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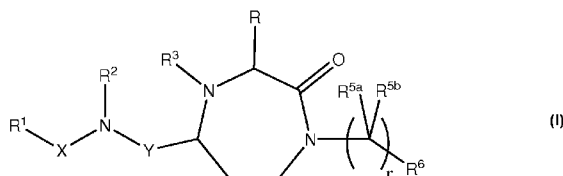
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(54) Title: METHODS OF MODULATING THE ACTIVITY OF THE MC3 AND/OR MC4 RECEPTORS AND TREATMENT
OF CONDITIONS RELATED TO THESE RECEPTORS



(57) Abstract: The present invention provides compounds of Formula (I) that are useful for modulating the biological activity of the melanocortin-3 receptor (MC3R) and / or the melanocortin-4 receptor (MC4R). Compounds of this invention can be used to treat diseases and/or conditions in which modulation of MC3R and / or MC4R is beneficial. Such diseases and/or conditions include, but are not limited to, obesity, eating disorders (such as cachexia, anorexia, weight gain, weight loss), metabolic syndrome, diabetes, sexual dysfunction (such as erectile dysfunction and female sexual dysfunction), anxiety, depression, inflammation, addiction and alcohol intake.

**METHODS OF MODULATING THE ACTIVITY OF THE MC3 AND/OR MC4 RECEPTORS
AND TREATMENT OF CONDITIONS RELATED TO THESE RECEPTORS**

FIELD OF THE INVENTION

The present invention relates to methods of modulating the activity of a receptor selected from the group consisting of the melanocortin-3 receptor and the melanocortin-4 receptor. In particular the present invention relates to the use of a family of 1,4-diazepan-2-ones and derivatives thereof to modulate the activity of the melanocortin-3 and / or melanocortin-4 receptors. The invention also relates to methods and uses of the compounds in the treatment of conditions in which agonism or antagonism of the melanocortin-3 and / or melanocortin-4 receptors is beneficial.

BACKGROUND OF THE INVENTION

The melanocortin-3 receptor (MC3R) and melanocortin-4 receptor (MC4R) are G-protein coupled receptors (GPCRs) belonging to the family of melanocortin receptors. There are five melanocortin receptors that have been isolated and cloned to date: MC1R, MC2R, MC3R, MC4R and MC5R. The melanocortin receptors participate in a variety of physiologic functions, providing a number of opportunities for therapeutic intervention in physiologic processes through alteration (i.e., a statistically significant increase or decrease) or modulation (e.g., up-regulation or down-regulation) of melanocortin receptor signalling activity.

Reviews of the melanocortin receptors and their potential as therapeutic targets have been published (Wikberg 2000, Wikberg 2001, Voisey 2003, Böhm 2006). The melanocortin receptor family members are regulated by natural peptide agonists such as adrenocorticotrophic hormone (ACTH) and the melanocyte stimulating hormones (α -, β -, γ -MSH) derived from pro-opiomelanocortin (POMC), and by peptide antagonists such as Agouti signal protein (ASP) and Agouti-related peptide (AGRP). The MC1R is widely expressed and is associated with pigmentation in melanocytes and with inflammation responses in many cells involved in the immune system. The MC2R differs from the other melanocortin receptors in that it binds only ACTH but not MSH ligands. It is highly expressed in the adrenal gland and controls corticosteroid synthesis. The MC3R is found in the brain, but also elsewhere in the body, and appears to play a role in the regulation of energy homeostasis, and possibly sexual dysfunction. The MC4R is found almost exclusively in the brain, with some reports of its presence elsewhere. It has been strongly associated with feeding control,

and also implicated with sexual desire. The MC5R is widely expressed in peripheral tissues, particularly in the exocrine glands, with some receptor also expressed in the brain.

MC3R (Gantz 1993a) and MC4R (Gantz 1993b) were first cloned and expressed from humans in 1993. Both MC3R and MC4R play a role in regulating energy balance and food intake (Adan 2006, Bertile 2006, Butler 2006, Emmerson 2007, Foster 2007, Lam 2007, Marks 2006, Nargund 2006, Schuler 2006, Wikberg 2008). MC4R knockout mice are obese and suffer from hyperphagia, hyperinsulinemia, and hyperglycemia (Huszar 1997). Genetic studies strongly associate MC4R sequence variants with obesity (Thorleifsson 2009, Willer 2009). MC3R knockout mice have increased fat mass and reduced lean body mass (Chen 2000, Butler 2000), while mice lacking both MC3R and MC4R become more obese than mice lacking only MC4R (Chen 2000).

MC3R and MC4R have also been associated with sexual dysfunction, particularly in the control of penile erection (Wessells 2005, King 2007, Shadiach 2007, Wikberg 2008). A more potent and stable cyclic analog of α -MSH, Ac-Nle-c[Asp-His-DPhe-Arg-Trp-Lys]-OH, (PT-141, bremelanotide) induces an erectile response in human patients with erectile dysfunction (Diamond 2004, Shadiack 2006). α -MSH shows immunosuppressive effects in humans, suppressing a variety of inflammation responses, and both MC3R and MC4R have been implicated in these immunomodulating activities (Catania 2004, Lasaga 2008, Getting 2003, Giuliani 2007). MC4R has also been linked to depression and anxiety disorders (Chaki 2005, Chaki 2007), hypertension (Hall 2000), and addiction, with MC4R agonists potentially useful for reducing or inhibiting alcohol consumption (Ploj 2002).

A variety of peptides (e.g. Holder 2002, Holder 2003), peptide derivatives (e.g. Mutulis 2005), peptidomimetics (e.g. Mazur 2003, Tian 2008) and small molecules (e.g. Hruby 2007, Todorovic 2005, Ujjainwalla 2007) that bind to and activate or inhibit MC3R and / or MC4R have been reported. However, there is still a need for compounds that act as agonists, antagonists, inverse agonists, allosteric modulators, or otherwise bind to and modulate the activity of one or both of these receptors, and which also possess desirable characteristics for therapeutic use.

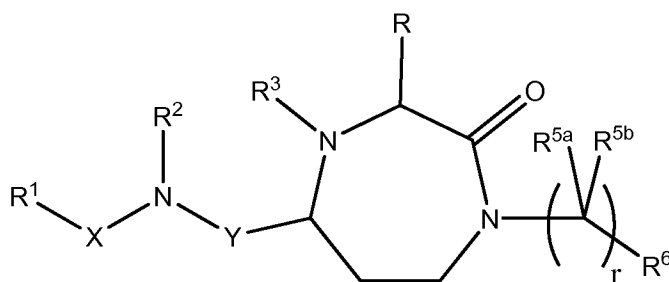
For the reasons described above it would be desirable to provide modulators of one or more receptors selected from the group consisting of MC3R and MC4R that could be useful in a number of therapeutic areas. Therapeutic regulation of biological signal transduction includes modulation of MC3R- and / or MC4R- mediated cellular events including, *inter alia*, inhibition or potentiation of interactions among MC3R- and / or MC4R- binding and activating

or deactivating molecules, or of other agents that regulate MC3R and / or MC4R activities. An increased ability to so regulate MC3R and / or MC4R may facilitate the development of methods for modulating receptor signalling or other biological processes, and for treating conditions associated with such pathways such as obesity, eating disorders (such as cachexia, anorexia, weight gain, weight loss), metabolic syndrome, diabetes, sexual dysfunction (such as erectile dysfunction and female sexual dysfunction), anxiety, depression, inflammation, addiction and alcohol intake.

Accordingly there is still the need to develop improved methods of modulating the activity of a receptor selected from the group consisting of MC3R and MC4R which would facilitate the treatment of MC3R- and / or MC4R- related conditions.

SUMMARY OF THE INVENTION

In one aspect the present invention provides a method of modulating the activity of a receptor selected from the group consisting of MC3R and MC4R or a fragment, analogue or functional equivalent thereof comprising exposing the receptor or a fragment or analogue or functional equivalent thereof to a compound of the formula (I):



Formula (I)

wherein

Y is a group of formula $-(CR^9R^{10})_n$;

X is selected from the group consisting $-C(=O)-$, $-OC(=O)-$, $-NHC(=O)-$, $-(CR^{11}R^{12})_s$, and $-S(=O)_2$;

R is an amino acid side chain group;

R^1 is selected from the group consisting of H, optionally substituted C_1 - C_{12} alkyl, optionally substituted $CH_2(C_6$ - C_{18} aryl) optionally substituted C_2 - C_{12} alkenyl, optionally substituted C_2 - C_{12} alkynyl, optionally substituted C_1 - C_{12} heteroalkyl, optionally substituted C_3 -

C₁₂cycloalkyl, optionally substituted C₂-C₁₂heterocycloalkyl, optionally substituted C₆-C₁₈aryl, and optionally substituted C₁-C₁₈heteroaryl;

R² and R³ are each independently selected from the group consisting of H, optionally substituted C₁-C₁₂alkyl, optionally substituted C₂-C₁₂alkenyl, optionally substituted C₂-C₁₂alkynyl, optionally substituted C₁-C₁₂heteroalkyl, optionally substituted C₃-C₁₂cycloalkyl, optionally substituted C₂-C₁₂heterocycloalkyl, optionally substituted C₆-C₁₈aryl, and optionally substituted C₁-C₁₈heteroaryl, or

R² and R³ may be joined to form a linker between the two nitrogen atoms to which they are attached, wherein the linker is selected from the group consisting of -C(=O)-, -CH₂-, -C(=O)CH₂- and -CH₂C(=O)- ;

R^{5a}, R^{5b} and R⁶ are each independently selected from the group consisting of H, halogen, hydroxy, optionally substituted C₁-C₁₂alkyl, optionally substituted C₂-C₁₂alkenyl, optionally substituted C₂-C₁₂alkynyl, optionally substituted C₁-C₁₂ heteroalkyl, optionally substituted C₁-C₁₀heteroalkenyl, optionally substituted C₃-C₁₂cycloalkyl, optionally substituted C₂-C₁₂heterocycloalkyl, optionally substituted C₆-C₁₈aryl, optionally substituted C₁-C₁₈heteroaryl, optionally substituted amino, optionally substituted carboxy, optionally substituted carboxamide, optionally substituted C₁-C₁₂alkyloxy, and optionally substituted thio;

each R⁹ and R¹⁰ is independently selected from the group consisting of H, optionally substituted C₁-C₁₂alkyl, optionally substituted C₆-C₁₈aryl, and optionally substituted C₁-C₁₈heteroaryl;

each R¹¹ and R¹² is independently selected from the group consisting of H, and optionally substituted C₁-C₁₂alkyl;

n is an integer selected from the group consisting of 1, 2, 3 and 4;

r is an integer selected from the group consisting of 0, 1, 2, 3, and 4;

s is an integer selected from the group consisting of 0, 1, 2, 3, and 4;

or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment the receptor or fragment or analogue or functional equivalent thereof is in a cell and the method comprises exposing the cell to a compound of formula (I). In one embodiment the invention provides a method of modulating the activity of a receptor selected from the group consisting of MC3R and MC4R or a fragment or analogue or functional equivalent thereof in a mammal comprising administering a MC3R- and / or MC4R -modulating amount of a compound of the invention to the mammal.

In yet a further aspect the invention provides the use of a compound of the formula (I) in modulating the activity of a receptor selected from the group consisting of MC3R and MC4R or a fragment, analogue or functional equivalent thereof.

In yet a further aspect the invention provides the use of a compound of formula (I) in the preparation of a medicament for modulating the activity of a receptor selected from the group consisting of MC3R and MC4R or a fragment or analogue or functional equivalent thereof in a mammal.

In yet a further aspect the invention provides the use of a compound of formula (I) in the preparation of a medicament for modulating the activity of MC3R or fragment or analogue or functional equivalent thereof in a mammal.

In yet a further aspect the invention provides the use of a compound of formula (I) in the preparation of a medicament for modulating the activity of MC4R or fragment or analogue or functional equivalent thereof in a mammal.

In yet a further aspect the invention provides the use of a compound of formula (I) in the preparation of a medicament for modulating the activity of both MC3R and MC4R or fragment or analogue or functional equivalent thereof in a mammal.

In yet an even further aspect the invention provides a method of preventing or treating a condition associated with the activity of a receptor selected from the group consisting of MC3R and MC4R or a fragment, analogue or functional equivalent thereof in a mammal the method comprising administering a therapeutically effective amount of a compound of formula (I) to the mammal.

The compound may be administered in any way known in the art although in one aspect the compound is administered topically. In another aspect the compound is administered orally. In another aspect the compound is administered parenterally. In one

embodiment of the method the condition is selected from the group consisting of obesity, eating disorders (such as cachexia, anorexia, weight gain, weight loss), metabolic syndrome, diabetes, sexual dysfunction (such as erectile dysfunction and female sexual dysfunction), anxiety, depression, inflammation, addiction and alcohol intake.

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In one embodiment the invention provides for the use of a compound of formula (I) in the preparation of a medicament for preventing or treating a condition associated with the activity of a receptor selected from the group consisting of MC3R and MC4R or a fragment, analogue or functional equivalent thereof in a mammal. In one aspect the medicament is adapted to be administered topically. In another aspect the medicament is adapted to be administered orally. In another aspect the compound is administered parenterally. In one embodiment of the method the condition is selected from the group consisting of obesity, eating disorders (such as cachexia, anorexia, weight gain, weight loss), metabolic syndrome, diabetes, sexual dysfunction (such as erectile dysfunction and female sexual dysfunction), anxiety, depression, inflammation, addiction and alcohol intake.

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DETAILED DESCRIPTION OF THE INVENTION

In this specification a number of terms are used which are well known to a skilled addressee. Nevertheless for the purposes of clarity a number of terms will be defined.

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As used herein, the term "unsubstituted" means that there is no substituent or that the only substituents are hydrogen.

The term "optionally substituted" as used throughout the specification denotes that the group may or may not be further substituted or fused (so as to form a condensed polycyclic system), with one or more non-hydrogen substituent groups. In certain embodiments the substituent groups are one or more groups independently selected from the group consisting of halogen, =O, =S, -CN, -NO₂, -CF₃, -OCF₃, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, heteroalkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, heteroarylalkyl, arylalkyl, cycloalkylalkenyl, heterocycloalkylalkenyl, arylalkenyl, heteroarylalkenyl, cycloalkylheteroalkyl, heterocycloalkylheteroalkyl, arylheteroalkyl, heteroarylheteroalkyl, hydroxy, hydroxyalkyl, alkyloxy, alkyloxyalkyl, alkyloxycycloalkyl, alkyloxyheterocycloalkyl, alkyloxyaryl, alkyloxyheteroaryl, alkyloxycarbonyl, alkylaminocarbonyl, alkenyloxy, alkynyloxy, cycloalkyloxy, cycloalkenyloxy, heterocycloalkyloxy, heterocycloalkenyloxy, aryloxy, phenoxy, benzyloxy, heteroaryloxy, arylalkyloxy, amino, alkylamino, acylamino, aminoalkyl, arylamino, sulfonylamino, sulfinylamino, sulfonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, sulfinyl,

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alkylsulfinyl, arylsulfinyl, aminosulfinylaminoalkyl, $-C(=O)OH$, $-C(=O)R^a$, $-C(=O)OR^a$, $C(=O)NR^aR^b$, $C(=NOH)R^a$, $C(=NR^a)NR^bR^c$, NR^aR^b , $NR^aC(=O)R^b$, $NR^aC(=O)OR^b$, $NR^aC(=O)NR^bR^c$, $NR^aC(=NR^b)NR^cR^d$, $NR^aSO_2R^b$, $-SR^a$, $SO_2NR^aR^b$, $-OR^a$, $OC(=O)NR^aR^b$, $OC(=O)R^a$ and acyl,

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wherein R^a , R^b , R^c and R^d are each independently selected from the group consisting of H, C_1 - C_{12} alkyl, C_1 - C_{12} haloalkyl, C_2 - C_{12} alkenyl, C_2 - C_{12} alkynyl, C_1 - C_{10} heteroalkyl, C_3 - C_{12} cycloalkyl, C_3 - C_{12} cycloalkenyl, C_1 - C_{12} heterocycloalkyl, C_1 - C_{12} heterocycloalkenyl, C_6 - C_{18} aryl, C_1 - C_{18} heteroaryl, and acyl, or any two or more of R^a , R^b , R^c and R^d , when taken together with the atoms to which they are attached form a heterocyclic ring system with 3 to 12 ring atoms.

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In one embodiment each optional substituent is independently selected from the group consisting of: halogen, $=O$, $=S$, $-CN$, $-NO_2$, $-CF_3$, $-OCF_3$, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, heteroalkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, hydroxy, hydroxyalkyl, alkyloxy, alkyloxyalkyl, alkyloxyaryl, alkyloxyheteroaryl, alkenyloxy, alkynyloxy, cycloalkyloxy, cycloalkenyloxy, heterocycloalkyloxy, heterocycloalkenyloxy, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, arylalkyloxy, amino, alkylamino, acylamino, aminoalkyl, arylamino, sulfonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, aminoalkyl, $-COOH$, $-SH$, and acyl.

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Examples of particularly suitable optional substituents include F, Cl, Br, I, CH_3 , CH_2CH_3 , OH, OCH_3 , CF_3 , OCF_3 , NO_2 , NH_2 , and CN.

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The term "amino acid side chain group" represents a natural or unnatural side chain group present in a protein. The term includes side chain moieties present in naturally occurring proteins including the naturally occurring amino acid side chain moieties identified in table 1 below.

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Table 1. Amino Acid Side Chain Moieties

Amino Acid Side Chain Moiety	Amino Acid
H	Glycine
CH_3	Alanine
$CH(CH_3)_2$	Valine
$CH_2CH(CH_3)_2$	Leucine
$CH(CH_3)CH_2CH_3$	Isoleucine

$(\text{CH}_2)_4\text{NH}_3^+$	Lysine
$(\text{CH}_2)_3\text{NHC}(\text{NH}_2)\text{NH}_2^+$	Arginine
$\text{CH}_2\text{-(imidazol-4-yl)}$	Histidine
CH_2COO^-	Aspartic Acid
$\text{CH}_2\text{CH}_2\text{COO}^-$	Glutamic acid
CH_2CONH_2	Asparagine
$\text{CH}_2\text{CH}_2\text{CONH}_2$	Glutamine
CH_2Ph	Phenylalanine
$\text{CH}_2\text{C}_6\text{H}_4\text{OH}$	Tyrosine
$\text{CH}_2\text{(Indolin-3-yl)}$	Tryptophan
CH_2SH	Cysteine
$\text{CH}_2\text{CH}_2\text{SCH}_3$	Methionine
CH_2OH	Serine
$\text{CH}(\text{OH})\text{CH}_3$	Threonine

In addition to naturally occurring amino acid side chain groups as identified above the term also includes derivatives or analogs thereof. As used herein the term derivative or analogue of an amino acid side chain group includes modifications and variations to naturally occurring side chain groups. With reference to the table above most of the naturally occurring amino acid side chain groups may be classified as alkyl, aryl, arylalkyl or heteroalkyl moieties. As such derivatives of amino acid side chain groups include straight or branched, cyclic or non-cyclic alkyl, aryl, heteroaryl, heteroarylalkyl, arylalkyl or heteroalkyl moieties.

