S)-2-[2-(1H-indol-3-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-carbamic acid tert-butyl ester (16)

A solution of 3-(4-{(S)-1-[(R)-1-(4-Methoxy-phenyl)-ethyl]-pyrrolidin-2-yl}-pyridin-2yl)-indole-1-carboxylic acid tert-butyl ester (160 mg, 0.31 mmol) in TFA (5 mL) is heated in microwave at 100°C for 30 min and concentrated down to give crude 3-((S)-4-pyrrolidin-2-yl-pyridine-2-yl)-1H-indole (**15**), which is used in next step without further purification.

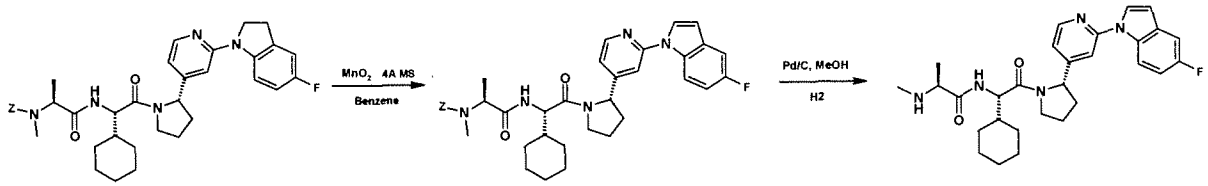
A solution of (S)-tert-butoxycarbonylamino-cyclohexyl-acetic acid (75 mg, 0.29 mmol), HOBt (46mg, 0.33 mmol) and HBTU (127mg, 0.33 mmol) in DMF (5 mL) is stirred at room temperature for 30 min. Then a solution of 3-((S)-4-pyrrolidin-2-yl-pyridine-2-yl)-1H-indole (**15**) in DMF (5 mL) is added, followed by diisopropylethylamine (198 mg, 1.50 mmol). After stirring at room temperature for 2 h, the reaction mixture is diluted with water and extracted with EtOAc. The combined organic layers are washed with water, sat. $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated down. The crude product is purified by flash chromatography on silica gel (EtOAc/Hexane: 5% ~ 40%) to give ((S)-1-Cyclohexyl-2-{(S)-2-[2- (1H-indol-3-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-carbamic acid tert-butyl ester as a yellow solid (120 mg, 78%). Mass M/Z=503.34 [M+1]

(S)-N-((S)-1-Cyclohexyl-2-{(S)-2-[2-[2-(1H-indol-3-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide (Example 28)

A solution of ((S)-1-Cyclohexyl-2-{(S)-2-[2- (1H-indol-3-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-carbamic acid tert-butyl ester (120 mg, 0.24 mmol) in DCM (2 mL) is added TFA (2 mL). After stirring at room temperature for 1h, the reaction mixture is concentrated down to give crude (S)-2-Amino-2-cyclohexyl-1-{(S)-2-[2-(1H-indole-3-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-ethanone, which is used in next step without purification.

A solution of Boc-N-methyl-L-α-alanine (46 mg, 0.22 mmol), HOBt (35 mg, 0.26 mmol) and HBTU (100 mg, 0.26 mmol) in DMF (5 mL) is stirred at room temperature for 30 min. Then a solution of (S)-2-Amino-2-cyclohexyl-1-{(S)-2-[2-(1H-indole-3-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-ethanone in DMF (5 mL) is added, followed by diisopropylethylamine (154 mg, 1.19 mmol). After stirring at room temperature for 2 h, the reaction mixture is diluted with water and extracted with EtOAc. The combined organic layers are washed with water, sat. $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated down. The crude product is dissolved in dichloromethane (2 mL) and TFA (2 mL) is added. The resulting mixture is stirred at room temperature for 1h and concentrated down to give a crude product, which is purified by prep. reverse phase HPLC (Column: Waters Sunfire Prep C18 OBD 5 uM 30×100 mm; Gradient: AcCN/water with 0.1% TFA: 10% ~ 70%)) to give (S)-N-((S)-1-Cyclohexyl-2-{(S)-2-[2-[2-(1H-indol-3-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide (91 mg, 56%) as a TFA salt. Mass M/Z=488.33 [M+1].

Preparation of Example 24 (S)-N-((S)-1-Cyclohexyl-2-{(S)-2-[2-(5-fluoro-indol-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide



18 19 Example 24

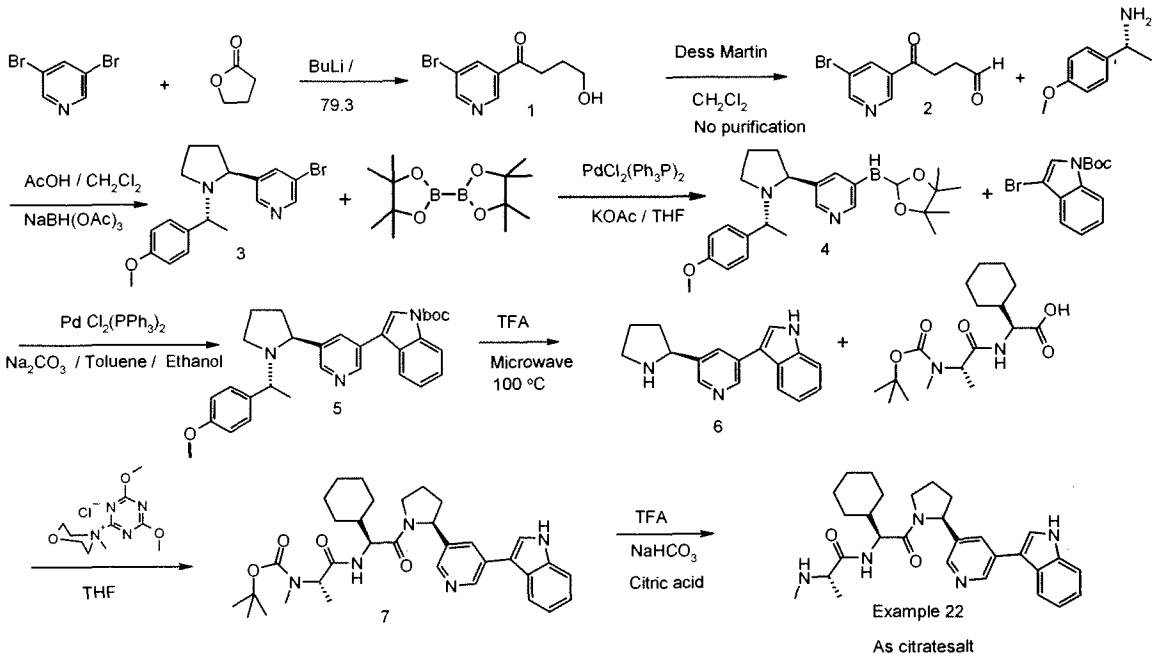
[(S)-1-((S)-1-Cyclohexyl-2-{(S)-2-[2-(5-fluoro-indol-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethylcarbamoyl)-ethyl]-methyl-carbamic acid benzyl ester (19)

A solution of [(S)-1-((S)-1-Cyclohexyl-2-{(S)-2-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-pridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethylcarbamoyl)-ethyl]-methyl-carbamic acid benzyl ester (18) (50 mg, 0.08 mmol, prepared with a similar procedure of **7**) in benzene (2 mL) is added the activated MnO_2 (72 mg, 820 mmol) and grounded 4 Á molecular sieves (0.1g). After stirring at 45°C for 1h, the reaction mixture is concentrated down to give crude [(S)-1-((S)-1-Cyclohexyl-2-{(S)-2-[2-(5-fluoro-indol-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethylcarbamoyl)-ethyl]-methyl-carbamic acid benzyl ester (**19**) (39 mg, 78%), which is used in next step without further purification. M/Z=640.1[M+1].

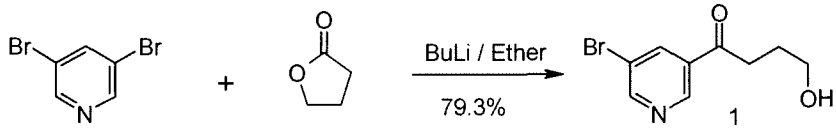
(S)-N-((S)-1-Cyclohexyl-2-{(S)-2-[2-(5-fluoro-indol-1-yl)-pyridin-4-yl]-pyrroli din-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide (Example 24)

A solution of [(S)-1-((S)-1-Cyclohexyl-2-{(S)-2-[2-(5-fluoro-indol-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethylcarbamoyl)-ethyl]-methyl-carbamic acid benzyl ester (**19**) (23 mg, 0.04 mmol) in 2 ml methanol, is added 23 mg of 10% Pd/C. The hydrogen gas balloon is connected with the reaction flask and the reaction is stirred at room temperature for 60 min. The catalyst is filtered out and the organic solvent is concentrated down under a reduced pressure. The crude product is purified by prep. Analogix column (Gradient: Ethyl acetate/MeOH=1:0 to 1:9) to give (S)-N-((S)-1-Cyclohexyl-2-{(S)-2-[2-(5-fluoro-indol-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide (**Example 24**) as a free base (9.9 mg, 55%). M/Z=506.1 [M+1].

Preparation of Example 22 (S)-N-((S)-1-Cyclohexyl-2-{(S)-2-[5-(1H-indol-3-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide



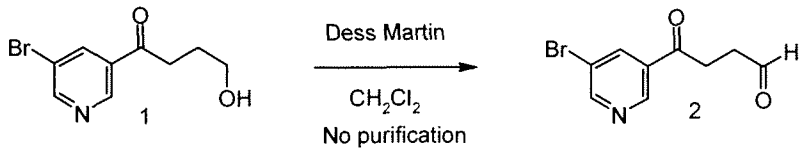
Step 1.



1-(5-Bromo-pyridin-3-yl)-4-hydroxy-butan-1-one (1)

To a solution of 3,5-bibromopyridine (20.0 g, 84.4 mmole) in 300 mL of ether at – 70°C, was slowly added BuLi (30.4 mL, 75.96 mmole, 2.5 M in hexane) (maintaining internal T< -65°C). After stirring at –70°C for 1 hour, γ-butyroactone (10.9 g, 126.6 mmole) was added slowly (maintaining internal T<-65°C). After stirring at –70°C for two hours, the reaction mixture was warmed to 0°C, and quenched with 100 mL of water and extracted with 2 x 150 mL of ether. The combined organic layers was concentrated and purified by chromatography (CH_2Cl_2 95%, EtOAc 5%) to give 1-(5-Bromo-pyridin-3-yl)-4-hydroxy-butan-1-one **1** (14.7 g, yield 79%) as pale yellow liquid.

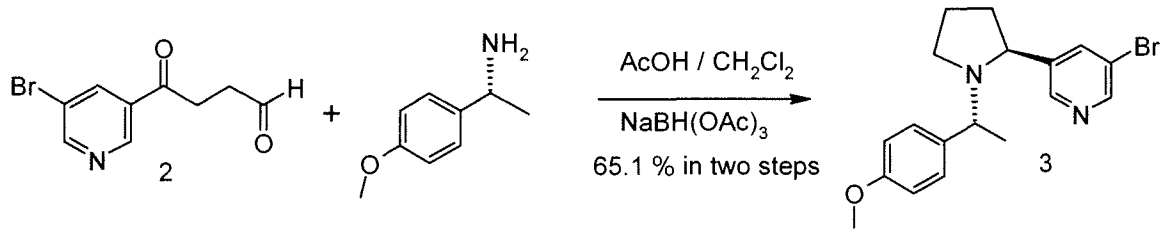
Step 2.



4-(5-Bromo-pyridin-3-yl)-4-oxo-butyraldehyde (2)

To a solution of 1-(5-Bromo-pyridin-3-yl)-4-hydroxy-butan-1-one **1** (5.0 g, 20.5 mmole) in 90 mL of CH_2Cl_2 at 25°C, was slowly added a solution of Dess-Martin periodinane (9.6 g, 22.5 mmole) in 70 mL of CH_2Cl_2. After stirring at 25°C for 20 minutes, the reaction mixture was diluted with 200 mL of ether and cooled by dry-ice-acetone bath. The solid precipitant was filtered out and discarded, and the filtrate was concentrated. The residue was diluted with 100 mL of ether and cooled by dry-ice-acetone bath and the precipitate was removed by filtration. The filtrate was concentrated to give 6.2 g of 4-(5-Bromo-pyridin-3-yl)-4-oxo-butyraldehyde **2** as a pale/brown oily liquid which turned to a pale brown solid after being cooled to 0°C, which was used without further purification for next step reaction.

Step 3.

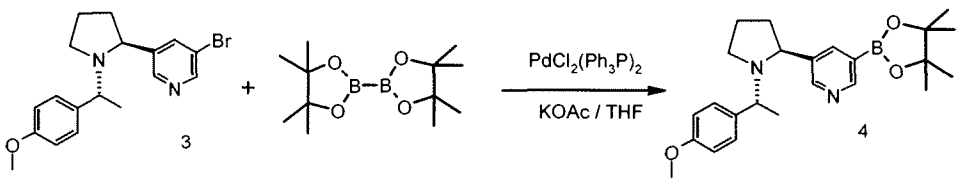


3-Bromo-5-{(S)-1-[(R)-1-(4-methoxy-phenyl)-ethyl]-pyrrolidin-2-yl}-pyridine (3)

To a solution of 4-(5-Bromo-pyridin-3-yl)-4-oxo-butyraldehyde **2** (crude from step 2, 20.5 mmole) in 150 mL of CH_2Cl_2 at –70°C, was slowly added 3.5 mL of acetic acid and

triacetoxyl sodium borohydride (10.2g, 48.0 mmole) and then R-(+)-1-(4-methoxyphenyl)ethylamine (3.9 g, 26.0 mmole) with stirring. After stirring at –70°C for 1 hour, the reaction mixture was warmed to room temperature. After stirring at room temperature for 2 hours, the reaction mixture was diluted with 200 ml of CH_2Cl_2, and washed with a solution of 50 mL of water and 20 mL of saturated sodium bicarbonate, and 2 X 100 mL of water. After concentration, the crude product (dr = 86 : 14 by HPLC analysis) was purified by flash column chromatography (CH_2Cl_2 95%, EtOAc 5%) to give 3-Bromo-5-{(S)-1-[(R)-1-(4-methoxy-phenyl)-ethyl]-pyrrolidin-2-yl}-pyridine **3** (3.2 g, yield 44% in two steps) as a light brown viscose liquid.

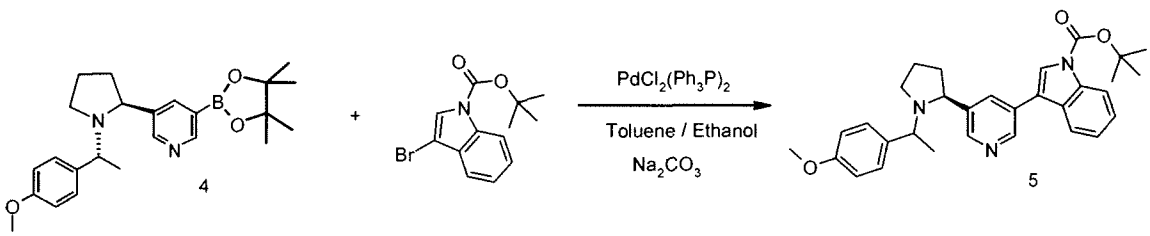
Step 4



3-{(S)-1-[(R)-1-(4-Methoxy-phenyl)-ethyl]-pyrrolidin-2-yl}-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine (4)

The mixture of 3-Bromo-5-{(S)-1-[(R)-1-(4-methoxy-phenyl)-ethyl]-pyrrolidin-2-yl}-pyridine **3** (2.5 g. 6.93 mmole), bis(pinacolato)diboron (2.46 g, 9.67 mmol), dichloro-bis(triphenylphosphine)palladium(II) (1.05g, 1.5 mmole) and potassium acetate (4.9 g, 50mmole) in 40 mL of THF was degassed under vaccum. After stirring at 80°C in a seal glass bottle with nitrogen for 2 hours, the reaction mixture was cooled to room temperature and diluted with 150 mL EtOAc. After filtration, the flitrate was washed with 2 X 100 mL of water and dried over Na_2SO_4, and concentrated to give 3-{(S)-1-[(R)-1-(4-Methoxy-phenyl)-ethyl]-pyrrolidin-2-yl}-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine **4** (4.99 g) as a deep brown gum, a crude product without further purification for next step reaction.