Amino acid side chain groups as discussed above also include optionally substituted derivatives of alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, or heteroalkyl moieties. The optional substituents may be selected from the group defined above. For example, the optional substituents may be selected from but are not limited to OH, Cl, Br, F, COOH, COOR^Z , CONH_2 , NH_2 , NHR^Z , NR^ZR^Z , SH, SR^Z , SO_2R^Z , SO_2H and SOR^Z wherein R^Z is an alkyl, aryl or arylalkyl moiety.

In the definitions of a number of substituents below it is stated that “the group may be a terminal group or a bridging group”. This is intended to signify that the use of the term is intended to encompass the situation where the group is a linker between two other portions of the molecule as well as where it is a terminal moiety. Using the term alkyl as an example, some publications would use the term “alkylene” for a bridging group and hence in these other publications there is a distinction between the terms “alkyl” (terminal group) and

"alkylene" (bridging group). In the present application no such distinction is made and most groups may be either a bridging group or a terminal group.

Several terms are prefaced by a modifier indicating the number of carbon atoms present in the moiety. For example, the modifier "C₁-C₆" in front of the term "alkyl" indicates that the alkyl moiety has from 1 to 6 carbon atoms. Further, the modifier "C₁-C₁₈" in front of the term "heteroaryl" indicates that the heteroaromatic ring may have from 1 to 18 carbon atoms as part of the total number of atoms in the ring system.

"Acyl" means an R-C(=O)- group in which the R group may be an alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group as defined herein. Examples of acyl include acetyl and benzoyl. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the carbonyl carbon.

"Acylamino" means an R-C(=O)-NH- group in which the R group may be an alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the nitrogen atom.

"Alkenyl" as a group or part of a group denotes an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched preferably having 2-14 carbon atoms, more preferably 2-12 carbon atoms, most preferably 2-6 carbon atoms, in the normal chain. The group may contain a plurality of double bonds in the normal chain and the orientation about each is independently E or Z. Exemplary alkenyl groups include, but are not limited to, ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl and nonenyl. The group may be a terminal group or a bridging group.

"Alkenyloxy" refers to an alkenyl-O- group in which alkenyl is as defined herein. Preferred alkenyloxy groups are C₁-C₆ alkenyloxy groups. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the oxygen atom.

"Alkyl" as a group or part of a group refers to a straight or branched aliphatic hydrocarbon group, preferably a C₁-C₁₄ alkyl, more preferably a C₁-C₁₀ alkyl, most preferably C₁-C₆ unless otherwise noted. Examples of suitable straight and branched C₁-C₆ alkyl substituents include methyl, ethyl, n-propyl, 2-propyl, n-butyl, sec-butyl, t-butyl, hexyl, and the like. The group may be a terminal group or a bridging group.

"Alkylamino" includes both mono-alkylamino and dialkylamino, unless specified. "Mono-alkylamino" means a Alkyl-NH- group, in which alkyl is as defined herein. "Dialkylamino" means a (alkyl)₂N- group, in which each alkyl may be the same or different
5 and are each as defined herein for alkyl. The alkyl group is preferably a C₁-C₆ alkyl group. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the nitrogen atom.

"Alkylaminocarbonyl" refers to a group of the formula (Alkyl)_x(H)_yNC(=O)- in which x
10 is 1 or 2, and the sum of x+y =2. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the carbonyl carbon.

"Alkyloxy" refers to an alkyl-O- group in which alkyl is as defined herein. Preferably
15 the alkyloxy is a C₁-C₆alkyloxy. Examples include, but are not limited to, methoxy and ethoxy. The group may be a terminal group or a bridging group.

"Alkyloxyalkyl" refers to an alkyloxy-alkyl- group in which the alkyloxy and alkyl
20 moieties are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the alkyl group.

"Alkyloxyary" refers to an alkyloxy-aryl- group in which the alkyloxy and aryl moieties
25 are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the aryl group.

"Alkyloxycarbonyl" refers to an alkyl-O-C(=O)- group in which alkyl is as defined
herein. The alkyl group is preferably a C₁-C₆ alkyl group. Examples include, but are not
30 limited to, methoxycarbonyl and ethoxycarbonyl. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the carbonyl carbon.

"Alkyloxycycloalkyl" refers to an alkyloxy-cycloalkyl- group in which the alkyloxy and
cycloalkyl moieties are as defined herein. The group may be a terminal group or a bridging
35 group. If the group is a terminal group it is bonded to the remainder of the molecule through the cycloalkyl group.

"Alkyloxyheteroaryl" refers to an alkyloxy-heteroaryl- group in which the alkyloxy and heteroaryl moieties are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the heteroaryl group.

"Alkyloxyheterocycloalkyl" refers to an alkyloxy-heterocycloalkyl- group in which the alkyloxy and heterocycloalkyl moieties are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the heterocycloalkyl group.

"Alkylsulfinyl" means an alkyl-S(=O)- group in which alkyl is as defined herein. The alkyl group is preferably a C₁-C₆ alkyl group. Exemplary alkylsulfinyl groups include, but not limited to, methylsulfinyl and ethylsulfinyl. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the sulfur atom.

"Alkylsulfonyl" refers to an alkyl-S(=O)₂- group in which alkyl is as defined above. The alkyl group is preferably a C₁-C₆ alkyl group. Examples include, but not limited to methylsulfonyl and ethylsulfonyl. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the sulfur atom.

"Alkynyl" as a group or part of a group means an aliphatic hydrocarbon group containing a carbon-carbon triple bond and which may be straight or branched preferably having from 2-14 carbon atoms, more preferably 2-12 carbon atoms, more preferably 2-6 carbon atoms in the normal chain. Exemplary structures include, but are not limited to, ethynyl and propynyl. The group may be a terminal group or a bridging group.

"Alkynyloxy" refers to an alkynyl-O- group in which alkynyl is as defined herein. Preferred alkynyloxy groups are C₁-C₆ alkynyloxy groups. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the oxygen atom.

"Aminoalkyl" means an NH₂-alkyl- group in which the alkyl group is as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the alkyl group.

"Aminosulfonyl" means an $\text{NH}_2\text{-S(=O)}_2\text{-}$ group. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the sulfur atom.

5 "Aryl" as a group or part of a group denotes (i) an optionally substituted monocyclic, or fused polycyclic, aromatic carbocycle (ring structure having ring atoms that are all carbon) preferably having from 5 to 12 atoms per ring. Examples of aryl groups include phenyl, naphthyl, and the like; (ii) an optionally substituted partially saturated bicyclic aromatic carbocyclic moiety in which a phenyl and a C_{5-7} cycloalkyl or C_{5-7} cycloalkenyl group are fused
10 together to form a cyclic structure, such as tetrahydronaphthyl, indenyl or indanyl. The group may be a terminal group or a bridging group. Typically an aryl group is a $\text{C}_6\text{-C}_{18}$ aryl group.

"Arylalkenyl" means an aryl-alkenyl- group in which the aryl and alkenyl are as defined herein. Exemplary arylalkenyl groups include phenylallyl. The group may be a
15 terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the alkenyl group.

"Arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl moieties are as defined herein. Preferred arylalkyl groups contain a C_{1-5} alkyl moiety. Exemplary arylalkyl
20 groups include benzyl, phenethyl, 1-naphthalenemethyl and 2-naphthalenemethyl. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the alkyl group.

"Arylalkyloxy" refers to an aryl-alkyl-O- group in which the alkyl and aryl are as defined
25 herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the oxygen atom.

"Arylamino" includes both mono-arylamino and di-arylamino unless specified. Mono-arylamino means a group of formula arylNH- , in which aryl is as defined herein.
30 di-arylamino means a group of formula $(\text{aryl})_2\text{N-}$ where each aryl may be the same or different and are each as defined herein for aryl. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the nitrogen atom.

35 "Arylheteroalkyl" means an aryl-heteroalkyl- group in which the aryl and heteroalkyl moieties are as defined herein. The group may be a terminal group or a bridging group. If

the group is a terminal group it is bonded to the remainder of the molecule through the heteroalkyl group.

"Aryloxy" refers to an aryl-O- group in which the aryl is as defined herein. Preferably
5 the aryloxy is a C₆-C₁₈aryloxy, more preferably a C₆-C₁₀aryloxy. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the oxygen atom.

"Arylsulfonyl" means an aryl-S(=O)₂- group in which the aryl group is as defined
10 herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the sulfur atom.

A "bond" is a linkage between atoms in a compound or molecule. The bond may be
15 a single bond, a double bond, or a triple bond.

"Carboxamide" refers to a group of the formula -C(=O)-NR₂ wherein each R is
independently H, alkyl, alkenyl, alkynyl, aryl or heteroaryl as defined herein.

"Cyclic group" refers to saturated, partially unsaturated or fully unsaturated
20 monocyclic, bicyclic or polycyclic ring system. Examples of cyclic groups include cycloalkyl, cycloalkenyl and aryl.

"Cycloalkenyl" means a non-aromatic monocyclic or multicyclic ring system
25 containing at least one carbon-carbon double bond and preferably having from 5-10 carbon atoms per ring. Exemplary monocyclic cycloalkenyl rings include cyclopentenyl, cyclohexenyl or cycloheptenyl. The cycloalkenyl group may be substituted by one or more substituent groups. The group may be a terminal group or a bridging group.

"Cycloalkyl" refers to a saturated monocyclic or fused or spiro polycyclic, carbocycle
30 preferably containing from 3 to 9 carbons per ring, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like, unless otherwise specified. It includes monocyclic systems such as cyclopropyl and cyclohexyl, bicyclic systems such as decalin, and polycyclic systems such as adamantane. The group may be a terminal group or a bridging group.

35 "Cycloalkylalkyl" means a cycloalkyl-alkyl- group in which the cycloalkyl and alkyl moieties are as defined herein. Exemplary monocycloalkylalkyl groups include cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl and cycloheptylmethyl. The group

may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the alkyl group.

5 "Cycloalkylalkenyl" means a cycloalkyl-alkenyl- group in which the cycloalkyl and alkenyl moieties are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the alkenyl group.

10 "Cycloalkylheteroalkyl" means a cycloalkyl-heteroalkyl- group in which the cycloalkyl and heteroalkyl moieties are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the heteroalkyl group.

15 "Cycloalkyloxy" refers to a cycloalkyl-O- group in which cycloalkyl is as defined herein. Preferably the cycloalkyloxy is a C₁-C₆cycloalkyloxy. Examples include, but are not limited to, cyclopropanoxy and cyclobutanoxy. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the oxygen atom.

20 "Cycloalkenyloxy" refers to a cycloalkenyl-O- group in which the cycloalkenyl is as defined herein. Preferably the cycloalkenyloxy is a C₁-C₆cycloalkenyloxy. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the oxygen atom.

25 "Haloalkyl" refers to an alkyl group as defined herein in which one or more of the hydrogen atoms has been replaced with a halogen atom selected from the group consisting of fluorine, chlorine, bromine and iodine. A haloalkyl group typically has the formula C_nH_(2n+1-m)X_m wherein each X is independently selected from the group consisting of F, Cl, Br and I. In groups of this type n is typically from 1 to 10, more preferably from 1 to 6, most preferably 1 to 3. m is typically 1 to 6, more preferably 1 to 3. Examples of haloalkyl include fluoromethyl, difluoromethyl and trifluoromethyl.

30

"Haloalkenyl" refers to an alkenyl group as defined herein in which one or more of the hydrogen atoms has been replaced with a halogen atom independently selected from the group consisting of F, Cl, Br and I.

35

"Haloalkynyl" refers to an alkynyl group as defined herein in which one or more of the hydrogen atoms has been replaced with a halogen atom independently selected from the group consisting of F, Cl, Br and I.

5 "Halogen" represents chlorine, fluorine, bromine or iodine.

"Heteroalkyl" refers to a straight- or branched-chain alkyl group preferably having from 2 to 14 carbons, more preferably 2 to 10 carbons in the chain, one or more of which has been replaced by a heteroatom selected from S, O, P and N. Exemplary heteroalkyls include
10 alkyl ethers, secondary and tertiary alkyl amines, amides, alkyl sulfides, and the like. The group may be a terminal group or a bridging group.

"Heteroaryl" either alone or part of a group refers to groups containing an aromatic ring (preferably a 5 or 6 membered aromatic ring) having one or more heteroatoms as ring
15 atoms in the aromatic ring with the remainder of the ring atoms being carbon atoms. Suitable heteroatoms include nitrogen, oxygen and sulphur. Examples of heteroaryl include thiophene, benzothiophene, benzofuran, benzimidazole, benzoxazole, benzothiazole, benzisothiazole, naphtho[2,3-b]thiophene, furan, isoindolizine, xantholene, phenoxatine, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, tetrazole, indole,
20 isoindole, 1H-indazole, purine, quinoline, isoquinoline, phthalazine, naphthyridine, quinoxaline, cinnoline, carbazole, phenanthridine, acridine, phenazine, thiazole, isothiazole, phenothiazine, oxazole, isooxazole, furazane, phenoxazine, 2-, 3- or 4- pyridyl, 2-, 3-, 4-, 5-, or 8- quinolyl, 1-, 3-, 4-, or 5- isoquinolyl, 1-, 2-, or 3- indolyl, and 2-, or 3-thienyl. The group may be a terminal group or a bridging group.

25

"Heteroarylalkyl" means a heteroaryl-alkyl group in which the heteroaryl and alkyl moieties are as defined herein. Preferred heteroarylalkyl groups contain a lower alkyl moiety. Exemplary heteroarylalkyl groups include pyridylmethyl. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the
30 molecule through the alkyl group.

"Heteroarylalkenyl" means a heteroaryl-alkenyl- group in which the heteroaryl and alkenyl moieties are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through
35 the alkenyl group.

"Heteroarylheteroalkyl" means a heteroaryl-heteroalkyl- group in which the heteroaryl and heteroalkyl moieties are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the heteroalkyl group.

"Heteroaryloxy" refers to a heteroaryl-O- group in which the heteroaryl is as defined herein. Preferably the heteroaryloxy is a C₁-C₁₂heteroaryloxy. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the oxygen atom.

"Heterocyclic" refers to saturated, partially unsaturated or fully unsaturated monocyclic, bicyclic or polycyclic ring system containing at least one heteroatom selected from the group consisting of nitrogen, sulfur and oxygen as a ring atom. Examples of heterocyclic moieties include heterocycloalkyl, heterocycloalkenyl and heteroaryl.

"Heterocycloalkenyl" refers to a heterocycloalkyl as defined herein but containing at least one double bond. The group may be a terminal group or a bridging group.

"Heterocycloalkyl" refers to a saturated monocyclic, bicyclic, or polycyclic ring containing at least one heteroatom selected from nitrogen, sulfur, oxygen, preferably from 1 to 3 heteroatoms in at least one ring. Each ring is preferably from 3 to 10 membered, more preferably 4 to 7 membered. Examples of suitable heterocycloalkyl substituents include pyrrolidyl, tetrahydrofuryl, tetrahydrothiofuranyl, piperidyl, piperazyl, tetrahydropyranyl, morpholino, 1,3-diazapane, 1,4-diazapane, 1,4-oxazepane, and 1,4-oxathiapane. The group may be a terminal group or a bridging group.

"Heterocycloalkylalkyl" refers to a heterocycloalkyl-alkyl- group in which the heterocycloalkyl and alkyl moieties are as defined herein. Exemplary heterocycloalkylalkyl groups include (2-tetrahydrofuryl)methyl, (2-tetrahydrothiofuranyl) methyl. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the alkyl group.

"Heterocycloalkylalkenyl" refers to a heterocycloalkyl-alkenyl- group in which the heterocycloalkyl and alkenyl moieties are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the alkenyl group.

"Heterocycloalkylheteroalkyl" means a heterocycloalkyl-heteroalkyl- group in which the heterocycloalkyl and heteroalkyl moieties are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the heteroalkyl group.

"Heterocycloalkyloxy" refers to a heterocycloalkyl-O- group in which the heterocycloalkyl is as defined herein. Preferably the heterocycloalkyloxy is a C₁-C₆heterocycloalkyloxy. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the oxygen atom.

"Heterocycloalkenyloxy" refers to a heterocycloalkenyl-O- group in which heterocycloalkenyl is as defined herein. Preferably the heterocycloalkenyloxy is a C₁-C₆ heterocycloalkenyloxy. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the oxygen atom.

"Hydroxyalkyl" refers to an alkyl group as defined herein in which one or more of the hydrogen atoms has been replaced with an OH group. A hydroxyalkyl group typically has the formula C_nH_(2n+1-x)(OH)_x. In groups of this type n is typically from 1 to 10, more preferably from 1 to 6, most preferably 1 to 3. x is typically 1 to 6, more preferably 1 to 3.

"Lower alkyl" as a group means unless otherwise specified, an aliphatic hydrocarbon group which may be straight or branched having 1 to 6 carbon atoms in the chain, more preferably 1 to 4 carbons such as methyl, ethyl, propyl (n-propyl or isopropyl) or butyl (n-butyl, isobutyl or tertiary-butyl). The group may be a terminal group or a bridging group.

"Sulfinyl" means an R-S(=O)- group in which the R group may be OH, alkyl, cycloalkyl, heterocycloalkyl; aryl or heteroaryl group as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the sulfur atom.

"Sulfinylamino" means an R-S(=O)-NH- group in which the R group may be OH, alkyl, cycloalkyl, heterocycloalkyl; aryl or heteroaryl group as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the nitrogen atom.

"Sulfonyl" means an R-S(=O)₂- group in which the R group may be OH, alkyl, cycloalkyl, heterocycloalkyl; aryl or heteroaryl group as defined herein. The group may be a

terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the sulfur atom.

"Sulfonylamino" means an $R-S(=O)_2-NH-$ group. The group may be a terminal
5 group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the nitrogen atom.

It is understood that included in the family of compounds of Formula (I) are isomeric forms including diastereoisomers, enantiomers, tautomers, and geometrical isomers in "E" or
10 "Z" configurational isomer or a mixture of E and Z isomers. It is also understood that some isomeric forms such as diastereomers, enantiomers, and geometrical isomers can be separated by physical and/or chemical methods and by those skilled in the art.

Some of the compounds of the disclosed embodiments may exist as single
15 stereoisomers, racemates, and/or mixtures of enantiomers and /or diastereomers. All such single stereoisomers, racemates and mixtures thereof, are intended to be within the scope of the subject matter described and claimed.