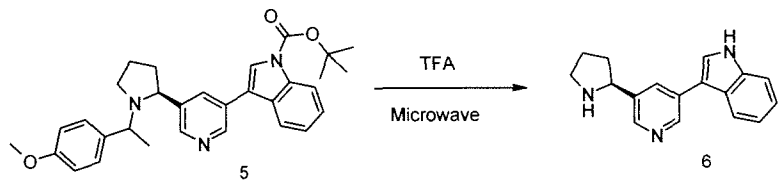
Step 5



3-(5-{(S)-1-[1-(4-Methoxy-phenyl)-ethyl]-pyrrolidin-2-yl}-pyridin-3-yl)-indole-1-carboxylic acid tert-butyl ester (5)

A mixture of 3-{(S)-1-[(R)-1-(4-Methoxy-phenyl)-ethyl]-pyrrolidin-2-yl}-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine **4** (crude, 6.93 mmole), 3-bromo-indole-1-carboxylic acid tert-butyl ester (2.46 g, 8.32 mmole), Na_2CO_3 (35 mL, 35 momle, 1 M aqueous) in a mixed solution of 50 mL of toluene and 20 mL of ethanol was degased under vaccum. After heat at 80 °C for 1.5 hours, the reaction mixture was cooled to room temperature and dilutied with 150 mL of EtOAc, and washed by 2 X 100 mL of water. The organic layer was filtered and concentrated. The crude producte was purified by flash chromatography (Hexane 70%, EtOAc 30%) to give 3-(5-{(S)-1-[1-(4-Methoxy-phenyl)-ethyl]-pyrrolidin-2-yl}-pyridin-3-yl)-indole-1-carboxylic acid tert-butyl ester **5** (2.02 g, 59 % in two steps) as light brown gum.

Step 6

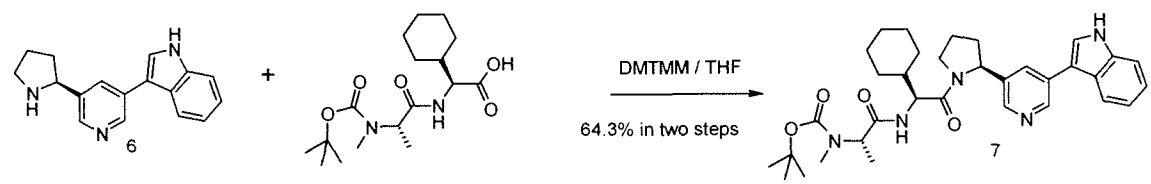


5 6

3-((S)-5-Pyrrolidin-2-yl-pyridin-3-yl)-1H-indole (6)

A solution of 3-(5-{(S)-1-[1-(4-Methoxy-phenyl)-ethyl]-pyrrolidin-2-yl}-pyridin-3-yl)-indole-1-carboxylic acid tert-butyl ester **5** (300 mg, 0.63 mmole) in 4 mL of TFA was heated at 100 °C in a microwave reactor for 20 minutes. The result solution was concentrated to remove TFA as much as possible. The residue was purified by HPLC (Column: Waters Sunfire, 30 X 30 mm; Mobile phase: CH_3CN 15% H_2O 85% with 0.1% TFA to CH_3CN 60% H_2O 40% with 0.1% TFA by gradient in 11 minutes; Flow rate 45 mL/minute; Detector: 215 nm UV) to give 3-((S)-5-Pyrrolidin-2-yl-pyridin-3-yl)-1H-indole **6** (78 mg, yield 49%) as white solid.

Step 7

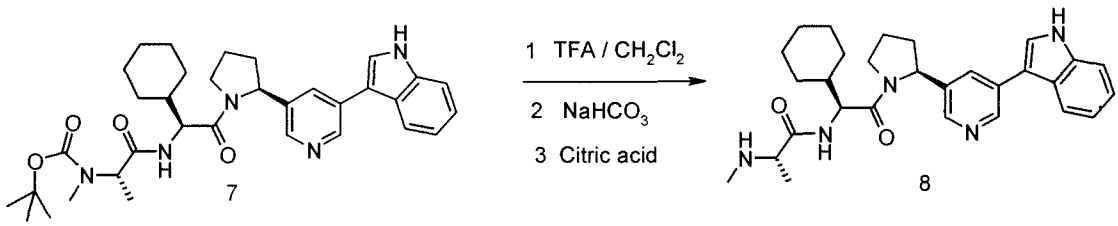


6 7

[(S)-1-((S)-1-Cyclohexyl-2-{(S)-2-[5-(1H-indol-3-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethylcarbamoyl)-ethyl]-methyl-carbamic acid tert-butyl ester (7)

To a solution of 3-((S)-5-Pyrrolidin-2-yl-pyridin-3-yl)-1H-indole **6** (78 mg, 0.30 mmole) and (S)-[(S)-2-(tert-Butoxycarbonyl-methyl-amino)-propionylamino]-cyclohexyl-acetic acid (111.6 mg, 0.33 mmole) in 5 ml of THF at 0 °C, was added 4-(4,6-Dimethoxy-[1,3,5]triazin-2-yl)-4-methyl-morpholinium chloride hydrate (98.6 mg, 0.36 mmole) in one portion. After stirring at 20 °C for 2 hours, the reaction mixture was diluted with 30 mL of EtOAc, washed with 3 X 10 mL of water and concentration to give [(S)-1-((S)-1-Cyclohexyl-2-{(S)-2-[5-(1H-indol-3-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethylcarbamoyl)-ethyl]-methyl-carbamic acid tert-butyl ester **7** (143.5 mg, crude) as pale yellow solid without further purification for next step.

Step 8



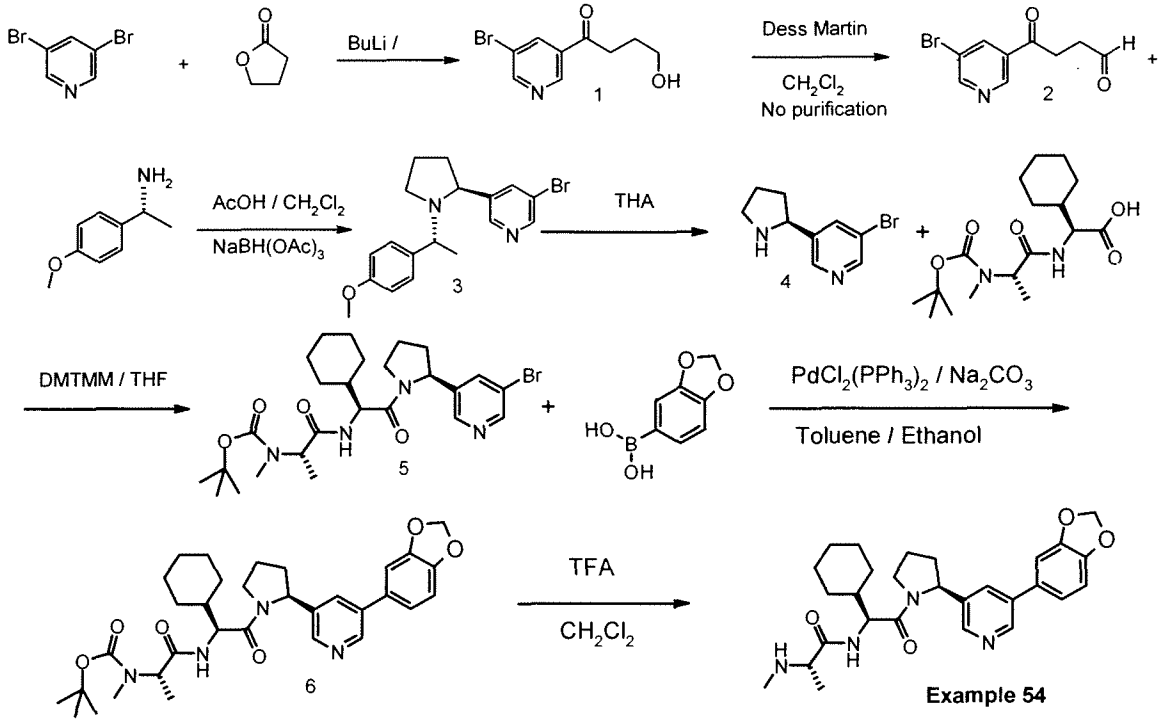
7 8

(S)-N-((S)-1-Cyclohexyl-2-{(S)-2-[5-(1H-indol-3-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide (8)

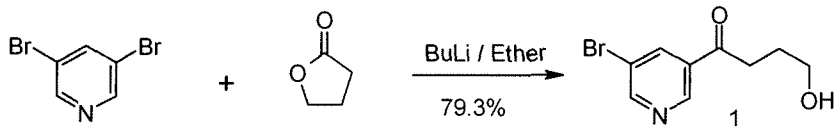
To a solution of [(S)-1-((S)-1-Cyclohexyl-2-{(S)-2-[5-(1H-indol-3-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethylcarbamoyl)-ethyl]-methyl-carbamic acid tert-butyl ester **7** (143 mg, crude) in 2 mL of CH_2Cl_2 at –20°C, was added 5 mL of TFA (pre-cooled to –20°C) slowly. After stirring at 0°C for 20 minutes, the reaction mixture was concentrated to remove TFA as much as possible at room temperature under high vacuum. The crude product was purified by reversed phase HPLC (Column: Waters Sunfire, 30 X 30 mm; Mobile phase: CH_3CN 15% H_2O 85% with 0.1% TFA to CH_3CN 60% H_2O 40% with 0.1% TFA by gradient in 11 minutes; Flow rate 40mL/minute; Detector: 215 nm UV) to give product as TFA salt which was dissolved in 30 mL of dichloromethane and basicfied by saturated sodium bicabonate to pH 8. The solution was dried over Na_2SO_4 and concentrated to give (S)-N-((S)-1-Cyclohexyl-2-{(S)-2-[5-(1H-indol-3-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide **Example 22** (17.4 mg) as white solid free base which was dissolved in 5 mL of water with 6.86 mg of citric acid and dried by freeze-drier to give (S)-N-((S)-1-Cyclohexyl-

2-{(S)-2-[5-(1H-indol-3-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide **Example 22** (22.2 mg, yield 12% in three steps) as white citrate salt.

Preparation of Example 54 (S)-N-{(S)-2-[(S)-2-(5-Benzo[1,3]dioxol-5-yl-pyridin-3-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethyl}-2-methylamino-propionamide.



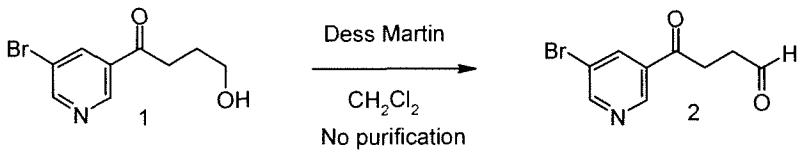
Step 1.



1-(5-Bromo-pyridin-3-yl)-4-hydroxy-butan-1-one (1)

To a solution of 3,5-bibromopyridine (20.0 g, 84.4 mmole) in 300 mL of ether at –70°C, was added BuLi (30.4 mL, 75.96 mmole, 2.5 M in hexane) slowly (maintaining internal T<-65°C). After stirring at –70°C for 1 hour, γ-butyroactone (10.9 g, 126.6 mmole) was added slowly (maintaining internal T<-65°C). After stirring at -70°C for two hours, the reaction mixture was warmed to 0°C, and quenched with 100 mL of water and extracted with 2 x 150 mL of ether. The combined organic layers was concentrated and purified by chromatography (CH_2Cl_2 95%, EtOAc 5%) to give 1-(5-Bromo-pyridin-3-yl)-4-hydroxy-butan-1-one **1** (14.7 g, yield 79%) as pale yellow liquid.

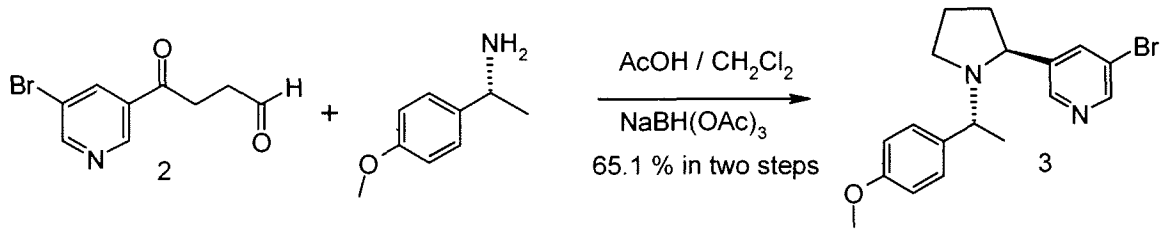
Step 2.



4-(5-Bromo-pyridin-3-yl)-4-oxo-butyraldehyde (2)

To a solution of 1-(5-Bromo-pyridin-3-yl)-4-hydroxy-butan-1-one **1** (5.0 g, 20.5 mmole) in 90mL of CH_2Cl_2 at 25°C, was slowly added a solution of Dess-Martin periodinane (9.6 g, 22.5 mmole) in 70mL of CH_2Cl_2. After stirring at 25°C for 20 minutes, the reaction mixture was diluted with 200mL of ether and cooled by dry-ice-acetone bath. The solid precipitant was filtered away and discarded. The filtrate was concentrated and residue was diluted with 100mL of ether, cooled with in a dry ice-acetone bath and the precipitant was removed by filtration. The filtrate was concentrated to give 6.2 g of 4-(5-Bromo-pyridin-3-yl)-4-oxo-butyraldehyde **2** as a pale/brown oily liquid which turned to a pale/brown solid after cooled to 0°C, without further purification for next step reaction.

Step 3.

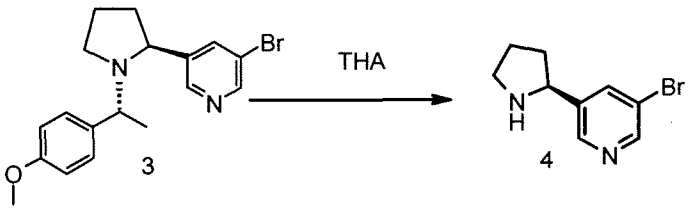


3-Bromo-5-{(S)-1-[(R)-1-(4-methoxy-phenyl)-ethyl]-pyrrolidin-2-yl}-pyridine (3)

To a solution of 4-(5-Bromo-pyridin-3-yl)-4-oxo-butyraldehyde **2** (crude from step 2, 20.5 mmole) in 150mL of CH_2Cl_2 at –70°C, was added 3.5mL of acetic acid and triacetoxyl sodium borohydride (10.2g, 48.0 mmole) and then R-(+)-1-(4-methoxyphenyl)ethylamine (3.9 g, 26.0 mmole) slowly with stirring. After stirring at -70 °C for 1 hour, the reaction mixture was warmed to room temperature. After stirring at room temperature for 2 hours, the reaction mixture was diluted with 200 ml of CH_2Cl_2, and washed with a solution of 50 mL of water and 20mL of saturated sodium bicarbonate, and 2 X 100mL of water. After concentration, the crude product (dr = 86 : 14 by HPLC analysis) was purified by flash column chromatography (CH_2Cl_2 95%, EtOAc 5%) to give 3-Bromo-5-{(S)-1-[(R)-1-(4-

methoxy-phenyl)-ethyl]-pyrrolidin-2-yl}-pyridine **3** (3.2 g, yield 44% in two steps) as a light brown viscose liquid.

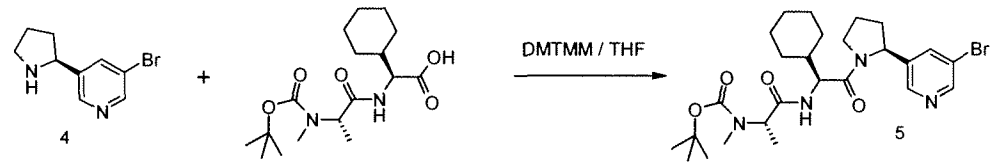
Step 4



3-((S)-5-Pyrrolidin-2-yl-pyridin-3-yl)-1H-indole (4)

A solution of 3-Bromo-5-{(S)-1-[(R)-1-(4-methoxy-phenyl)-ethyl]-pyrrolidin-2-yl}-pyridine **3** (3.64g, 10.0 mmole) in 5 mL of TFA was heated at 120°C in a microwave reactor for 30 minutes. The resulting solution was concentrated to remove TFA. The residue was dissolved in 150mL of CH_2Cl_2 and basicfied by 5 mL of saturated $NaHCO_3$. The solution was washed by 2 x 10mL of water, dried over Na_2SO_4 and concentrated to give 3-((S)-5-Pyrrolidin-2-yl-pyridin-3-yl)-1H-indole **4** (2.4 g, crude) as deep brown gum without further purification for the next step reaction.