The present invention includes all pharmaceutically acceptable isotopically-labeled
20 compounds of formula (I) wherein one or more atoms have the same atomic number as, but an atomic mass or mass number different from, the atomic mass or mass number usually found in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention
25 include isotopes of hydrogen, such as 2H and 3H , carbon, such as ^{11}C , ^{13}C and ^{14}C , chlorine, such as ^{36}Cl , fluorine, such ^{18}F , iodine, such as ^{123}I and ^{125}I , nitrogen, such as ^{13}N and ^{15}N , oxygen, such as ^{15}O , ^{17}O and ^{18}O , phosphorus, such as ^{32}P , and sulphur, such as ^{35}S .

Certain isotopically-labeled compounds of formula (I), for example, those
30 incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* 3H , and carbon-14, *i.e.* ^{14}C , are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with heavier isotopes such as deuterium, *i.e.* 2H , may afford certain
35 therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

Substitution with positron emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

Additionally, Formula (I) is intended to cover, where applicable, solvated as well as unsolvated forms of the compounds. Thus, each formula includes compounds having the indicated structure, including the hydrated as well as the non-hydrated forms.

The term "pharmaceutically acceptable salts" refers to salts that retain the desired biological activity of the above-identified compounds, and include pharmaceutically acceptable acid addition salts and base addition salts. Suitable pharmaceutically acceptable acid addition salts of compounds of Formula (I) may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, sulfuric, and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, heterocyclic carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, fumaric, maleic, alkyl sulfonic, arylsulfonic. Additional information on pharmaceutically acceptable salts can be found in Remington's Pharmaceutical Sciences, 19th Edition, Mack Publishing Co., Easton, PA 1995. In the case of agents that are solids, it is understood by those skilled in the art that the inventive compounds, agents and salts may exist in different crystalline or polymorphic forms, all of which are intended to be within the scope of the present invention and specified formulae.

"Prodrug" means a compound that undergoes conversion to a compound of formula (I) within a biological system, usually by metabolic means (e.g. by hydrolysis, reduction or oxidation). For example an ester prodrug of a compound of formula (I) containing a hydroxyl group may be convertible by hydrolysis *in vivo* to the parent molecule. Suitable esters of compounds of formula (I) containing a hydroxyl group, are for example acetates, citrates, lactates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylene-bis- β -hydroxynaphthoates, gestisates, isethionates, di-*p*-toluoyltartrates, methanesulphonates, ethanesulphonates, benzenesulphonates, *p*-toluenesulphonates,

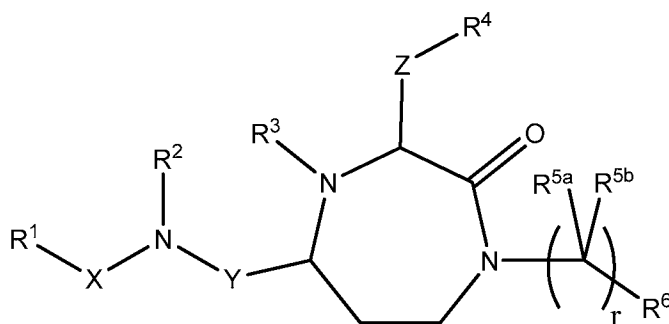
cyclohexylsulphamates and quinates. As another example an ester prodrug of a compound of formula (I) containing a carboxy group may be convertible by hydrolysis *in vivo* to the parent molecule. (Examples of ester prodrugs are those described by F.J. Leinweber, Drug Metab. Res.,18:379, 1987). Similarly, an acyl prodrug of a compound of formula (I) containing an amino group may be convertible by hydrolysis *in vivo* to the parent molecule (Many examples of prodrugs for these and other functional groups, including amines, are described in Prodrugs: Challenges and Rewards (Parts 1 and 2); Ed V. Stella, R. Borchardt, M. Hageman, R.Oliyai, H. Maag and J Tilley; Springer, 2007).

The term "therapeutically effective amount" or "effective amount" is an amount sufficient to effect beneficial or desired clinical results. An effective amount can be administered in one or more administrations. An effective amount is typically sufficient to palliate, ameliorate, stabilize, reverse, slow or delay the progression of the disease state.

The term "functional equivalent" is intended to include variants of the specific receptor described herein. It will be understood that receptors may have isoforms, such that while the primary, secondary, tertiary or quaternary structure of a given receptor isoform is different to the prototypical receptor; the molecule maintains biological activity as a receptor. Isoforms may arise from normal allelic variation within a population and include mutations such as amino acid substitution, deletion, addition, truncation, or duplication. Also included within the term "functional equivalent" are variants generated at the level of transcription.

In the methods and uses of the invention it is observed that certain of the compounds of the Formula (I), are more active than others and therefore it is desirable to use these compounds in the methods and uses of the present invention.

In the methods and uses of the invention a particularly useful subset of compounds of formula (I) are compounds of formula (Ia) as shown below.



Formula (Ia)

wherein

R^1 , R^2 , R^3 , R^{5a} , R^{5b} , R^6 , X, Y and r are as defined above,

5 Z is a group of formula $-(CR^{13}R^{14})_q-$;

R^4 is selected from the group consisting of H, optionally substituted C_1 - C_{12} alkyl, optionally substituted C_2 - C_{12} alkenyl, optionally substituted C_2 - C_{12} alkynyl, optionally substituted C_3 - C_{12} cycloalkyl, optionally substituted C_6 - C_{18} aryl, optionally substituted C_1 -
10 C_{18} heteroaryl, $NR^{4a}R^{4b}$, $C(=O)R^{15}$, $C(=O)NR^{16}R^{17}$, $-C(=NR^{16})NR^{17}R^{18}$, SR^{20} , $SC(=O)R^{20}$, SO_2R^{20} , OR^{20} , $ONR^{16}R^{17}$, $OCR^{17}R^{18}R^{20}$, $OC(=O)R^{20}$, $OC(=O)OR^{20}$, $OC(=O)NR^{16}R^{17}$, and $ONR^{16}C(=NR^{17})NR^{18}R^{19}$;

R^{4a} is selected from the group consisting of H, optionally substituted C_1 - C_{12} alkyl, optionally substituted C_2 - C_{12} alkenyl, optionally substituted C_2 - C_{12} alkynyl, optionally substituted C_1 - C_{12} heteroalkyl, optionally substituted C_3 - C_{12} cycloalkyl, optionally substituted C_2 - C_{12} heterocycloalkyl, optionally substituted C_6 - C_{18} aryl, optionally substituted C_1 -
15 C_{18} heteroaryl, $C(=O)R^{15a}$, $C(=O)NR^{15a}R^{16a}$, $C(=O)OR^{15a}$, SO_2R^{15a} , $C(=O)H$, $-C(=NR^{15a})NR^{16a}R^{17a}$, and OR^{15a} ,

20

R^{4b} is selected from the group consisting of H, optionally substituted C_1 - C_{12} alkyl, optionally substituted C_2 - C_{12} alkenyl, optionally substituted C_2 - C_{12} alkynyl, optionally substituted C_1 - C_{12} heteroalkyl, optionally substituted C_3 - C_{12} cycloalkyl, optionally substituted C_2 - C_{12} heterocycloalkyl, optionally substituted C_6 - C_{18} aryl, optionally substituted C_1 -
25 C_{18} heteroaryl, $C(=O)R^{15a}$, $C(=O)NR^{15a}R^{16a}$, $C(=O)OR^{15a}$, or

R^{4a} and R^{4b} when taken together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic moiety, or

30 one of R^{4a} and R^{4b} when taken together with any R^{13} or R^{14} and the atoms to which they are attached forms an optionally substituted heterocyclic moiety;

R^{13} and R^{14} are each independently selected from the group consisting of H, halogen, OH, C_1 - C_{12} alkyl, C_6 - C_{18} aryl, C_1 - C_{12} hydroxyalkyl, C_1 - C_{12} haloalkyl, C_1 - C_{12} alkyloxy and C_1 -
35 C_{12} haloalkyloxy, or

when taken together with the carbon to which they are attached R^{13} and R^{14} form an optionally substituted C_3 - C_{12} cycloalkyl, or an optionally substituted C_1 - C_{12} heterocycloalkyl group, or

5 one of R^{13} and R^{14} when taken together with one of R^{4a} , and R^{4b} and the atoms to which they are attached form an optionally substituted heterocyclic moiety, or

one of R^{13} and R^{14} when taken together with one of R^{15} , R^{16} , R^{17} , R^{18} , R^{19} or R^{20} and the atoms to which they are attached form an optionally substituted cyclic moiety;

10

each R^{15} , R^{15a} , R^{16} , R^{16a} , R^{17} , R^{17a} , R^{18} , R^{19} and R^{20} is independently selected from the group consisting of H, optionally substituted C_1 - C_{12} alkyl, optionally substituted C_1 - C_{12} heteroalkyl, optionally substituted C_3 - C_{12} cycloalkyl, optionally substituted C_2 - C_{12} heterocycloalkyl, optionally substituted C_6 - C_{18} aryl, and optionally substituted C_1 - C_{18} heteroaryl,

15 or

any two of R^{15} , R^{15a} , R^{16} , R^{16a} , R^{17} , R^{17a} , R^{18} , R^{19} and R^{20} when taken together with the atoms to which they are attached form an optionally substituted cyclic group, or

20 one of R^{15} , R^{16} , R^{17} , R^{18} , R^{19} and R^{20} when taken together with one of R^{13} and R^{14} and the atoms to which they are attached form an optionally substituted cyclic moiety;

q is an integer selected from the group consisting of 0, 1, 2, 3, 4, and 5;

25 or a pharmaceutically acceptable salt or prodrug thereof.

In the methods and uses of the invention a particularly useful subset of compounds of formula (I) are compounds where Y is a group of the formula $-(CR^9R^{10})_n$ -. In one embodiment of the suitable compounds n is 1 and Y is $-CR^9R^{10}$ -. In another embodiment of the suitable compounds n is 2 and Y is $-CR^9R^{10}CR^9R^{10}$ -.
30

In one embodiment of the compounds suitable for use in the invention each R^9 and R^{10} is independently selected from H and CH_3 . In one specific embodiment R^9 and R^{10} are both H. Accordingly in one embodiment of the compounds suitable for use in the invention Y is $-CH_2$ -. In another embodiment of compounds suitable for use in the invention Y is $-CH_2CH_2$ -. In yet an even further embodiment of compounds suitable for use in the invention Y is $-C(CH_3)_2$ -.
35

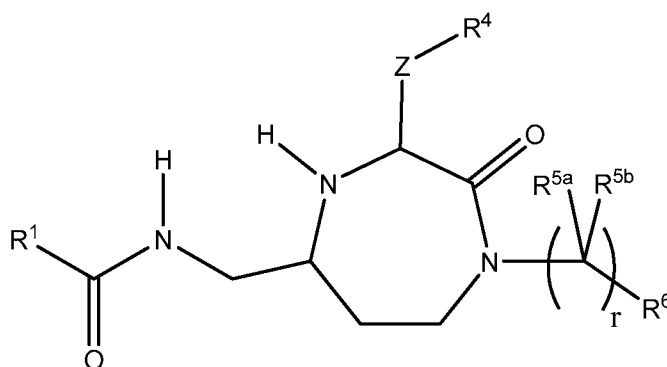
In one embodiment of the compounds suitable for use in the invention R^2 is H or C_1 - C_6 alkyl. In a specific embodiment R^2 is H.

5 In one embodiment of the compounds suitable for use in the invention R^3 is H or C_1 - C_6 alkyl. In a specific embodiment R^3 is H.

In one embodiment of the compounds suitable for use in the invention X is selected from the group consisting of $-C(=O)-$ and $-(CR^{11}R^{12})_s-$. In one specific embodiment X is -
 10 $C(=O)-$. In one embodiment of the compounds suitable for use in the invention X is $-(CR^{11}R^{12})_s-$, s is 1. In another embodiment of compounds suitable for use in the invention X is $-(CR^{11}R^{12})_s-$, s is 2. In one form of each of these embodiments R^{11} and R^{12} are each independently selected from the group consisting of H and C_1 - C_6 alkyl. In a specific embodiment both R^{11} and R^{12} are H, and s is 1 such that X is $-CH_2-$.

15

In one embodiment of the compounds suitable for use in the present invention $R = -Z-R^4$, $R^2 = H$, $R^3 = H$, $X = C(=O)$ and $Y = CH_2$. This provides compounds of formula (Ib).



Formula (Ib)

20

wherein R^1 , R^4 , R^{5a} , R^{5b} , R^6 , Z and r are as defined above.

In one embodiment of the compounds suitable for use in the invention and in particular the compounds of formula (Ia) and (Ib) R^4 is selected from the group consisting of
 25 H, C_1 - C_{12} alkyl, optionally substituted C_2 - C_{12} alkenyl, optionally substituted C_2 - C_{12} alkynyl, C_3 - C_{12} cycloalkyl, optionally substituted C_6 - C_{18} aryl, optionally substituted C-linked C_1 - C_{18} heteroaryl, $C(=O)R^{15}$, $C(=O)NR^{16}R^{17}$, $-C(=NR^{16})NR^{17}R^{18}$, SR^{20} , $SC(=O)R^{20}$, SO_2R^{20} , OR^{20} , $ONR^{16}R^{17}$, $OCR^{17}R^{18}R^{20}$, $OC(=O)R^{20}$, $OC(=O)OR^{20}$, $OC(=O)NR^{16}R^{17}$, and $ONR^{16}C(=NR^{17})NR^{18}R^{19}$.

30

In one specific embodiment R^4 is optionally substituted C_1 - C_{18} heteroaryl. In another embodiment R^4 is optionally substituted C_3 - C_{12} cycloalkyl. In another embodiment R^4 is C_1 - C_{12} alkyl

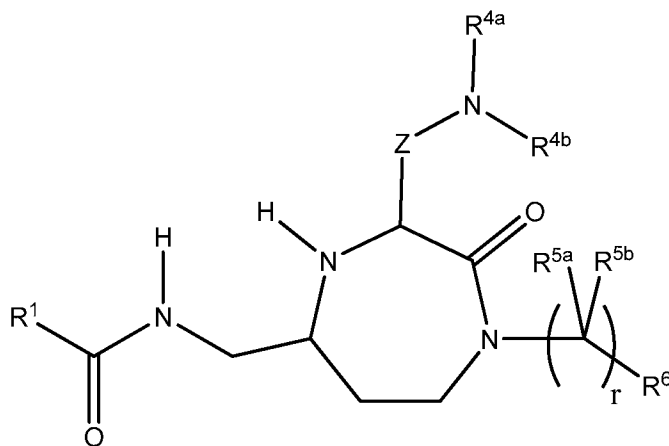
5 In another specific embodiment R^4 is $C(=O)NR^{16}R^{17}$.

In another specific embodiment R^4 is $C(=O)NR^{16}R^{17}$ and R^{16} and R^{17} , when taken together with the nitrogen atom to which they are attached, form an optionally substituted C_2 - C_{12} heterocycloalkyl group. In specific embodiments R^{15} and R^{16} when taken together with the
 10 nitrogen atom to which they are attached form an optionally substituted heterocycloalkyl group selected from the group consisting of piperidin-1-yl, pyrrolidin-1-yl, azetidin-1-yl, azepan-1-yl, morpholin-4-yl, and piperazin-1-yl.

In one embodiment of the compounds suitable for use in the invention R^{16} is selected
 15 from the group consisting of H, CH_3 , CH_2CH_3 , $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH(CH_3)CH_2CH_3$, $CH_2CH(CH_3)_2$, $C(CH_3)_3$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, benzyl, and phenyl, or a halogenated derivative thereof.

In one embodiment of the compounds suitable for use in the invention R^{17} is selected
 20 from the group consisting of H, CH_3 , CH_2CH_3 , $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH(CH_3)CH_2CH_3$, $CH_2CH(CH_3)_2$, $C(CH_3)_3$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, benzyl, and phenyl, or a halogenated derivative thereof.

In one embodiment of the methods and uses of the invention the compound of formula
 25 (Ib) used is one in which $R^4 = NR^{4a}R^{4b}$. Accordingly a useful subset of compounds for use in the methods and uses of the present invention are compounds of formula (Ic):



Formula (Ic)

wherein R^1 , R^{4a} , R^{4b} , R^{5a} , R^{5b} , R^6 , and Z are as defined above

In one embodiment of the compounds suitable for use in the invention, r is selected from the group consisting of 0, 1, 2, 3, and 4. In one specific embodiment r is 0. In another specific embodiment r is 1. In yet a further specific embodiment r is 2. In yet a further specific embodiment r is 3. In an even further specific embodiment r is 4.

In the compounds of the invention Z is a group of formula $-(CR^{13}R^{14})_q-$. In one embodiment of the compounds suitable for use in the invention, and in particular the compounds of formula (I), formula (Ia), formula (Ib), and formula (Ic), R^{13} and R^{14} are independently selected from H and C_1 - C_6 alkyl. In one embodiment R^{13} and R^{14} are each independently selected from H and CH_3 . In one specific embodiment R^{13} and R^{14} are both H. In yet another embodiment at least one of R^{13} and R^{14} when taken together with at least one of R^{4a} and R^{4b} and the atoms to which they are attached form an optionally substituted heterocycloalkyl group. In one embodiment Z is $-(CH_2)_q-$

In one embodiment of the compounds suitable for use in the invention q is an integer selected from the group consisting of 0, 1, 2, 3, 4, and 5. In one specific embodiment q is 1. In another specific embodiment q is 2, in yet an even further specific embodiment q is 3, and in yet an even further specific embodiment q is 4.

In one form of the compounds suitable for use in the invention R^{4a} is selected from the group consisting of H, $-C(=N)NH_2$, $-C(=N)N(CH_3)_2$, $-C(=N)NCH(CH_3)_2$, $-C(=O)CH_3$, $-C(=O)cyclohexyl$, CH_3 , CH_2CH_3 , $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH(CH_3)CH_2CH_3$, $CH_2CH(CH_3)_2$, $C(CH_3)_3$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, benzyl, and phenyl, or a halogenated derivative thereof. In one form of the compounds suitable for use in the invention R^{4b} is selected from the group consisting of H, CH_3 , CH_2CH_3 , $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH(CH_3)CH_2CH_3$, $CH_2CH(CH_3)_2$, $C(CH_3)_3$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, benzyl, and phenyl, or a halogenated derivative thereof.

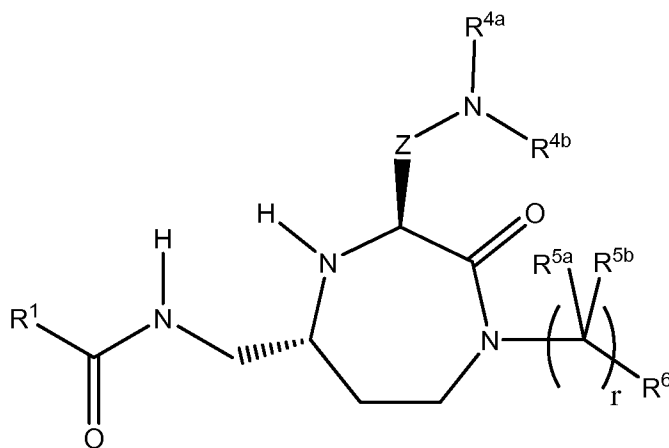
In another form of the compounds suitable for use in the invention R^{4a} and R^{4b} when taken together with the nitrogen atom to which they are attached form an optionally substituted C_2 - C_{12} heterocycloalkyl group, an optionally substituted C_2 - C_{12} heterocycloalkenyl group or an optionally substituted C_1 - C_{18} heteroaryl group.

In a particular embodiment of the compounds suitable for use in the invention R^{4a} and R^{4b} when taken together with the nitrogen atom to which they are attached form an optionally

substituted heterocycloalkyl group selected from the group consisting of piperidin-1-yl, pyrrolidin-1-yl, azepan-1-yl, azetidin-1-yl, piperazin-1-yl, and morpholin-4-yl.

In one embodiment of the methods and uses of the invention, the compound of formula (I) is one in which one of R^{4a} and R^{4b} when taken together with the nitrogen atom to which it is attached and one of R^{13} and R^{14} and the carbon atom to which it is attached form an optionally substituted C_2 - C_{12} heterocycloalkyl group. In a particular embodiment one of R^{4a} and R^{4b} when taken together with the nitrogen atom to which it is attached and one of R^{13} and R^{14} and the carbon atom to which it is attached form an optionally substituted heterocycloalkyl group selected from the group consisting of piperidinyl, pyrrolidinyl, azepanyl, azetidiny, morpholinyl, and piperazinyl.

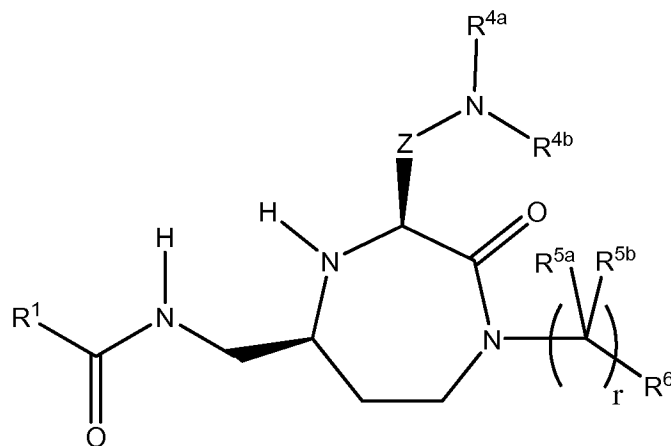
In one embodiment of the methods and uses of the invention the compound of formula (I) used is one in which the stereoisomeric configuration of the diazepanone is (3S,5R), as in formula (Id):



Formula (Id)

wherein R^1 , R^{4a} , R^{4b} , R^{5a} , R^{5b} , R^6 , and Z are as defined for formula (Ic).

In another embodiment of the methods and uses of the invention the compound of formula (I) used is one in which the stereoisomeric configuration of the diazepanone is (3S,5S), as in formula (Ie):



Formula (Ie)

wherein R^1 , R^{4a} , R^{4b} , R^{5a} , R^{5b} , R^6 , A and Z are as defined for formula (Ic).

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In one specific embodiment of the compounds suitable for use in the invention R^1 is selected from the group consisting of an optionally substituted amino acid, optionally substituted C_2 - C_{12} alkenyl, optionally substituted C_6 - C_{18} aryl, optionally substituted $CH_2(C_6$ - C_{18} aryl), and optionally substituted C_1 - C_{18} heteroaryl.

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In another specific embodiment of the compounds suitable for use in the invention R^1 -X is an optionally substituted amino acid.

In one specific embodiment of the compounds suitable for use in the invention R^1 is optionally substituted C_6 - C_{18} aryl. The C_6 - C_{18} aryl may be a monocyclic, bicyclic or polycyclic moiety. In certain embodiments the C_6 - C_{18} aryl is a monocyclic moiety. In certain embodiments the C_6 - C_{18} aryl is a bicyclic moiety.

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In one specific embodiment of the compounds suitable for use in the invention R^1 is optionally substituted $CH_2(C_6$ - C_{18} aryl). The C_6 - C_{18} aryl may be a monocyclic, bicyclic or polycyclic moiety. In certain embodiments the C_6 - C_{18} aryl is a monocyclic moiety. In certain embodiments the C_6 - C_{18} aryl is a bicyclic moiety.

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In one specific embodiment R^1 is an optionally substituted C_6 - C_{18} aryl selected from the group consisting of optionally substituted phenyl, biphenyl, and optionally substituted naphthyl. In another specific embodiment R^1 is an optionally substituted $CH_2(C_6$ - C_{18} aryl) with the aryl group selected from the group consisting of optionally substituted phenyl, biphenyl, and optionally substituted naphthyl. The moieties may be unsubstituted or may be

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substituted with one or more optional substituents. A wide variety of optional substituents may be used as defined above. Examples of particularly suitable optional substituents include, but are not limited to, F, Br, Cl, methyl, trifluoromethyl, ethyl, 2,2,2-trifluoroethyl, isopropyl, propyl, 2-ethyl-propyl, 3,3-dimethyl-propyl, butyl, isobutyl, 3,3-dimethyl-butyl, 2-ethyl-butyl, pentyl, 2-methyl-pentyl, pent-4-enyl, hexyl, heptyl, octyl, phenyl, NH₂, cyano, phenoxy, hydroxy, methoxy, ethoxy, pyrrol-1-yl, and 3,5-dimethyl-pyrazol-1-yl.

The substituents may be located at any substitutable position around the aryl ring available for substitution as would be clear to a skilled addressee. Examples of suitably optionally substituted phenyl compounds include, but are not limited to, 2-methoxy-phenyl, 3-methoxy-phenyl, 4-methoxy-phenyl, 2-trifluoromethyl-phenyl, 3-trifluoromethyl-phenyl, 4-trifluoromethyl-phenyl, 2-chloro-phenyl, 3-chloro-phenyl, 4-chloro-phenyl, 4-bromo-phenyl, 2-fluoro-phenyl, 3-fluoro-phenyl, 4-fluoro-phenyl, 4-hydroxy-phenyl, 4-phenyl-phenyl, 4-methyl-phenyl, 2,4-dichloro-phenyl, 3,4-dichloro-phenyl, 2,5-dichloro-phenyl, 2,6-difluoro-phenyl, 2-chloro-6-fluoro-phenyl, 3-fluoro-4-chloro-phenyl, 3-methyl-4-chloro-phenyl, 3-chloro-4-fluoro-phenyl, 3-chloro-4-methyl-phenyl, 2-hydroxy-phenyl, 3-hydroxy-phenyl, 4-hydroxy-phenyl, 4-ethoxy-phenyl, 3-phenoxy-phenyl, 4-phenoxy-phenyl, 2-methyl-phenyl, 3-methyl-phenyl, 4-methyl-phenyl, 4-isopropyl-phenyl, 4-cyano-phenyl, 3,4-dimethyl-phenyl, 2,4-dimethyl-phenyl, 4-*t*-butyl-phenyl, 2,4-dimethoxy-phenyl, and 3,4-methylenedioxy-phenyl.

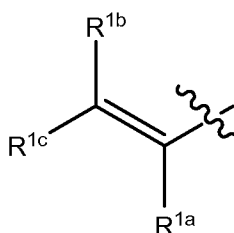
When R¹ is optionally substituted biphenyl the point of attachment of R¹ to the remainder of the molecule may be at the 2-, 3- or 4- position relative to the point of attachment of the second phenyl ring. As such the biphenyl may be an optionally substituted biphen-2-yl, or an optionally substituted biphen-3-yl, or an optionally substituted biphen-4-yl. In general the optionally substituted biphenyl is an optionally substituted biphen-4-yl. The optionally substituted biphenyl may be substituted in any suitable position.

When R¹ is optionally substituted naphthyl the point of attachment of R¹ to the remainder of the molecule may be at the 1 or 2 position. As such the naphthyl may be an optionally substituted naphth-1-yl, or an optionally substituted naphth-2-yl. In general the optionally substituted naphthyl is an optionally substituted naphth-2-yl. The optionally substituted naphthyl may be substituted in any suitable position. Examples of suitably optionally substituted naphth-2-yls include, but are not limited to, 6-fluoro-naphth-2-yl, 6-bromo-naphth-2-yl, 6-chloro-naphth-2-yl, 1-methoxy-naphth-2-yl, 3-methoxy-naphth-2-yl, 6-methoxy-naphth-2-yl, 1-hydroxy-naphth-2-yl, and 6-amino-naphth-2-yl.

In one specific embodiment of the compounds suitable for use in the invention R^1 is optionally substituted C_1 - C_{18} heteroaryl. The C_1 - C_{18} heteroaryl may be a monocyclic, bicyclic or polycyclic moiety. In certain embodiments the C_1 - C_{18} heteroaryl is a monocyclic moiety. In certain embodiments the C_1 - C_{18} heteroaryl is a bicyclic moiety. Examples of suitable heteroaryl moieties include, but are not limited to, indol-2-yl, indol-3-yl, quinolin-2-yl, quinolin-3-yl, isoquinolin-3-yl, quinoxaline-2-yl, benzo[b]furan-2-yl, benzo[b]thiophen-2-yl, benzo[b]thiophen-5-yl, thiazole-4-yl, benzimidazole-5-yl, benzotriazol-5-yl, furan-2-yl, benzo[d]thiazole-6-yl, pyrazole-1-yl, pyrazole-4-yl and thiophen-2-yl. These may also be optionally substituted as discussed above.

In one specific embodiment of the compounds suitable for use in the invention R^1 is an optionally substituted C_2 - C_{12} alkenyl. The optionally substituted alkenyl may contain one or more double bonds with each of the double bonds being independently in the E or Z configuration. In one embodiment of the invention the alkenyl contains a single double bond which is in the E configuration.

In one specific form of this embodiment R^1 is an optionally substituted C_2 - C_{12} alkenyl of the formula:

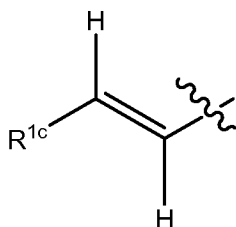


R^{1a} is selected from the group consisting of H, halogen and optionally substituted C_1 - C_{12} alkyl;

R^{1b} and R^{1c} are each independently selected from the group consisting of H, halogen, optionally substituted C_1 - C_{12} alkyl, optionally substituted C_2 - C_{12} alkenyl, optionally substituted C_2 - C_{12} alkynyl, optionally substituted C_1 - C_{12} heteroalkyl, optionally substituted C_3 - C_{12} cycloalkyl, optionally substituted C_2 - C_{12} heterocycloalkyl, optionally substituted C_6 - C_{18} aryl, and optionally substituted C_1 - C_{18} heteroaryl.

In one form of this embodiment R^{1a} is H. In one form of this embodiment R^{1b} is H. This provides compounds where R^1 is of the formula:

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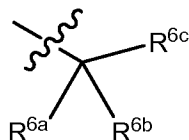
In one embodiment of the compounds of the invention R^{1c} is optionally substituted C_6 - C_{18} aryl. The C_6 - C_{18} aryl may be monocyclic, bicyclic or polycyclic moiety. In certain
 5 embodiments the C_6 - C_{18} aryl is a monocyclic moiety. In certain embodiments the C_6 - C_{18} aryl is a bicyclic moiety.

In one specific embodiment R^{1c} is an optionally substituted C_6 - C_{18} aryl selected from the group consisting of optionally substituted phenyl and optionally substituted naphthyl. The
 10 moieties may be unsubstituted or may be substituted with one or more optional substituents. A wide variety of optional substituents may be used as defined above. Examples of particularly suitable optional substituents include, but are not limited to, F, Br, Cl, methyl, trifluoromethyl, ethyl, 2,2,2-trifluoroethyl, isopropyl, propyl, 2-ethyl-propyl, 3,3-dimethyl-propyl, butyl, isobutyl, 3,3-dimethyl-butyl, 2-ethyl-butyl, pentyl, 2-methyl-pentyl, pent-4-enyl, hexyl,
 15 heptyl, octyl, phenyl, NH_2 , cyano, phenoxy, hydroxy, methoxy, ethoxy, methylenedioxy, pyrrol-1-yl, and 3,5-dimethyl-pyrazol-1-yl.

The substituents may be located at any substitutable position around the aryl ring available for substitution as would be clear to a skilled addressee. Examples of suitable
 20 optionally substituted phenyl compounds include, but are not limited to, 2-methoxy-phenyl, 3-methoxy-phenyl, 4-methoxy-phenyl, 2-trifluoromethyl-phenyl, 3-trifluoromethyl-phenyl, 4-trifluoromethyl-phenyl, 2-chloro-phenyl, 3-chloro-phenyl, 4-chloro-phenyl, 4-bromo-phenyl, 2-fluoro-phenyl, 3-fluoro-phenyl, 4-fluoro-phenyl, 4-hydroxy-phenyl, 4-phenyl-phenyl, 4-methyl-phenyl, 2,4-dichloro-phenyl, 3,4-dichloro-phenyl, 2,5-dichloro-phenyl, 2,6-difluoro-phenyl, 2-
 25 chloro-6-fluoro-phenyl, 3-fluoro-4-chloro-phenyl, 3-methyl-4-chloro-phenyl, 3-chloro-4-fluoro-phenyl, 3-chloro-4-methyl-phenyl, 2-hydroxy-phenyl, 3-hydroxy-phenyl, 4-hydroxy-phenyl, 4-ethoxy-phenyl, 3-phenoxy-phenyl, 4-phenoxy-phenyl, 2-methyl-phenyl, 3-methyl-phenyl, 4-methyl-phenyl, 4-isopropyl-phenyl, 4-cyano-phenyl, 3,4-dimethyl-phenyl, 2,4-dimethyl-phenyl, 4-t-butyl-phenyl, 2,4-dimethoxy-phenyl, and 3,4-methylenedioxy-phenyl.

In one embodiment of the compounds suitable for use in the invention R^{5a} and R^{5b} are independently selected from H and C_1 - C_6 alkyl. In one embodiment R^{5a} and R^{5b} are each independently selected from H and CH_3 . In one specific embodiment R^{5a} and R^{5b} are both H.

In one embodiment of the compounds suitable for use in the invention R^6 is an optionally substituted alkyl group. In one embodiment invention R^6 is an optionally substituted alkyl group of the formula:



In one embodiment R^{6b} is H.

In one embodiment R^{6a} and R^{6c} are each independently selected from the group consisting of H, optionally substituted C_1 - C_{12} alkyl, optionally substituted C_2 - C_{12} alkenyl, optionally substituted C_6 - C_{18} aryl and optionally substituted C_1 - C_{18} heteroaryl.

In one embodiment R^{6a} and R^{6c} are each independently selected from the group consisting of optionally substituted C_1 - C_{12} alkyl, optionally substituted C_2 - C_{12} alkenyl, optionally substituted C_6 - C_{18} aryl and optionally substituted C_1 - C_{18} heteroaryl.

In one embodiment R^{6a} is selected from the group consisting of ethyl, 2,2,2-trifluoroethyl, isopropyl, isopropenyl, propyl, 2-ethyl-propyl, 3,3-dimethyl-propyl, butyl, 2-methyl-butyl, isobutyl, 3,3-dimethyl-butyl, 2-ethyl-butyl, pentyl, 2-methyl-pentyl, optionally substituted phenyl and optionally substituted C_1 - C_5 heteroaryl.

In one embodiment R^{6a} is optionally substituted phenyl or optionally substituted C_1 - C_{18} heteroaryl.

In one embodiment R^{6c} is selected from the group consisting of ethyl, 2,2,2-trifluoroethyl, isopropyl, isopropenyl, propyl, 2-ethyl-propyl, 3,3-dimethyl-propyl, butyl, 2-methyl-butyl, isobutyl, 3,3-dimethyl-butyl, 2-ethyl-butyl, pentyl, 2-methyl-pentyl, optionally substituted phenyl and optionally substituted C_1 - C_5 heteroaryl.

In one embodiment R^{6c} is methyl, ethyl, phenyl or optionally substituted C_1 - C_5 heteroaryl.

In one embodiment of the compounds suitable for use in the invention, r is 1, R^{5a} is H, and R^{5b} is selected from the group consisting of optionally substituted carboxy and optionally substituted carboxamide.

In one form of this embodiment R^6 is selected from the group consisting of H, optionally substituted C_1 - C_{12} alkyl, optionally C_6 - C_{18} aryl, or optionally substituted C_1 - C_{18} heteroaryl. In a further form of this embodiment, the optionally substituted alky group is selected from the group consisting of an optionally substituted $CH_2(C_6$ - C_{18} aryl) group and an optionally substituted $CH_2(C_1$ - C_{18} heteroaryl) group.