Step 5

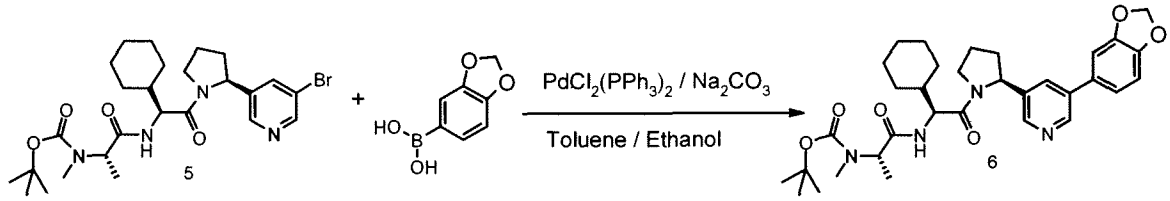


((S)-1-{(S)-2-[(S)-2-(5-Bromo-pyridin-3-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethylcarbamoyl}-ethyl)-methyl-carbamic acid tert-butyl ester (5)

To a solution of 3-((S)-5-Pyrrolidin-2-yl-pyridin-3-yl)-1H-indole **4** (2.4 g, crude) and (S)-[(S)-2-(tert-Butoxycarbonyl-methyl-amino)-propionylamino]-cyclohexyl-acetic acid (3.42g, 10.0 mmole) in 100ml of THF at 0°C, was added 4-(4,6-Dimethoxy-[1,3,5]triazin-2-yl)-4-methyl-morpholinium chloride hydrate (3.04g, 11.0mmole) in one portion. After stirring at 20°C for 2 hours, the reaction mixture was diluted with 100mL of EtOAc, and washed with 3 X 50mL of water. After concentration, the crude product was purified by flash column chromatography (CH_2Cl_2 95%, MeOH 5%) to give ((S)-1-{(S)-2-[(S)-2-(5-Bromo-pyridin-3-yl)-pyrrolidin-1-yl]-1-

cyclohexyl-2-oxo-ethylcarbamoyl}-ethyl)-methyl-carbamic acid tert-butyl ester **5** (2.47 g, yield 45% in two steps) as a yellow solid.

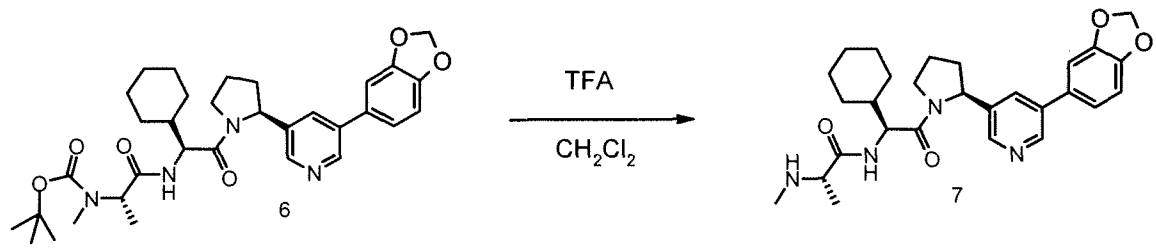
Step 6



((S)-1-{(S)-2-[(S)-2-(5-Benzo[1,3]dioxol-5-yl-pyridin-3-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethylcarbamoyl}-ethyl)-methyl-carbamic acid tert-butyl ester (6)

The mixture of ((S)-1-{(S)-2-[(S)-2-(5-Bromo-pyridin-3-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethylcarbamoyl}-ethyl)-methyl-carbamic acid tert-butyl ester **5** (168 mg, 0.31 mmole), 3,4-(methylene dioxy)pheny boronic acid (60.7 mg, 0.37 mmole), Na_2CO_3 (1.8 mL, 1.8 momle, 1 M aqueous) in a mixed solution of 8 mL of toluene and 3 mL of ethanol was degased under vaccum. After heat at 80°C for 1.5 hours, the reaction mixture was cooled to room temperature and diluted with 30 mL of EtOAc, and washed by 3 X 15 mL of water. The organic layer was filtered and concentrated to give 3-(5-{(S)-1-[1-(4-Methoxy-phenyl)-ethyl]-pyrrolidin-2-yl}-pyridin-3-yl)-indole-1-carboxylic acid tert-butyl ester **6** as crude producte without further purification for next step reaction.

Step 7



(S)-N-{(S)-2-[(S)-2-(5-Benzo[1,3]dioxol-5-yl-pyridin-3-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethyl}-2-methylamino-propionamide (Example 54)

To a solution of [(S)-1-((S)-1-Cyclohexyl-2-{(S)-2-[5-(1H-indol-3-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethylcarbamoyl)-ethyl]-methyl-carbamic acid tert-butyl ester **6** (crude) in 2 mL of CH_2Cl_2 at –20°C, was slowly added 5 mL of TFA (pre-cooled to –20°C). After stirring at 0°C for 20 minutes, the reaction mixture was concentrated to remove TFA as much as possible

at room temperature under high vacuum. The crude product was purified by reversed phase HPLC (Column: Waters Sunfire, 30 X 30 mm; Mobile phase: CH_3CN 15%/H_2O 85% with 0.1% TFA to CH_3CN 60%/H_2O 40% with 0.1% TFA by gradient in 11 minutes; Flow rate 40mL/minute; Detector: 215 nm UV) and concentrated to give (S)-N-((S)-1-Cyclohexyl-2-{(S)-2-[5-(1H-indol-3-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide **Example 54** (96.1 mg, yield 52% in two steps) as white TFA salt.

In order to measure the ability of the inventive compounds to bind the BIR3 peptide binding pocket an ELISA and a cell based assays are utilized.

Example 136

Elisa

Compounds are incubated with GST-BIR3 fusion protein and biotinylated SMAC peptide (AVPFAQK) in stretavidin-coated 96 well plates. For XIAP BIR3 Smac Elisa, a GST-BIR3 fusion containing amino acids 248-358 from XIAP is used. For CIAP1 BIR3 Smac Elisa, a GST-BIR3 fusion containing amino acids 259-364 from CIAP1 is used. Following a 30 minute incubation, wells are extensively washed. The remaining GST-BIR3 fusion protein is monitored by ELISA assay involving first, incubation with goat anti-GST antibodies followed by washing and incubation with alkaline phosphatase conjugated anti-goat antibodies. Signal is amplified using Attophos (Promega) and read with Cytoflour Ex 450nm/40 and Em 580nm. IC_{50}'s correspond to concentration of compound which displaces half of GST-BIR3 signal. The IC_{50} for non-biotinylated Smac is 400 nM. The IC_{50} values of compounds of Examples 1-103 in the described ELISA assays ranged from <0.001 – 10 μM.

Example 137

Cell Proliferation Assay

The ability of compounds to inhibit tumor cell growth *in vitro* is monitored using the CellTiter 96® AQ_{ueous} Non-Radioactive Cell Proliferation Assay (Promega). This assay is composed of solutions of a novel tetrazolium compound [3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt; MTS] and an electron coupling reagent (phenazine methosulfate) PMS. MTS is bioreduced by cells into a formazan product, the absorbance of which is measured at 490nm. The conversion of MTS into the aqueous soluble formazan product is accomplished by dehydrogenase enzymes found in metabolically active cells. The quantity of formazan product as measured by the

amount of 490nm absorbance is directly proportional to the number of living cells in culture. The IC_{50} values of compounds described in Examples 1-103 in this cell assays ranged from <0.001 – 50μM.

Example 138

Tablets 1 comprising compounds of the formula (I)

Tablets, comprising, as active ingredient, 50 mg of any one of the compounds of formula (I) mentioned in the preceding Examples 1-103 of the following composition are prepared using routine method:

Composition:	
Active Ingredient	50 mg
Wheat starch	60 mg
Lactose	50 mg
Colloidal silica	5 mg
Talcum	9 mg
Magnesium stearate	1 mg
Total	175 mg

Manufacture: The active ingredient is combined with part of the wheat starch, the lactose and the colloidal silica and the mixture pressed through a sieve. A further part of the wheat starch is mixed with 5-fold amount of water on a water bath to form a paste and the mixture made first is kneaded with this paste until a weakly plastic mass is formed.

The dry granules are pressed through a sieve having a mesh size of 3 mm, mixed with a pre-sieved mixture (1 mm sieve) of the remaining corn starch, magnesium stearate and talcum and compressed to form slightly biconvex tablets.

Example 139

Tablets 2 comprising compounds of the formula (I)

Tablets, comprising, as active ingredient, 100 mg of any one of the compounds of formula (I) of Examples 1-103 are prepared with the following standard procedures:

Composition:	
Active Ingredient	100 mg
Crystalline lactose	240 mg
Avicel	80 mg
PVPPXL	20 mg
Aerosil	2 mg
Magnesium stearate	5 mg
Total	447 mg

Manufacture: The active ingredient is mixed with the carrier materials and compressed by means of a tabletting machine (Korsch EKO, Stempeldurchmesser 10 mm).

Example 140

Capsules, comprising as active ingredient, 100 mg of any one of the compounds of formula (I) given in Examples 1-103, of the following composition are prepared according to standard procedures

Composition:	
Active Ingredient	100 mg
Avicel	200 mg
PVPPXL	15 mg
Aerosil	2 mg
Magnesium stearate	1.5 mg
Total	318.5 mg

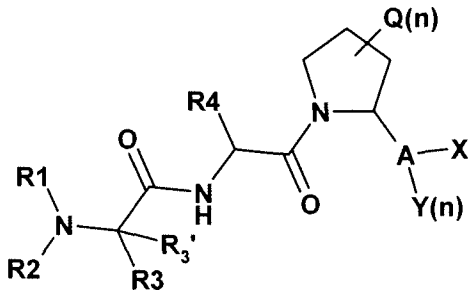
Manufacturing is done by mixing the components and filling them into hard gelatine capsules, size 1.

The term "active ingredient" as used herein refers to a compound of Formula I-VII or a pharmaceutically acceptable salt thereof, as defined herein.

The above preferred embodiments are given to illustrate the scope and spirit of the present invention. The descriptions provided herein will make apparent to those skilled in the art other embodiments and examples. These other embodiments and examples are within the contemplation of the present invention. Therefore, the present invention should be limited only by the appended claims.

WHAT IS CLAIMED IS:

1. A compound of formula I:



Formula I

and pharmaceutically acceptable salts thereof, wherein

R_1 is H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl or C_3-C_{10} cycloalkyl, which R_1 may be unsubstituted or substituted;

R_2 is H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_{10} cycloalkyl which R_2 may be unsubstituted or substituted;

R_1 and R_2 may be taken together to form a ring or het;

R_3 and R_3' are independently H, CF_3, C_2F_5, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, CH_2-Z or R_2 and R_3 taken together with the nitrogen atom to which they are attached form het, wherein alkyl, alkenyl, alkynyl or het ring may be unsubstituted or substituted;

Z is H, OH, F, Cl, CH_3, CH_2Cl, CH_2F or CH_2OH;

R_4 is $C_{0\text{-}10}$ alkyl, $C_{0\text{-}10}$ alkyl-$C_{3\text{-}10}$ cycloalkyl, $C_{0\text{-}10}$alkyl-$C_{6\text{-}10}$aryl, $C_{0\text{-}10}$alkyl-het, wherein any carbon may be replaced with a heteroatom or group from the list N, O, $S(O)_r$ and any atom may be unsubstituted or substituted;

A is a 6 membered heteroaryl ring or an 8-12 membered fused ring system that may include one 5-7 membered heterocyclic ring containing 1, 2, or 3 heteroring atoms selected from N, O and S, which any position of the rings is unsubstituted or substituted with one or more Q's;

r is 0, 1, or 2;

Q and Y are independently H, F, Cl, Br, I, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, aryl C_1-C_{10} alkoxy, OH, O-C_1-C_{10}-alkyl, $(CH_2)_{0\text{-}6}$-C_3-C_7 cycloalkyl, aryl, aryl C_1-C_{10} alkyl, O-$(CH_2)_{0\text{-}6}$ aryl, $(CH_2)_{1\text{-}6}$het, het, O-$(CH_2)_{1\text{-}6}$het, -OR_{11}, $C(O)R_{11}$, -$C(O)N(R_{11})(R_{12})$, $N(R_{11})(R_{12})$,SR_{11}, $S(O)R_{11}$,$S(O)_2$ R_{11}, $S(O)_2$-$N(R_{11})(R_{12})$, or NR_{11}-$S(O)_2$-(R_{12}), wherein alkyl, cycloalkyl and aryl

are unsubstituted or substituted, independent Q's may be joined to form a 5-10 membered ring;

X is aryl, C_3-C_{10} cycloalkyl, or het, substituted or unsubstituted, in which substituents on aryl, C_3-C_{10} cycloalkyl and het are alkyl, halo, lower alkoxy, NR_5R_6, CN, NO_2 or SR_5;

R_5 and R_6 are independently H, F, Cl, Br, I, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, aryl C_1-C_{10} alkoxy, OH, O-C_1-C_{10}-alkyl, $(CH_2)_{0-6}$-C_3-C_7 cycloalkyl, aryl, aryl C_1-C_{10} alkyl, O-$(CH_2)_{0-6}$ aryl, $(CH_2)_{1-6}$het, het, O-$(CH_2)_{1-6}$het, -OR_{11}, C(O)R_{11}, -C(O)N(R_{11})(R_{12}), N(R_{11})(R_{12}),SR_{11}, S(O)R_{11},S(O)$_2$ R_{11}, S(O)$_2$-N(R_{11})(R_{12}), or NR_{11}-S(O)$_2$-(R_{12}),

each n is independently 0, 1, 2, 3, 4, 5, 6 or 7;

het is a 5-7 membered monocyclic heterocyclic ring containing 1-4 heteroring atoms selected from N,O and S or an 8-12 membered fused ring system that includes one 5-7 membered heterocyclic ring containing 1, 2, or 3 heteroring atoms selected from N, O and S, which het is unsubstituted or substituted;

R_{11} and R_{12} are independently H, C_1-C_{10} alkyl, $(CH_2)_{0-6}$-C_3-C_7cycloalkyl, $(CH_2)_{0-6}$-$(CH)_{0-1}$(aryl)$_{1-2}$,C(O)-C_1-C_{10}alkyl, -C(O)-$(CH_2)_{0-6}$-C_3-C_7cycloalkyl, -C(O)-O-$(CH_2)_{0-6}$-aryl, -C(O)-$(CH_2)_{0-6}$-O-fluorenyl, C(O)-NH-$(CH_2)_{0-6}$-aryl, C(O)-$(CH_2)_{0-6}$-aryl, C(O)-$(CH_2)_{0-6}$-het, -C(S)-C_1-C_{10}alkyl, -C(S)-$(CH_2)_{0-6}$-C_3-C_7cycloalkyl, -C(S)-O-$(CH_2)_{0-6}$-aryl, -C(S)-$(CH_2)_{0-6}$-O-fluorenyl, C(S)-NH-$(CH_2)_{0-6}$-aryl, -C(S)-$(CH_2)_{0-6}$-aryl or C(S)-$(CH_2)_{0-6}$-het, C(O)R_{11}, C(O)$NR_{11}R_{12}$, C(O)OR_{11}, S(O)nR_{11}, S(O)$_m$$NR_{11}R_{12}$, m = 1 or 2, C(S)$R_{11}$, C(S)$NR_{11}R_{12}$, C(S)$OR_{11}$, wherein alkyl, cycloalkyl and aryl are unsubstituted or substituted; or R_{11} and R_{12} together with the nitrogen atom form het;

wherein the alkyl substituents of R_{11} and R_{12} may be unsubstituted or substituted by one or more substituents selected from C_1-C_{10}alkyl, halogen, OH, O-C_1-C_6alkyl, -S-C_1-C_6alkyl, CF_3 or $NR_{11}R_{12}$;

substituted cycloalkyl substituents of R_{11} and R_{12} are substituted by one or more substituents selected from a C_2-C_{10} alkene; C_1-C_6alkyl; halogen; OH; O-C_1-C_6alkyl; S-C_1-C_6alkyl,CF_3; or $NR_{11}R_{12}$ and

substituted het or substituted aryl of R_{11} and R_{12} are substituted by one or more substituents selected from halogen, hydroxy, C_1-C_4 alkyl, C_1-C_4 alkoxy, nitro, CN O-C(O)-C_1-C_4alkyl and C(O)-O-C_1-C_4-alkyl;

wherein the substituents on R_1, R_2, R_3, R_4, Q, and A and X groups are independently halo, hydroxy, lower alkyl, lower alkenyl, lower alkynyl, lower alkanoyl, lower alkoxy, aryl, aryl lower alkyl, amino, amino lower alkyl, diloweralkylamino, lower alkanoyl, amino lower alkoxy, nitro, cyano, cyano lower alkyl, carboxy, lower carbalkoxy, lower alkanoyl, aryloyl, lower

arylalkanoyl, carbamoyl, N-mono- or N,N-dilower alkyl carbamoyl, lower alkyl carbamic acid ester, amidino, guanidine, ureido, mercapto, sulfo, lower alkylthio, sulfoamino, sulfonamide, benzosulfonamide, sulfonate, sulfanyl lower alkyl, aryl sulfonamide, halogen substituted aryl sulfonate, lower alkylsulfinyl, arylsulfinyl; aryl-lower alkylsulfinyl, lower alkylarylsulfinyl, lower alkylsulfonyl, arylsulfonyl, aryl-lower alkylsulfonyl, lower aryl alkyl lower alkylarylsulfonyl, halogen-lower alkylmercapto, halogen-lower alkylsulfonyl, phosphono ($-P(=O)(OH)_2$), hydroxy-lower alkoxy phosphoryl or di-lower alkoxyphosphoryl, $(R_9)NC(O)-NR_{10}R_{13}$, lower alkyl carbamic acid ester or carbamates or $-NR_8R_{14}$, wherein R_8 and R_{14} can be the same or different and are independently H or lower alkyl, or R_8 and R_{14} together with the N atom form a 3- to 8-membered heterocyclic ring containing a nitrogen heteroring atoms and may optionally contain one or two additional heteroring atoms selected from nitrogen, oxygen and sulfur, which heterocyclic ring may be unsubstituted or substituted with lower alkyl, halo, lower alkenyl, lower alkynyl, hydroxy, lower alkoxy, nitro, amino, lower alkyl, amino, diloweralkyl amino, cyano, carboxy, lower carbalkoxy, formyl, lower alkanoyl, oxo, carbarmoyl, N-lower or N, N-dilower alkyl carbamoyl, mercapto, or lower alkylthio, and