In one embodiment of the invention the compound used is not a compound selected from the group consisting of

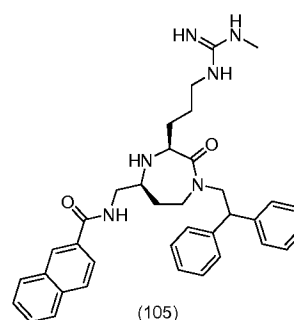
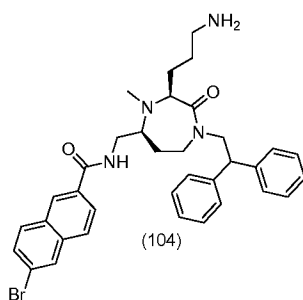
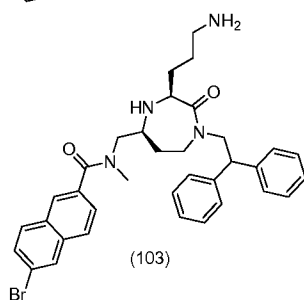
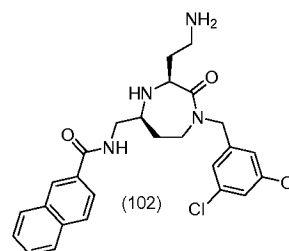
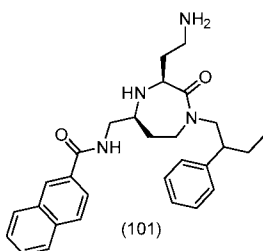
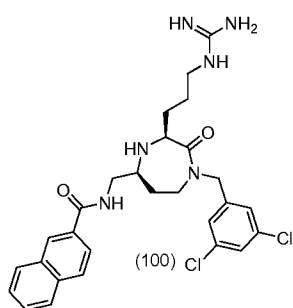
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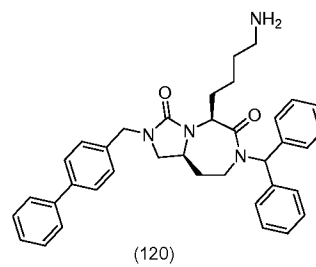
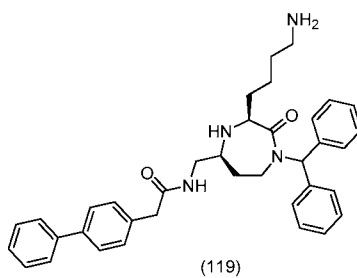
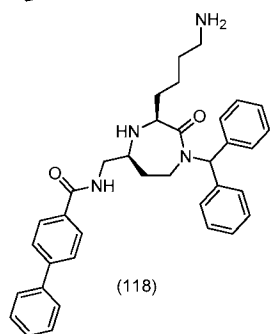
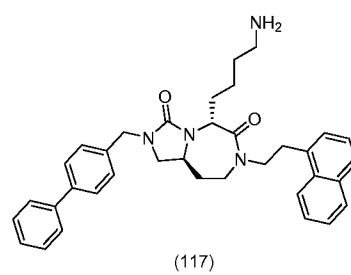
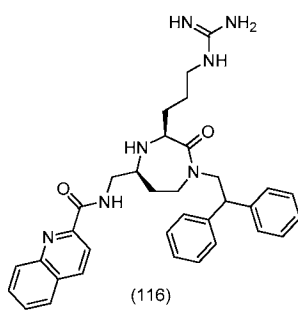
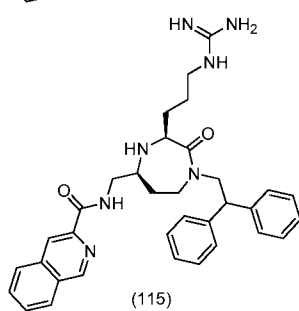
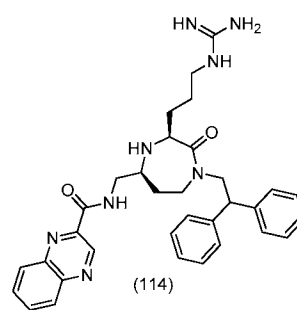
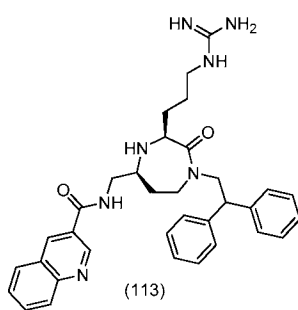
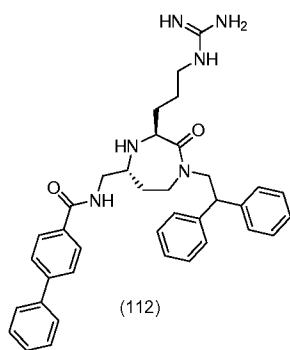
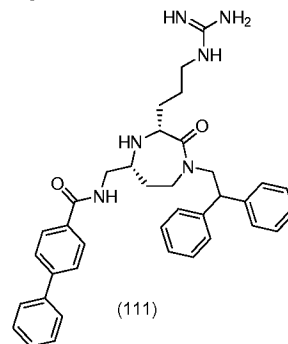
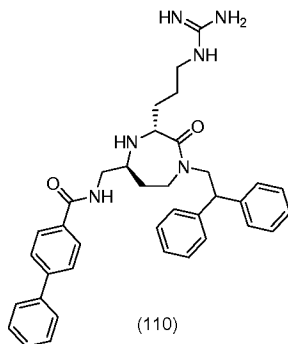
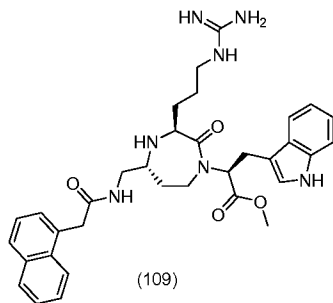
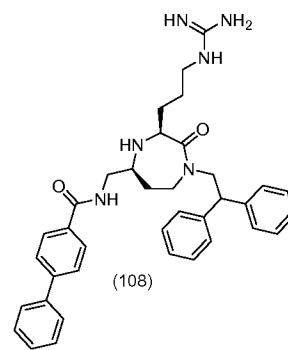
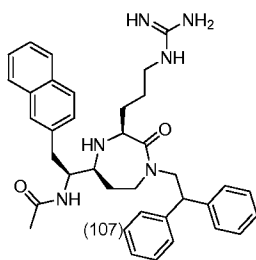
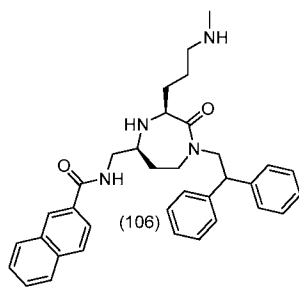
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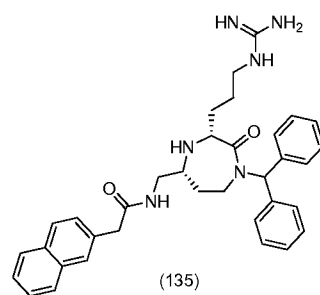
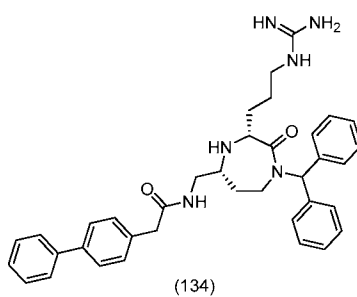
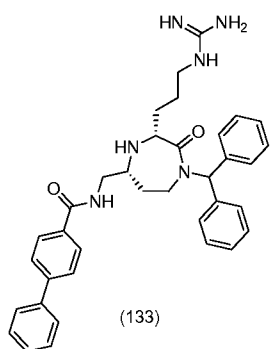
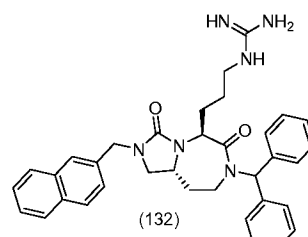
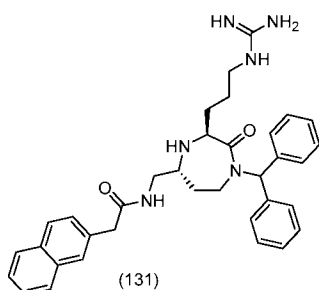
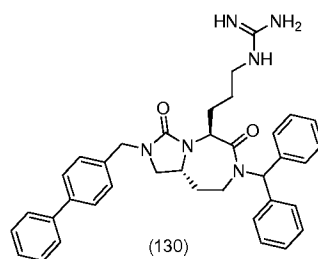
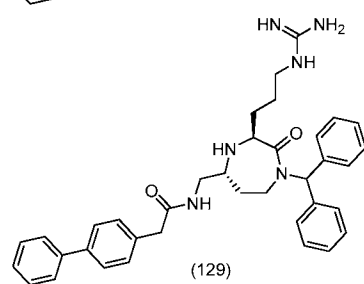
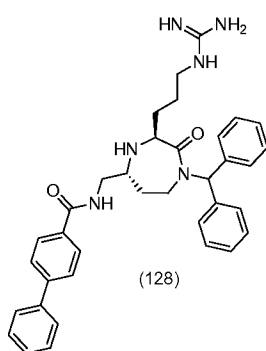
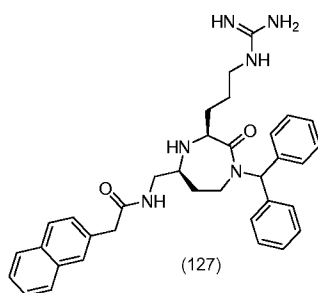
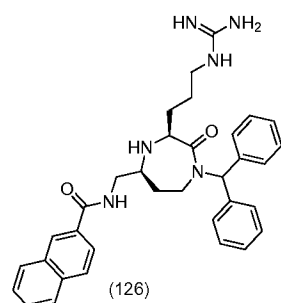
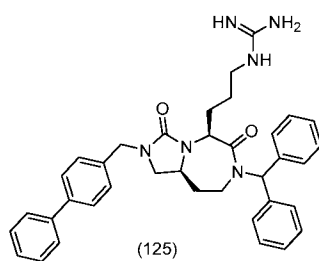
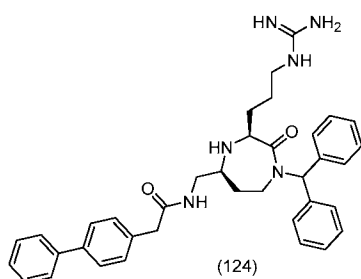
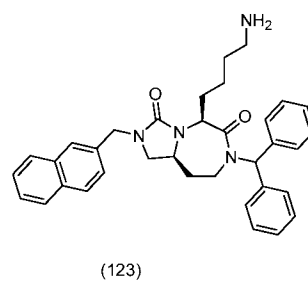
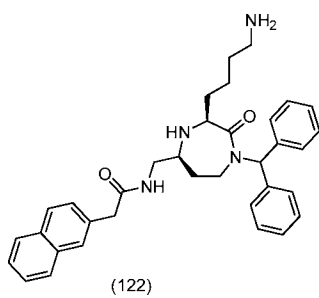
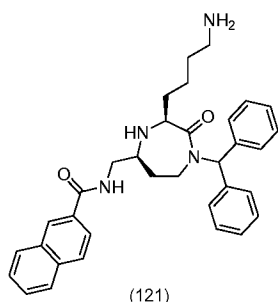
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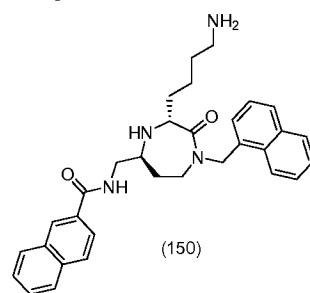
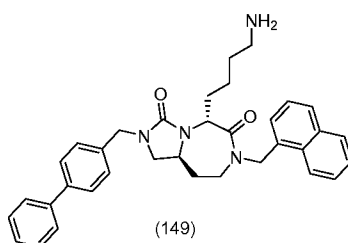
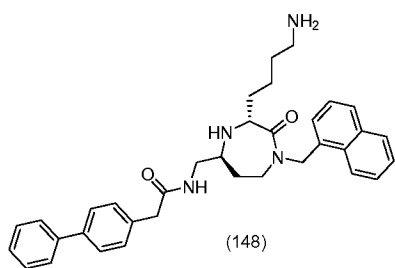
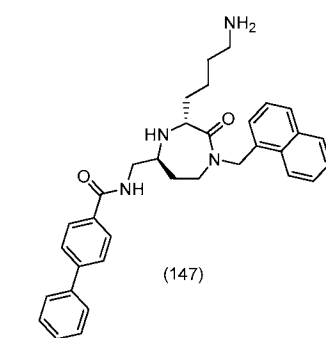
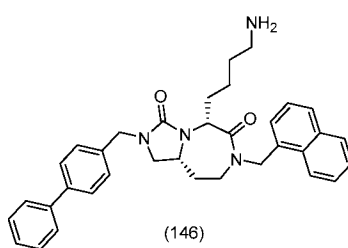
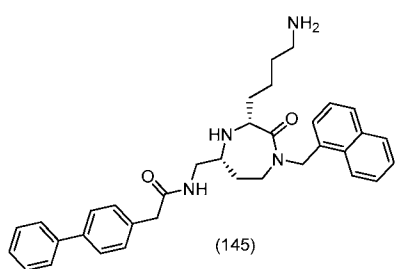
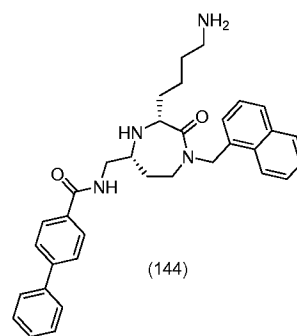
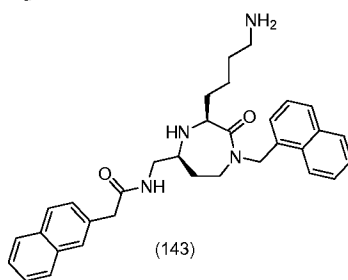
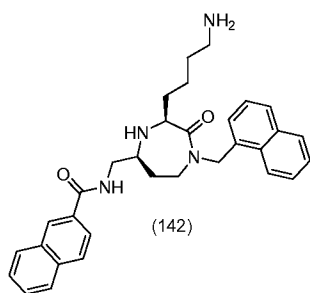
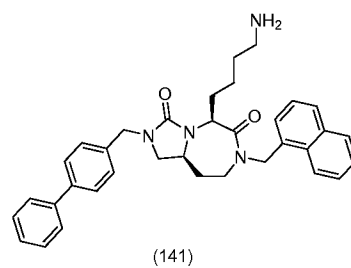
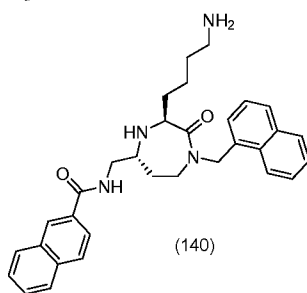
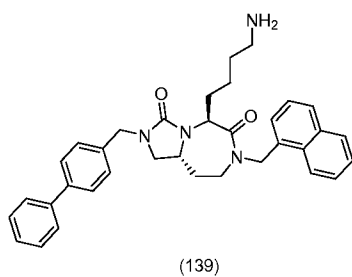
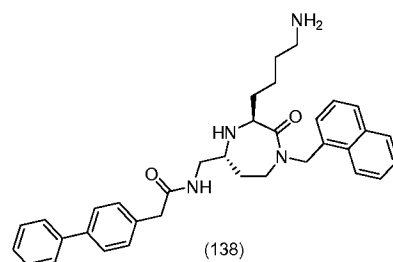
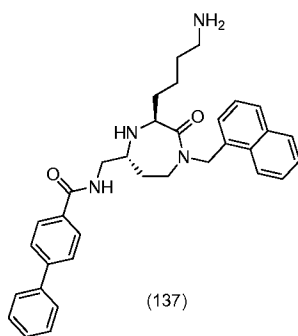
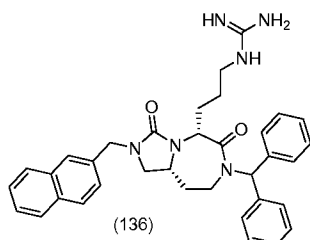
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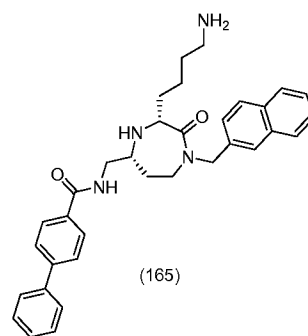
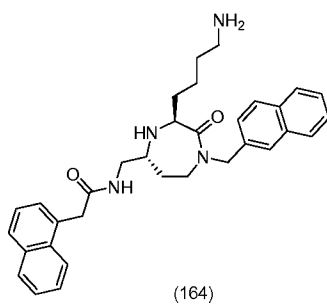
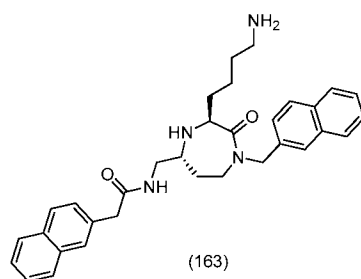
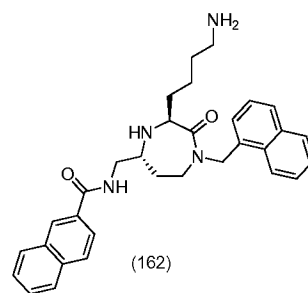
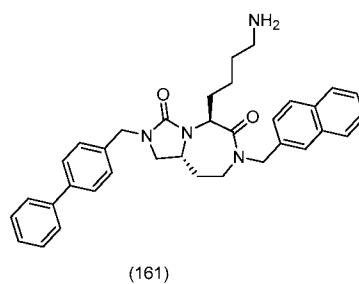
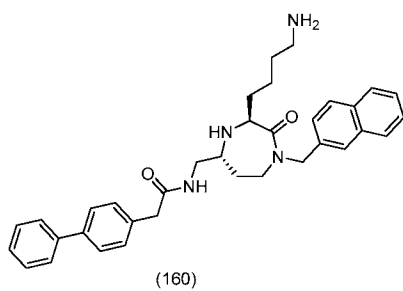
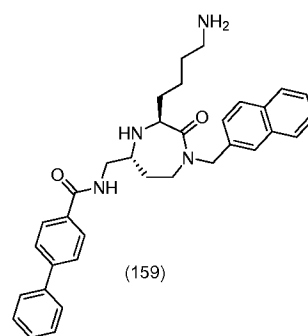
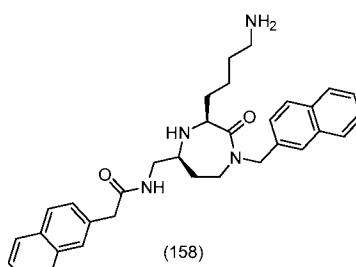
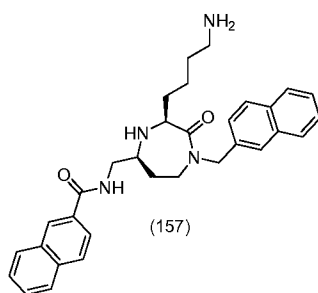
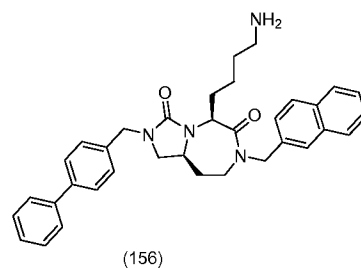
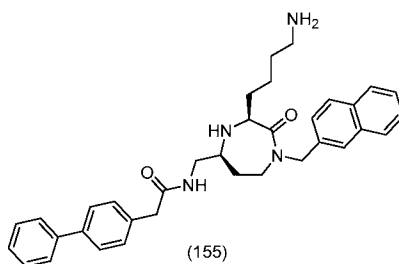
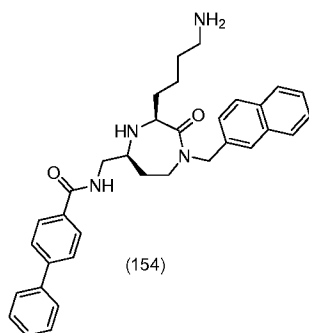
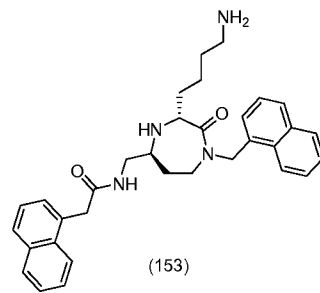
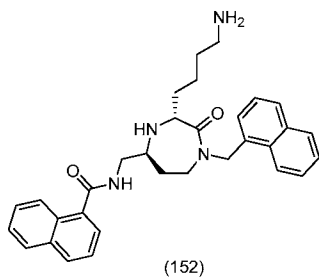
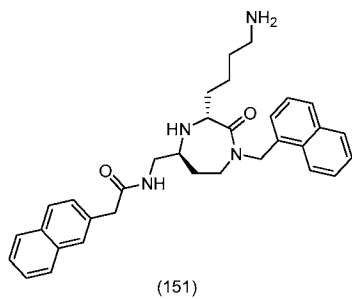
Specific compounds suitable for use in the methods and uses of the invention include the following:

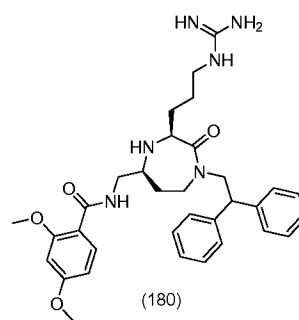
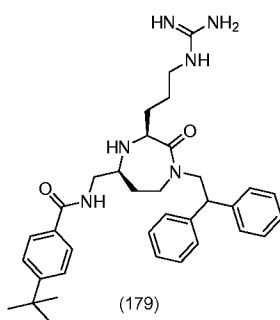
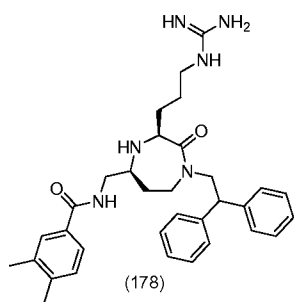
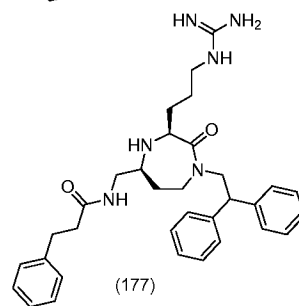
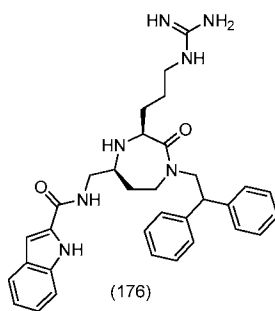
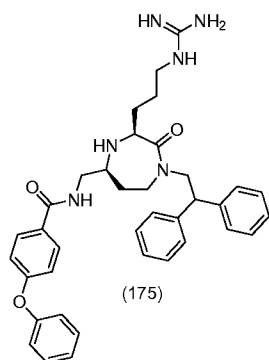
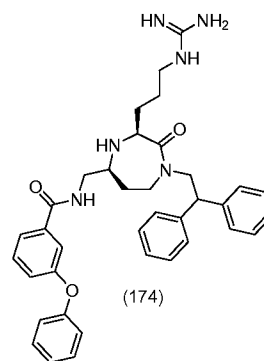
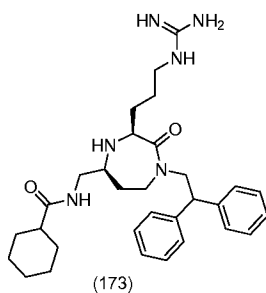
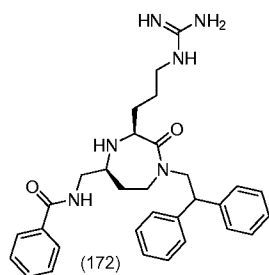
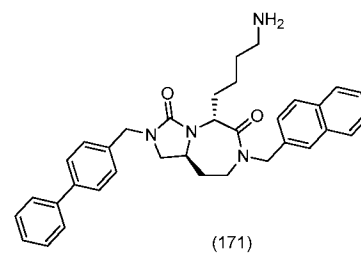
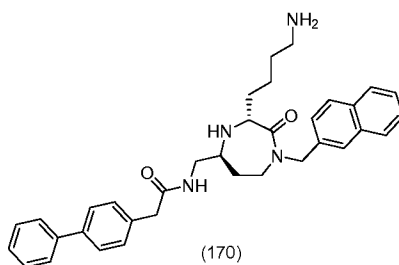
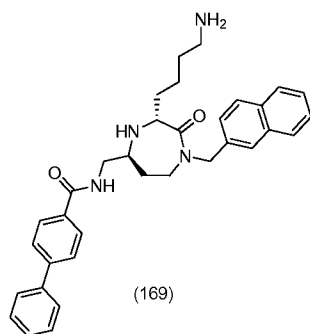
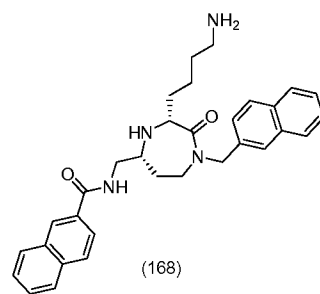
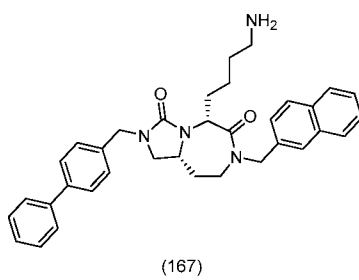
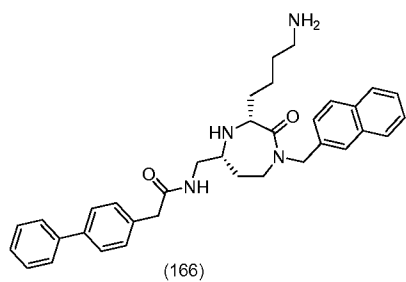


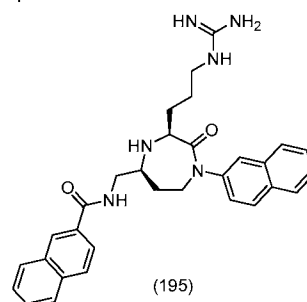
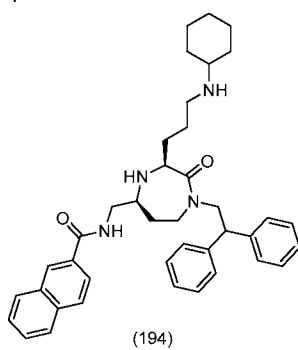
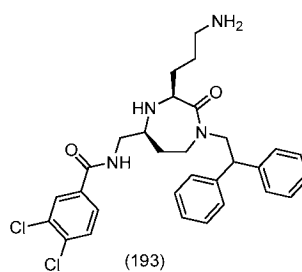
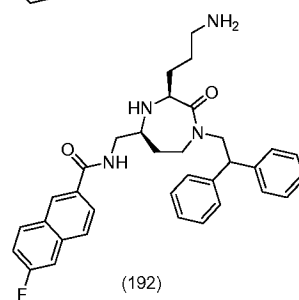
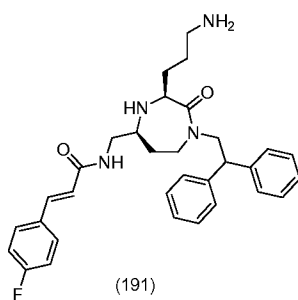
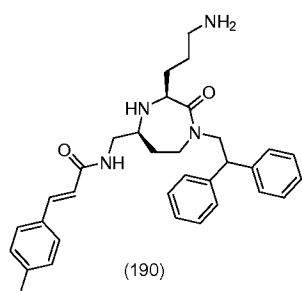
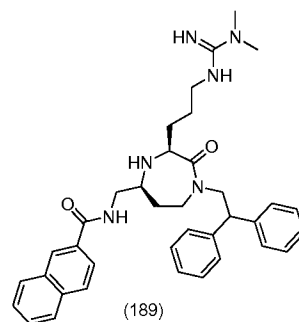
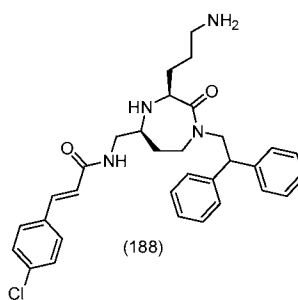
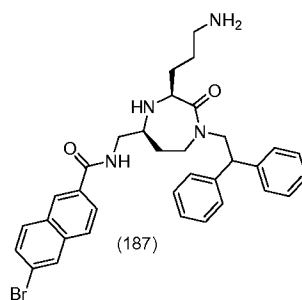
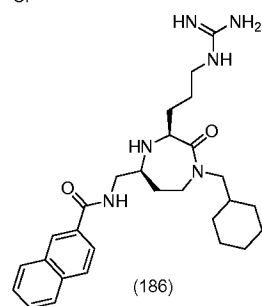
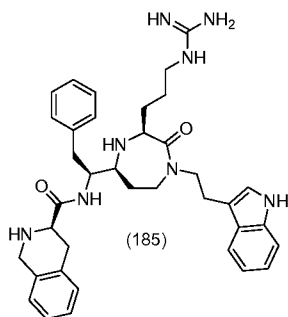
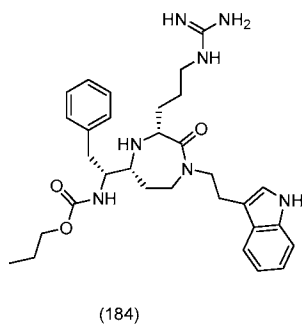
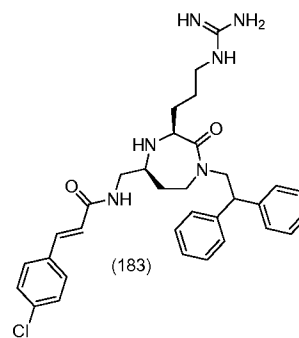
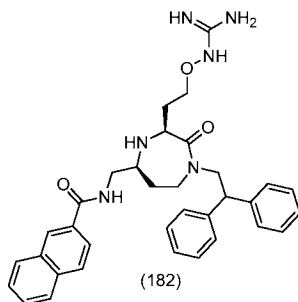
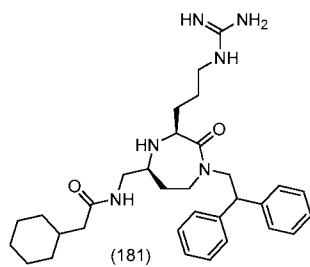


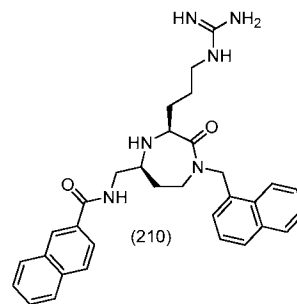
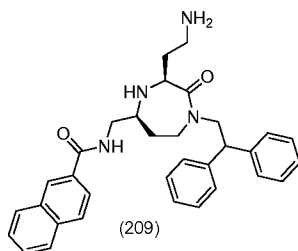
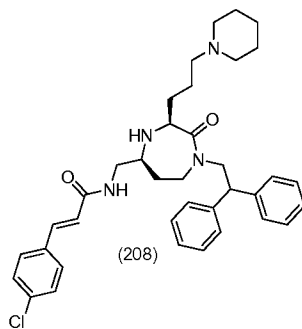
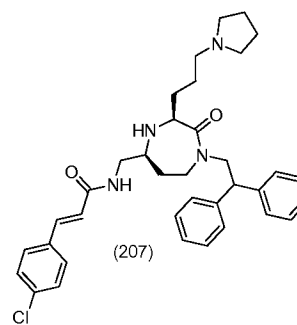
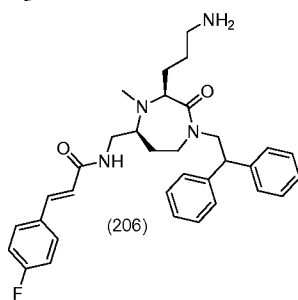
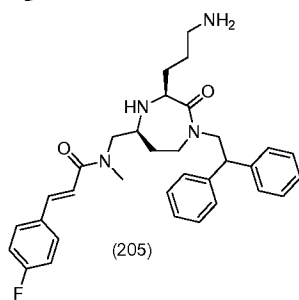
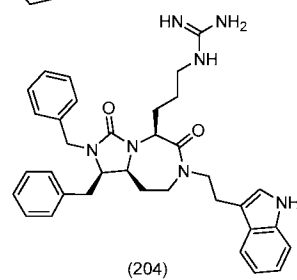
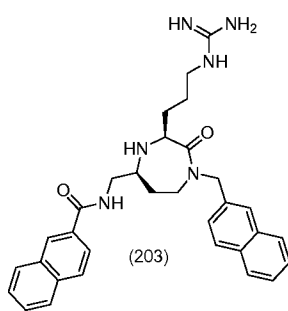
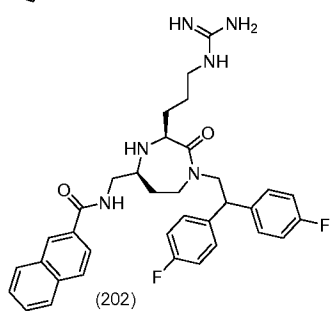
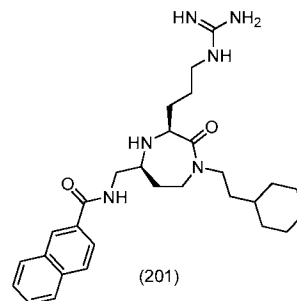
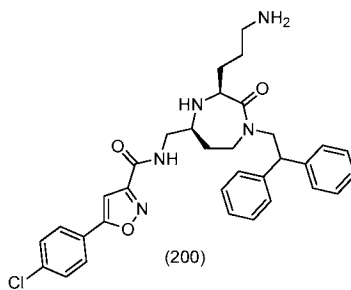
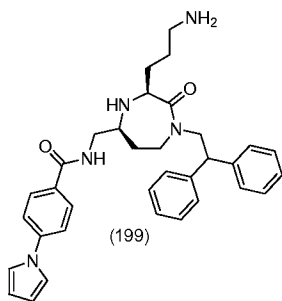
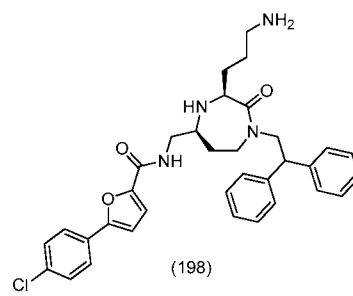
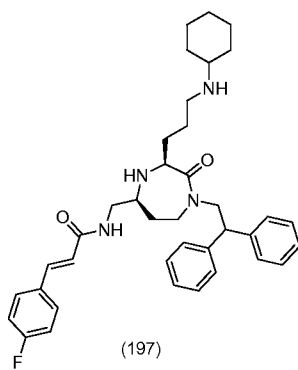
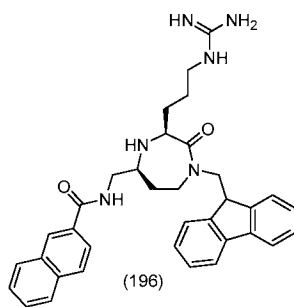


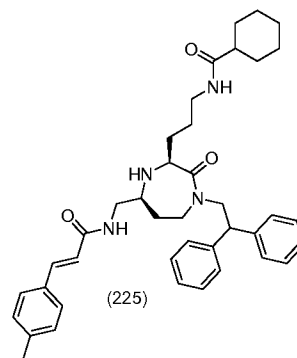
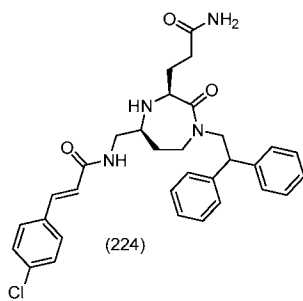
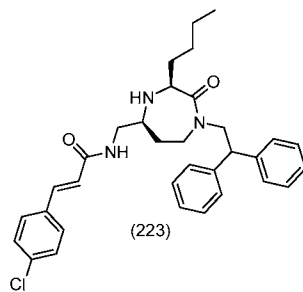
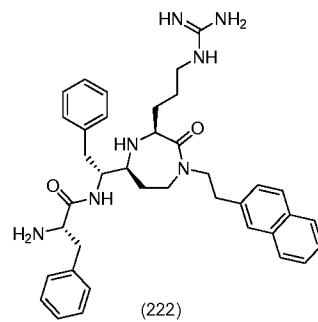
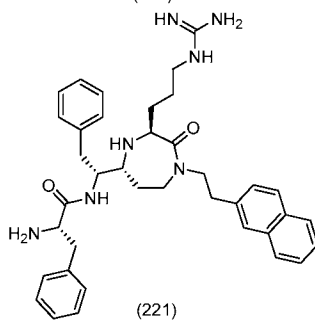
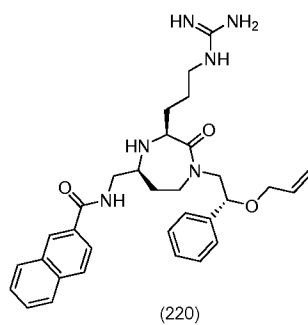
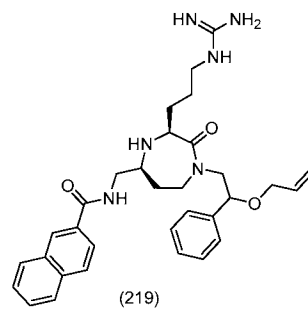
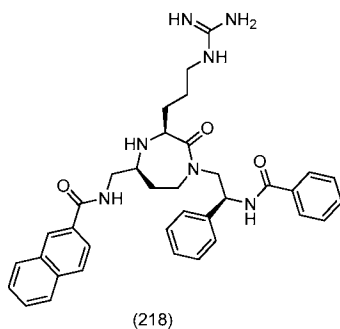
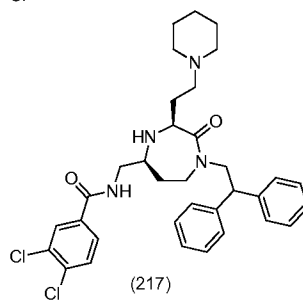
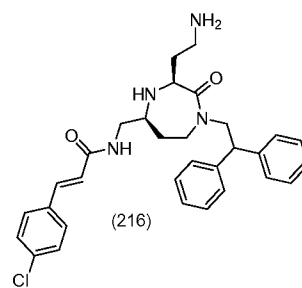
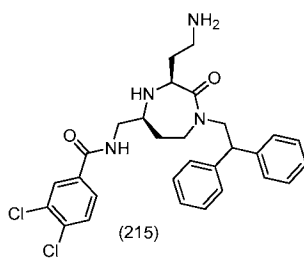
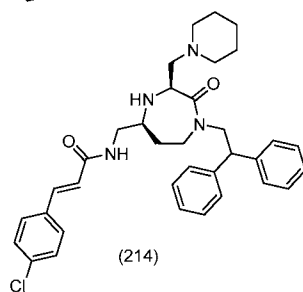
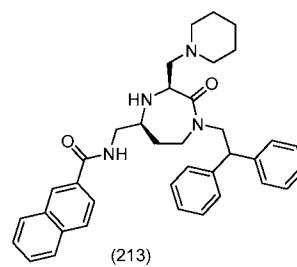
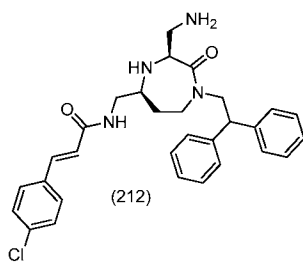
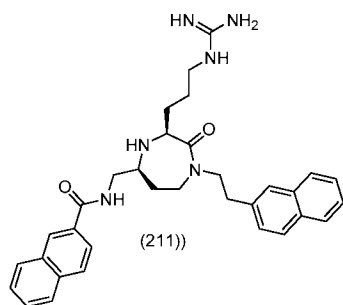