R_9, R_{10}, and R_{13} are independently hydrogen, lower alkyl, halogen substituted lower alkyl, aryl, aryl lower alkyl, halogen substituted aryl, halogen substituted aryl lower alkyl.

2. A compound according to claim 1 wherein:

R_1 is H, C_1-C_4 alkyl, which R_1 may be unsubstituted or substituted;

R_2 is H, C_1-C_4 alkyl, which R_2 may be unsubstituted or substituted;

R_3 and R_3' are independently H, or C_1-C_4 alkyl;

R_4 is C_5-C_7 cycloalkyl, especially cyclohexyl, or C_1-C_4 alkyl, especially isopropyl;

A is a 6 membered heteroaryl ring or an 8-12 membered fused ring system that may include one 5-7 membered heterocyclic ring containing 1, 2, or 3 heteroring atoms selected from N, O and S, which any position of the rings is unsubstituted or substituted with one or more Q's;

Q and Y are independently H, F, Cl, Br, I, C_1-C_{10} alkyl, C_1-C_{10} alkoxy;

X is aryl, C_3-C_{10} cycloalkyl, or het, which may be substituted or unsubstituted.

3. A compound according to claim 1 wherein:

R_1 is H, or methyl;

R_2 is H, or methyl;

one of R_3 and R_3' a is H and the other is methyl;

R_4 is cyclohexyl, or isopropyl;

A is pyridyl, pyrimidinyl, indolyl, benzothiazolyl, or quinolinyl which may be unsubstituted or substituted with lower alkyl such as methyl, or halo;
Q and Y are independently H, F or Cl, lower alkyl, especially methyl, ethyl, t- butyl or isopropyl, said lower alkyl may be substituted such as trifluoromethyl, lower alkoxy such as methoxy, lower alkyl amino such as dimethyl amino; and
X is quinolinyl, isoquinolyl, benzothiazolyl, pyridinyl, indolyl, benzoimidazolyl, naphthyl, benzo[1,3]dioxolyl, benzofurnayl, naphthyridine, pyrrolo[2,3b]pyridinyl, indanzolyl, benzotriazolyl, indazolyl, 2-oxobenzo-oxazolyl, or phenyl, which may be substituted or unsubstituted.

4. A pharmaceutical composition comprising a therapeutically effective amount of a compound accoding to Claim 1.

5. A method for treating a mammal suffering from a proliterative disease which comprises administering to said mammal in need of treatment a therapeutically effective amount of a compound according to Claim 1.

6. A method of modulating cell proliferation comprising administering an effective amount of the compound according to Claim 1 to modulate cell proliferation to a cell or mammal in need thereof.

7. A method of inhibiting cell proliferation comprising administering an effective amount of a compound according to Claim 1 to inhibit cell proliferation to a cell or mammal in need thereof.

8. The method according to Claim 7 wherein the cell proliferation that is inhibited is cancer cell proliferation.

9. A method of treating a mammal afflicted with cancer comprising administering to said mammal a therapeutically effective amount of a compound according to Claim 1.

10. A compound selected from:
N-{ 1-Cyclohexyl-2-[2-(1*H*-indol-3-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide;

N-{ 1-Cyclohexyl-2-[2-(1*H*-indol-3-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide;

N-{ 1-Cyclohexyl-2-[2-(1*H*-indol-2-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[2-(2,3-dihydro-indol-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[5-(2,3-dihydro-indol-1-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[5-(2,3-dihydro-indol-1-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[2-(3,4-dihydro-2*H*-quinolin-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[2-(2,3-dihydro-pyrrolo[2,3-*b*]pyridin-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamidel;

N-{1-Cyclohexyl-2-[2-(5-indol-1-yl-pyridin-3-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[5-(3,4-dihydro-2*H*-quinolin-1-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-oxo-2-{ 2-[2-(2-oxo-3,4-dihydro-2*H*-quinolin-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-ethyl)-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[2-(6-fluoro-2,3-dihydro-indol-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-(1-{ 2-[2-(6-Fluoro-2,3-dihydro-indol-1-yl)-pyridin-4-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-2-methylamino-propionamide;

N-{ 1-Cyclohexyl-2-[2-(2-isoquinolin-4-yl-pyridin-4-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide;

N-{ 1-Cyclohexyl-2-[2-(2-isoquinolin-4-yl-pyridin-4-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-{ 1-Cyclohexyl-2-[2-(2-indazol-1-yl-pyridin-4-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide;

N-{ 2-[2-(5-Benzofuran-3-yl-pyridin-3-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethyl}-2-methylamino-propionamide;

N-{ 2-[2-(2-Benzoimidazol-1-yl-pyridin-4-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethyl}-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[2-(3-methyl-indol-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

2-Methylamino-*N*-(2-methyl-1-{ 2-[2-(3-methyl-indol-1-yl)-pyridin-4-yl]-pyrrolidine-1-carbonyl}-propyl)-propionamide;

N-(1-Cyclohexyl-2-{ 2-[5-(1*H*-indol-3-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-{ 2-[2-(2-Benzotriazol-1-yl-pyridin-4-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethyl}-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[2-(5-fluoro-indol-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[2-(6-fluoro-3,4-dihydro-2*H*-quinolin-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[2-(1*H*-indol-2-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[5-(5-fluoro-2,3-dihydro-indol-1-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[2-(1*H*-indol-3-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-(1-{ 2-[2-(6-Fluoro-indol-1-yl)-pyridin-4-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[2-(6-fluoro-indol-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[2-(6-fluoro-indol-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-oxo-2-{ 2-[5-(2-oxo-benzooxazol-3-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-ethyl)-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[2-(1,3-dihydro-isoindol-2-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[2-(3,4-dihydro-1*H*-isoquinolin-2-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-{ 2-[2-(5-Benzoimidazol-1-yl-pyridin-3-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethyl}-2-methylamino-propionamide;

N-{ 2-[2-(5-Benzotriazol-1-yl-pyridin-3-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethyl}-2-methylamino-propionamide;

N-{ 1-Cyclohexyl-2-[2-(5-indazol-1-yl-pyridin-3-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[2-(5-fluoro-3-methyl-indol-1-yl)-pyridin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-(1-{ 2-[2-(5-Fluoro-3-methyl-indol-1-yl)-pyridin-4-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[5-(3,4-dihydro-2*H*-quinolin-1-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-ethyl)-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[5-(3-methyl-indol-1-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[5-(5-fluoro-3-methyl-indol-1-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[5-(5-fluoro-indol-1-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-{ 1-Cyclohexyl-2-oxo-2-[2-(5-pyrrolo[2,3-*b*]pyridin-1-yl-pyridin-3-yl)-pyrrolidin-1-yl]-ethyl}-2-methylamino-propionamide;

N-{ 2-[2-(2-Benzoimidazol-1-yl-3-fluoro-pyridin-4-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethyl}-2-methylamino-propionamide;

N-{ 1-[2-(2-Benzoimidazol-1-yl-pyridin-4-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-2-methylamino-propionamide;

3-(5-{ 1-[2-Cyclohexyl-2-(2-methylamino-propionylamino)-acetyl]-pyrrolidin-2-yl}-pyridin-3-yl)-indole-1-carboxylic acid dimethylamide;