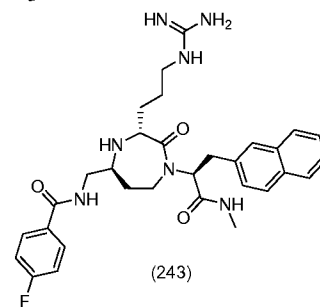
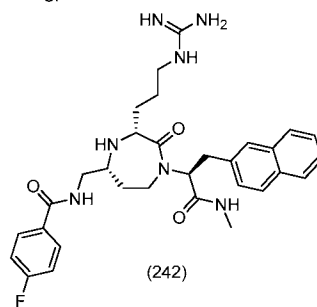
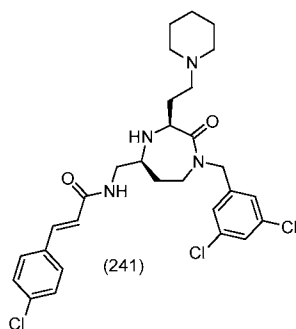
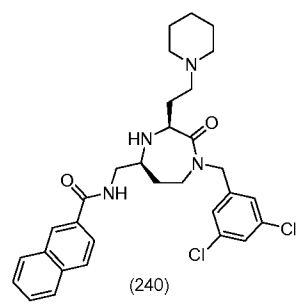
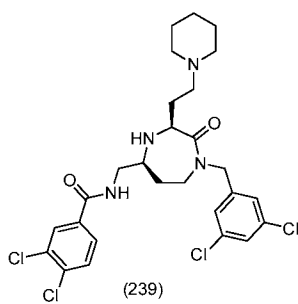
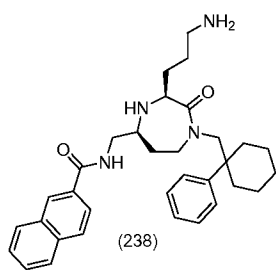
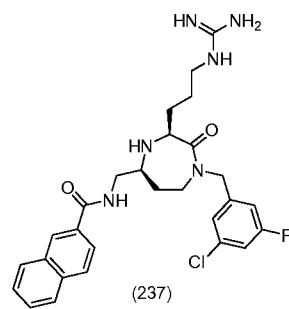
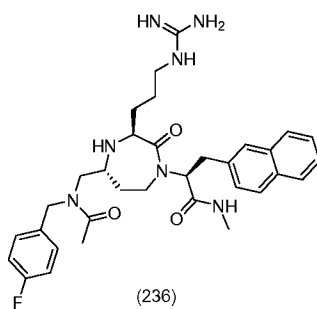
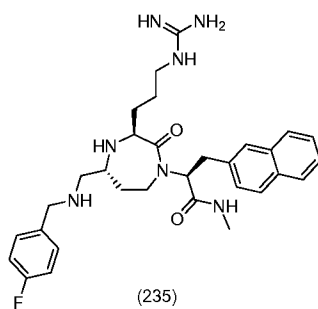
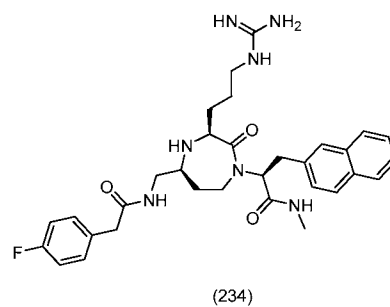
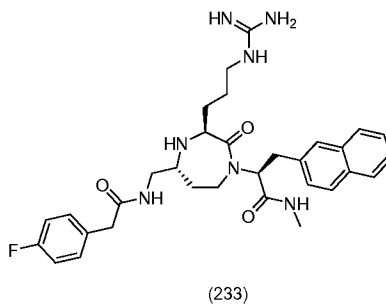
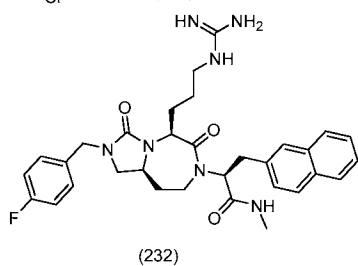
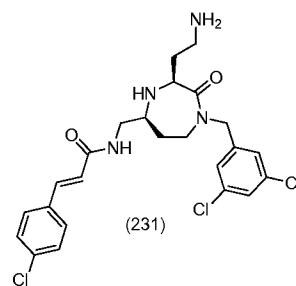
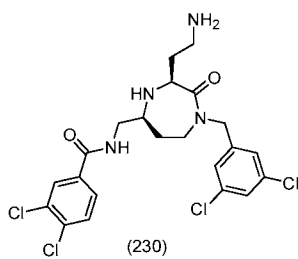
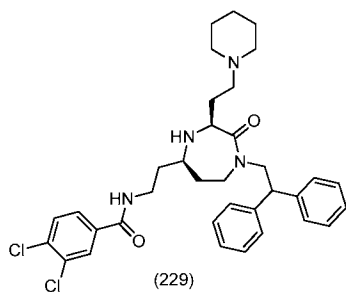
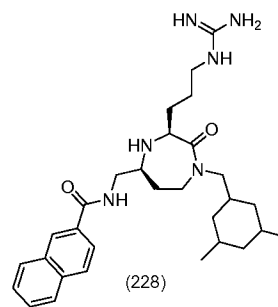
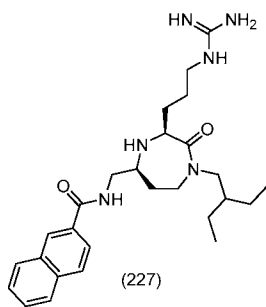
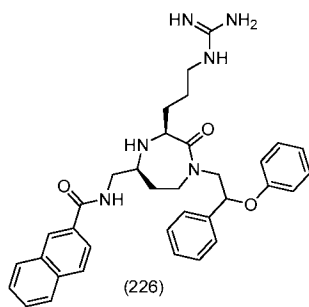


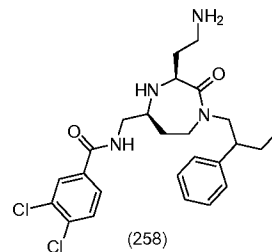
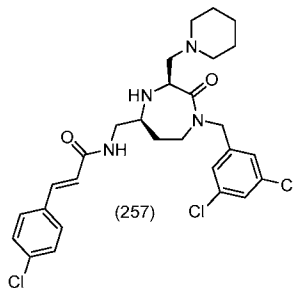
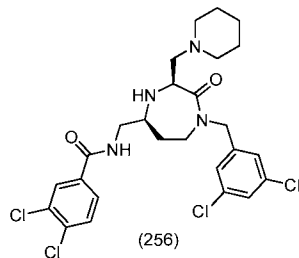
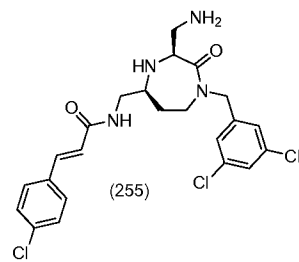
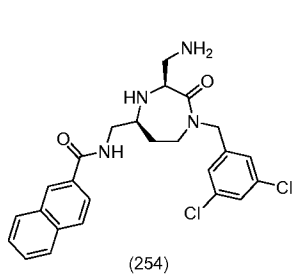
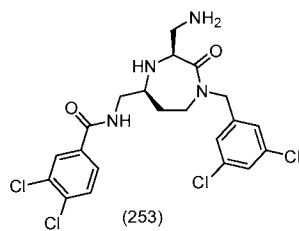
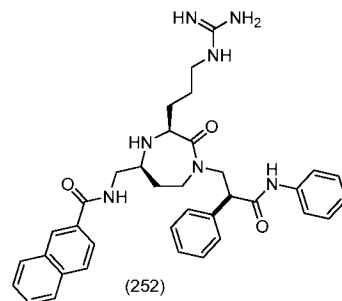
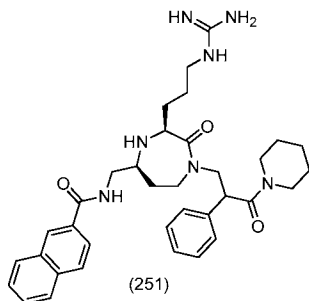
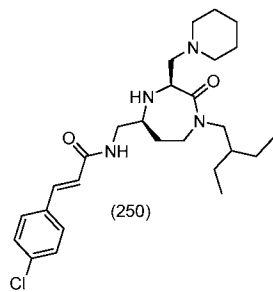
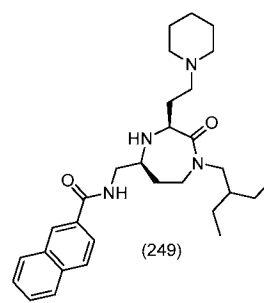
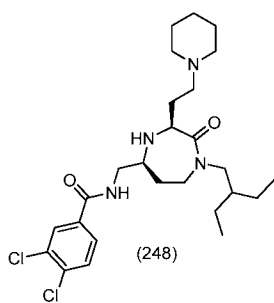
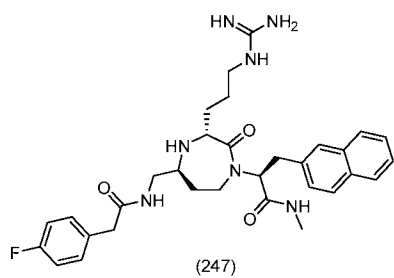
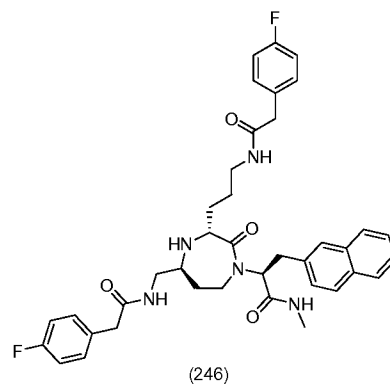
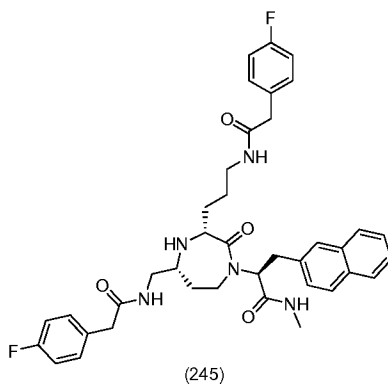
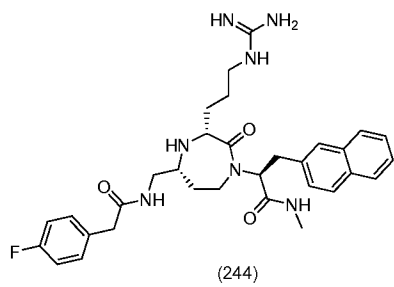


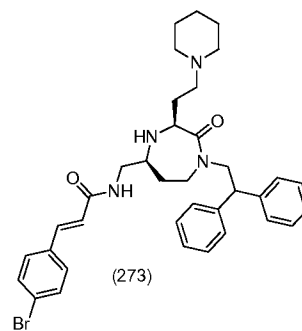
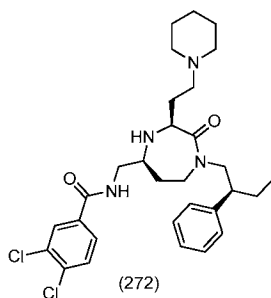
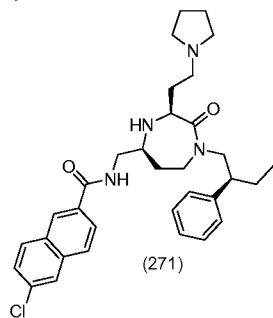
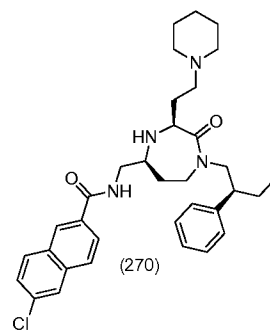
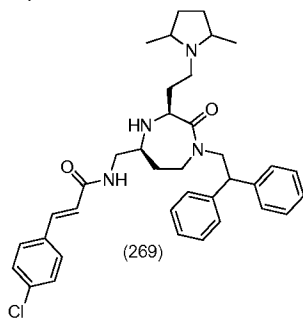
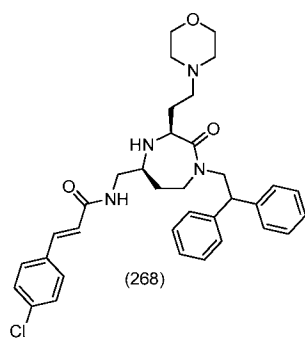
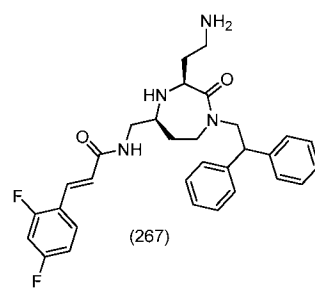
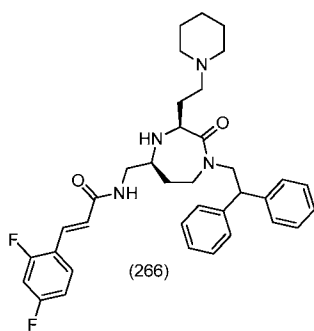
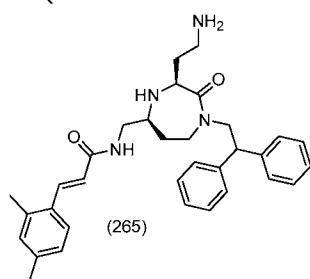
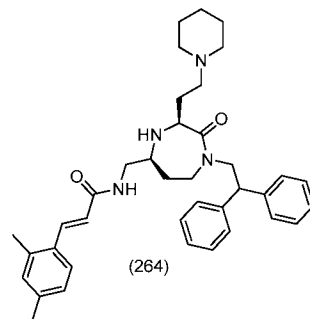
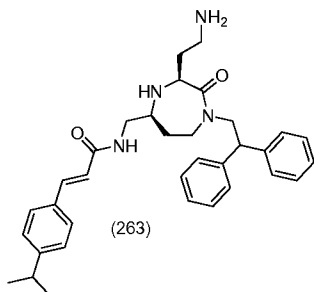
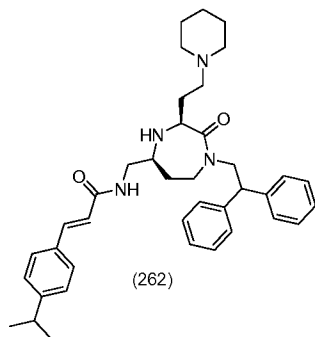
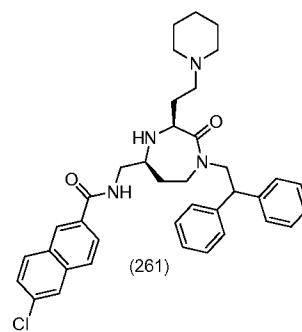
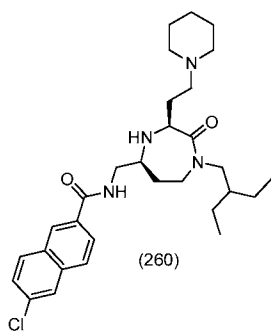
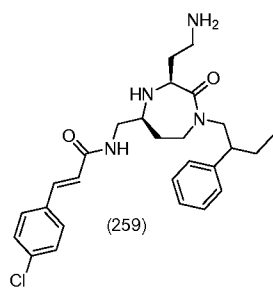