N-(1-Cyclohexyl-2-{ 2-[5-(1-ethyl-1*H*-indol-3-yl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-{ 1-Cyclohexyl-2-[2-(5-naphthalen-1-yl-pyridin-3-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[4-(6-fluoro-2,3-dihydro-indol-1-yl)-pyridin-2-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[4-(5-fluoro-2,3-dihydro-indol-1-yl)-pyridin-2-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-(2-{ 2-[5-(5-Chloro-2-methoxy-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-1-cyclohexyl-2-oxo-ethyl)-2-methylamino-propionamide;

N-{ 1-Cyclohexyl-2-oxo-2-[2-(5-o-tolyl-pyridin-3-yl)-pyrrolidin-1-yl]-ethyl}-2-methylamino-propionamide;

N-{ 2-[2-(5-Benzo[1,3]dioxol-5-yl-pyridin-3-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethyl}-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-oxo-2-{ 2-[5-(3-trifluoromethyl-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-ethyl)-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[5-(3-isopropyl-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-{ 1-Cyclohexyl-2-[2-(5-naphthalen-2-yl-pyridin-3-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide;

N-{ 1-Cyclohexyl-2-oxo-2-[2-(7-phenyl-4,5,6,7-tetrahydro-benzothiazol-2-yl)-pyrrolidin-1-yl]-ethyl}-2-methylamino-propionamide;

N-{ 1-Cyclohexyl-2-oxo-2-[2-(1-phenyl-isoquinolin-7-yl)-pyrrolidin-1-yl]-ethyl}-2-methylamino-propionamide;

N-{ 1-Cyclohexyl-2-oxo-2-[2-(7-phenyl-6,7-dihydro-5*H*-[2]pyrindin-4-yl)-pyrrolidin-1-yl]-ethyl}-2-methylamino-propionamide;

N-{ 1-Cyclohexyl-2-oxo-2-[2-(5-phenyl-5,6,7,8-tetrahydro-quinolin-3-yl)-pyrrolidin-1-yl]-ethyl}-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[7-(4-fluoro-phenyl)-benzothiazol-2-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-(2-{ 2-[2-Chloro-5-(3-trifluoromethyl-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-1-cyclohexyl-2-oxo-ethyl)-2-methylamino-propionamide;

N-(2-{ 2-[5-(3,5-Bis-trifluoromethyl-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-1-cyclohexyl-2-oxo-ethyl)-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-oxo-2-{ 2-[5-(2-trifluoromethyl-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-ethyl)-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[5-(3,5-dimethyl-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-(2-{ 2-[5-(4-tert-Butyl-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-1-cyclohexyl-2-oxo-ethyl)-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[5-(4-fluoro-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-{ 1-Cyclohexyl-2-oxo-2-[2-(5-*p*-tolyl-pyridin-3-yl)-pyrrolidin-1-yl]-ethyl}-2-methylamino-propionamide;

N-{ 1-Cyclohexyl-2-oxo-2-[2-(5-*m*-tolyl-pyridin-3-yl)-pyrrolidin-1-yl]-ethyl}-2-methylamino-propionamide;

N-[2-(2-[2,3']Bipyridinyl-5'-yl-pyrrolidin-1-yl)-1-cyclohexyl-2-oxo-ethyl]-2-methylamino-propionamide;

N-[2-(2-[3,3']Bipyridinyl-5-yl-pyrrolidin-1-yl)-1-cyclohexyl-2-oxo-ethyl]-2-methylamino-propionamide;

N-[2-(2-[3,4']Bipyridinyl-5-yl-pyrrolidin-1-yl)-1-cyclohexyl-2-oxo-ethyl]-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[6-(6-fluoro-2,3-dihydro-indol-1-yl)-2-methyl-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[6-(5-fluoro-2,3-dihydro-indol-1-yl)-2-methyl-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-{ 1-Cyclohexyl-2-[2-(6-indol-1-yl-2-methyl-pyrimidin-4-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide;

N-{ 1-Cyclohexyl-2-[2-(6-indol-1-yl-pyrimidin-4-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide;

N-{ 1-Cyclohexyl-2-[2-(2-methyl-6-*o*-tolyl-pyrimidin-4-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide;

N-{ 1-Cyclohexyl-2-oxo-2-[2-(6-*o*-tolyl-pyrimidin-4-yl)-pyrrolidin-1-yl]-ethyl}-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[2-methyl-6-(3-methyl-indol-1-yl)-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[2-methyl-6-(3-trifluoromethyl-phenyl)-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-{ 2-[2-(6-Benzoimidazol-1-yl-2-methyl-pyrimidin-4-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethyl}-2-methylamino-propionamide;

N-{ 1-Cyclohexyl-2-[2-(2-methyl-6-naphthalen-1-yl-pyrimidin-4-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide;

N-{ 2-[2-(6-Benzo[1,3]dioxol-5-yl-2-methyl-pyrimidin-4-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethyl}-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[6-(3-isopropyl-phenyl)-2-methyl-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[6-(2,3-dihydro-indol-1-yl)-2-methyl-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-{ 1-Cyclohexyl-2-[2-(2-methyl-6-naphthalen-2-yl-pyrimidin-4-yl)-pyrrolidin-1-yl]-2-oxo-ethyl}-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[6-(5-fluoro-2,3-dihydro-indol-1-yl)-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-(1-{ 2-[6-(5-Fluoro-2,3-dihydro-indol-1-yl)-2-methyl-pyrimidin-4-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-2-methylamino-propionamide;

N-{ 2-[2-(6-Benzofuran-3-yl-2-methyl-pyrimidin-4-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxo-ethyl}-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[6-(1*H*-indol-3-yl)-2-methyl-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[6-(1*H*-indol-3-yl)-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-(1-{ 2-[6-(1*H*-Indol-3-yl)-2-methyl-pyrimidin-4-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[6-(5-fluoro-3-methyl-indol-1-yl)-2-methyl-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-(1-{ 2-[6-(5-Fluoro-3-methyl-indol-1-yl)-2-methyl-pyrimidin-4-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[6-(5-fluoro-3-methyl-indol-1-yl)-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[6-(5-fluoro-indol-1-yl)-2-methyl-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

N-(1-{ 2-[6-(5-Fluoro-indol-1-yl)-2-methyl-pyrimidin-4-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-2-methylamino-propionamide;

N-(1-Cyclohexyl-2-{ 2-[6-(5-fluoro-indol-1-yl)-pyrimidin-4-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-2-methylamino-propionamide;

3-(6-{ 1-[2-Cyclohexyl-2-(2-methylamino-propionylamino)-acetyl]-pyrrolidin-2-yl}-2-methyl-pyrimidin-4-yl)-indole-1-carboxylic acid dimethylamide;

3-(2-Methyl-6-{ 1-[3-methyl-2-(2-methylamino-propionylamino)-butyryl]-pyrrolidin-2-yl}-pyrimidin-4-yl)-indole-1-carboxylic acid dimethylamide;

3-(6-{ 1-[2-Cyclohexyl-2-(2-methylamino-propionylamino)-acetyl]-pyrrolidin-2-yl}-pyrimidin-4-yl)-indole-1-carboxylic acid dimethylamide;

N-(1-{ 2-[6-(6-Fluoro-2,3-dihydro-indol-1-yl)-2-methyl-pyrimidin-4-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-2-methylamino-propionamide; and pharmaceutically acceptable salts thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/080875

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K5/06 A61K38/05 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2006/069063 A (GENENTECH INC [US]; COHEN FREDERICK [US]; TSUI VICKIE HSIAO-WEI [US];) 29 June 2006 (2006-06-29) page 1, lines 21,22 claims 1-21	1-10
X	WO 2005/097791 A (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; PALERMO MARK G [US]; SHAR) 20 October 2005 (2005-10-20) page 1, lines 1-7 claims 1-26	1-10

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 February 2008	27/02/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Marzi, Elena

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2007/106192 A (GENENTECH INC [US]; KOEHLER MICHAEL F T [US]; GAZZARD LEWIS J [US]; TS) 20 September 2007 (2007-09-20) page 1, paragraph 1 claims 1-21 pages 24-32; examples 1,3,7-21,27-30,32-34,38,39,49,50,53,57,58, 61,62	1-10
Y	WO 2004/007529 A (UNIV PRINCETON [US]; MCLENDON GEORGE [US]; KIPP RACHEL A [US]; CASE MA) 22 January 2004 (2004-01-22) page 1, paragraph 4 claims 1-47	1-10
Y	WO 2006/014361 A (GENENTECH INC [US]; COHEN FREDERICK [US]; DESHAYES KURT [US]; FAIRBROT) 9 February 2006 (2006-02-09) page 1, lines 21,22 claims 1-21	1-10

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 5-9 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.1

Claims Nos.: -

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/080875

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2007/080875

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