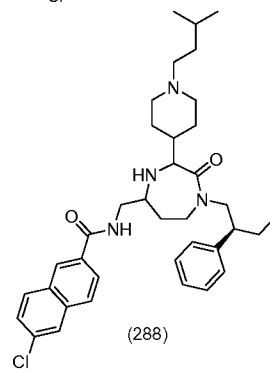
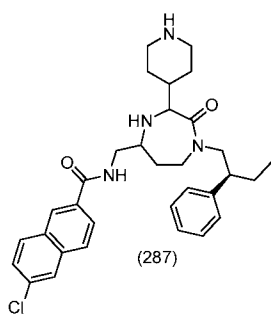
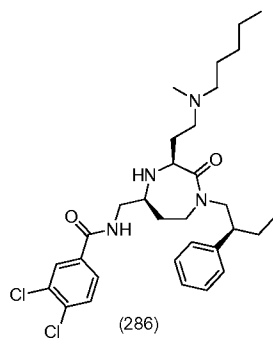
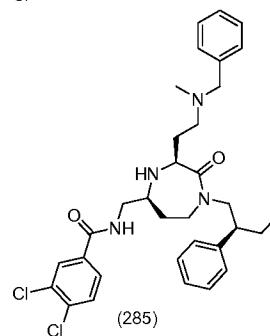
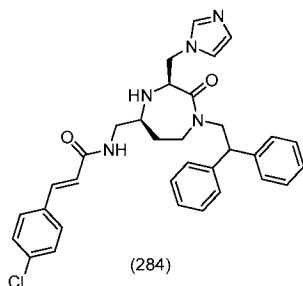
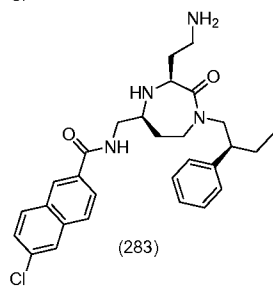
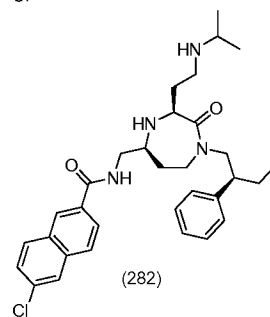
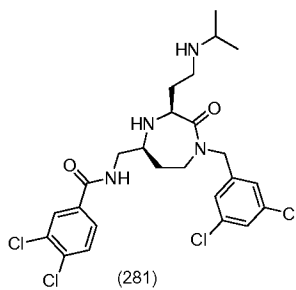
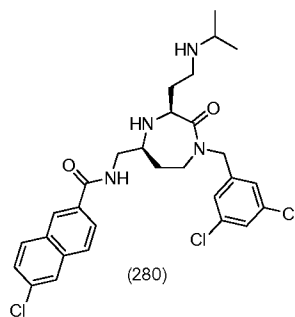
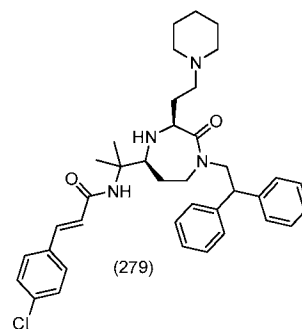
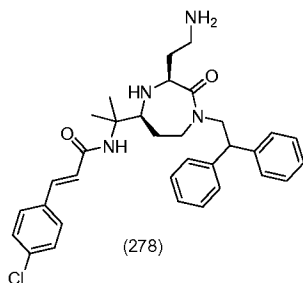
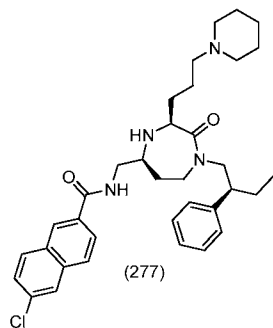
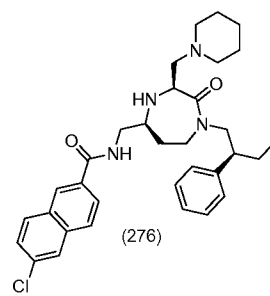
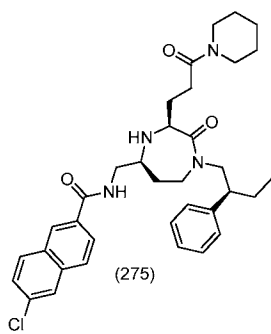
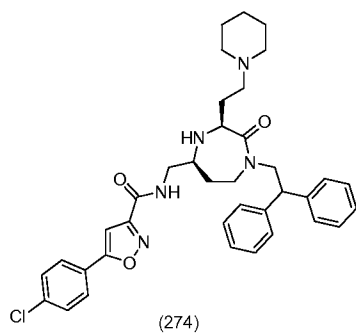




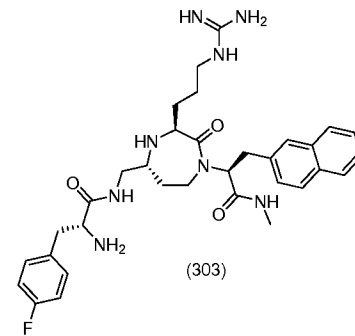
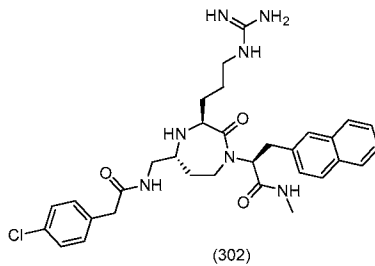
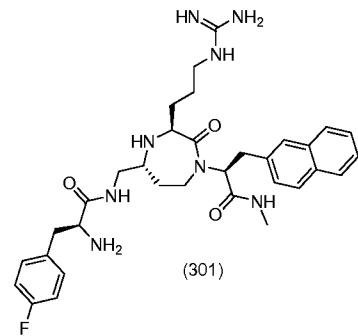
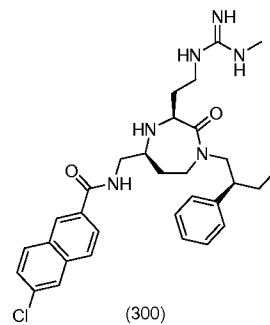
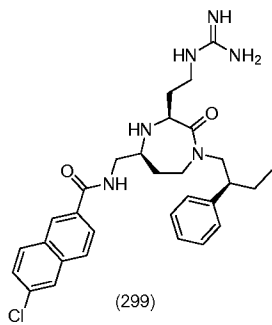
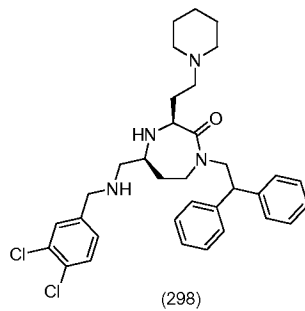
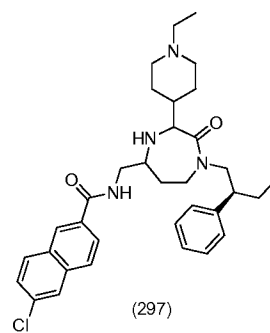
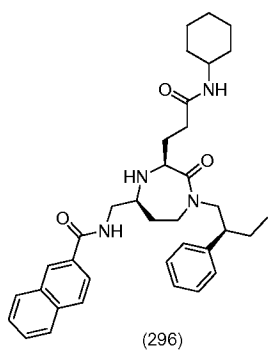
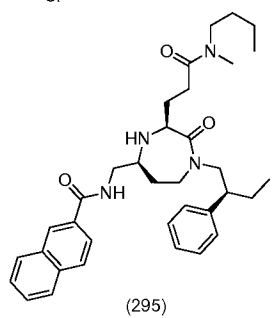
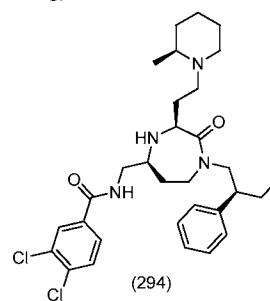
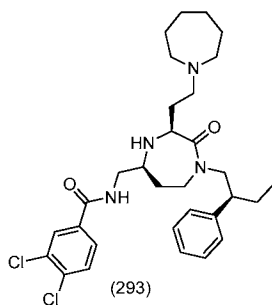
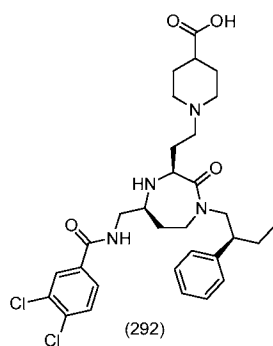
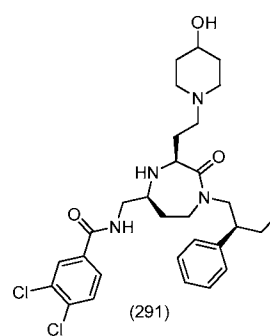
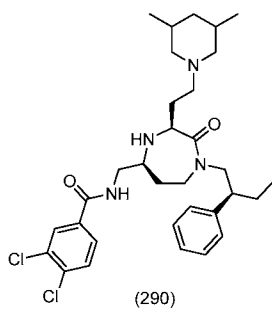
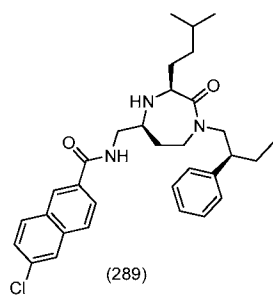


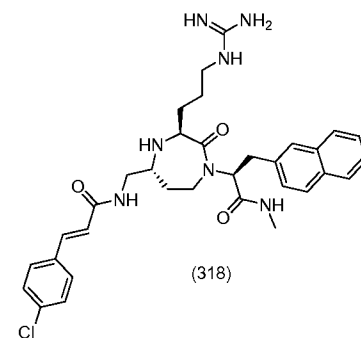
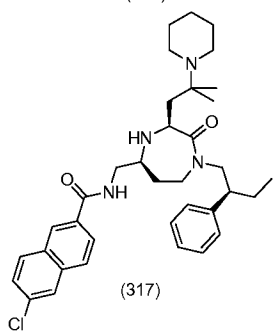
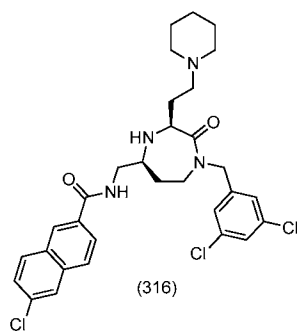
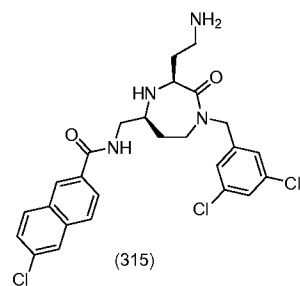
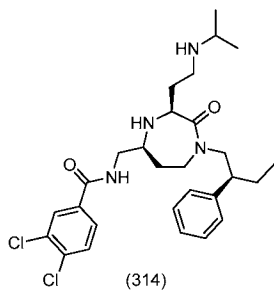
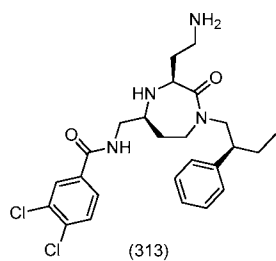
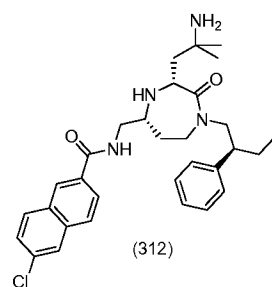
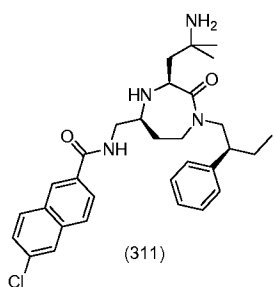
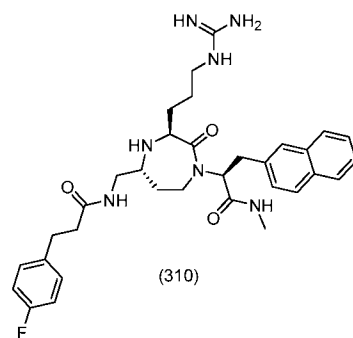
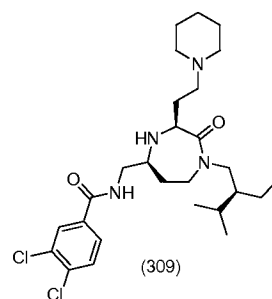
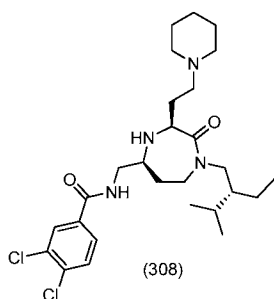
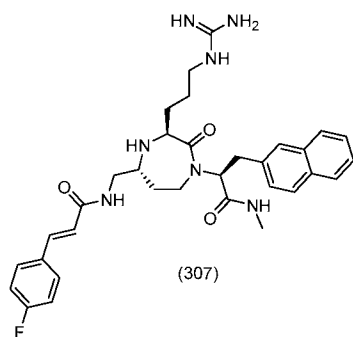
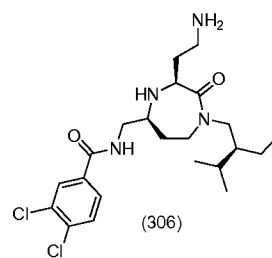
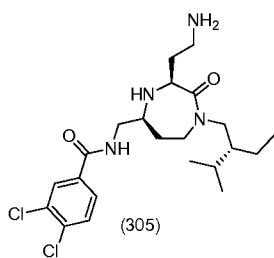
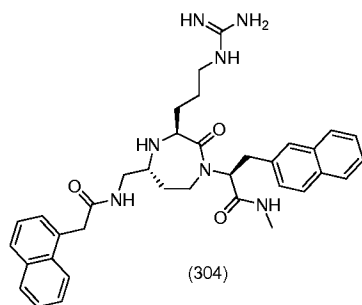


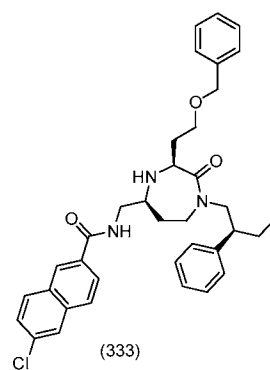
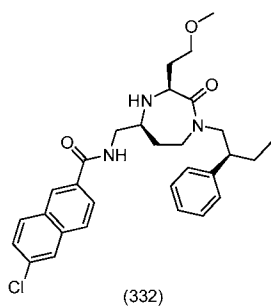
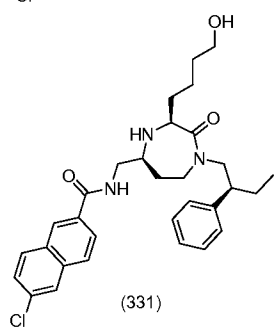
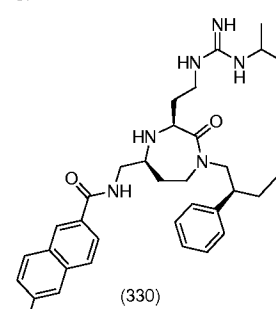
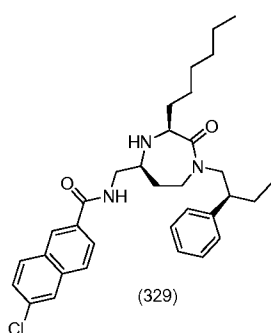
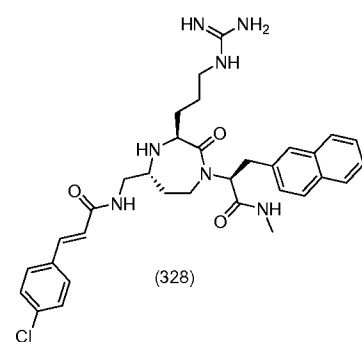
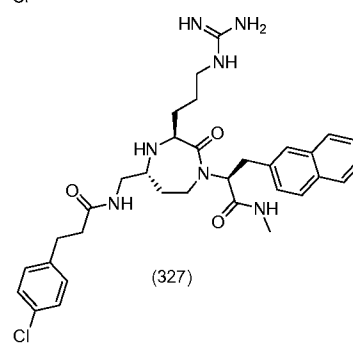
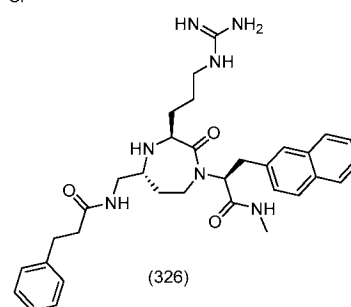
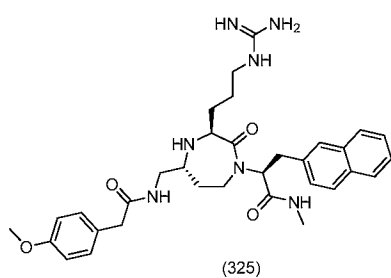
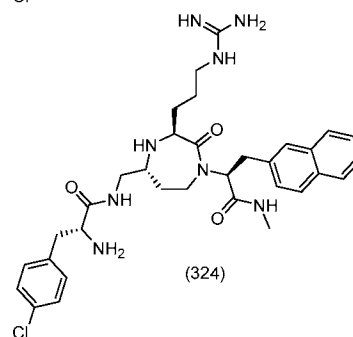
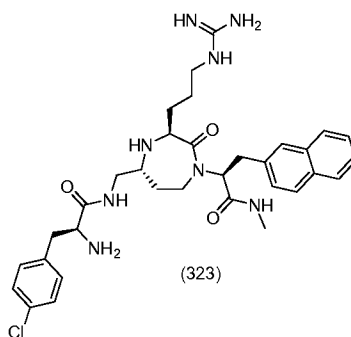
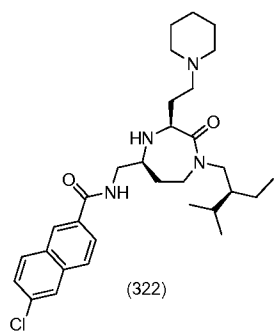
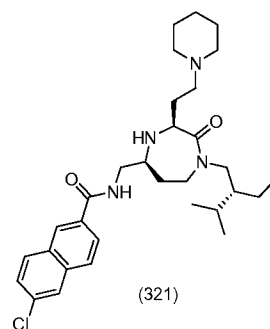
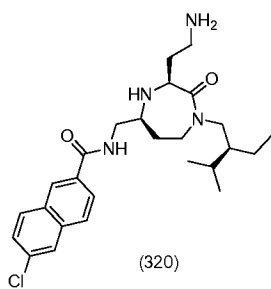
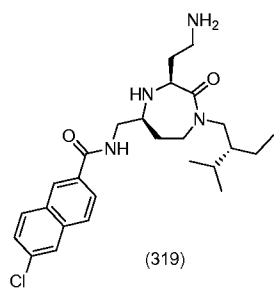


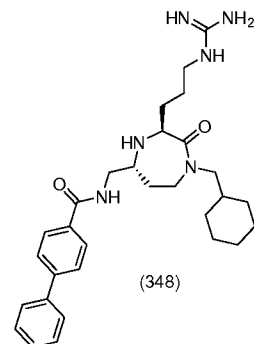
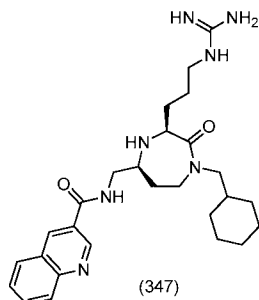
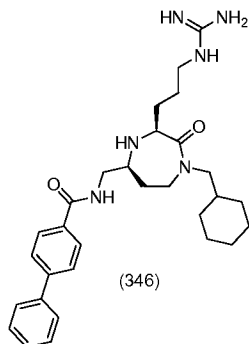
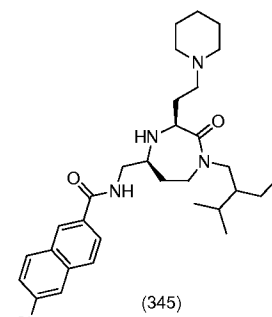
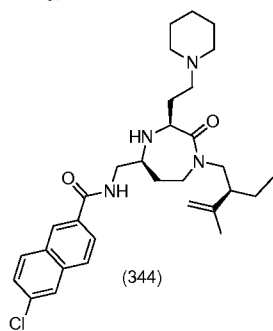
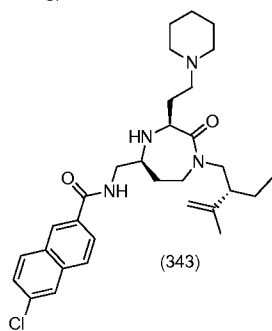
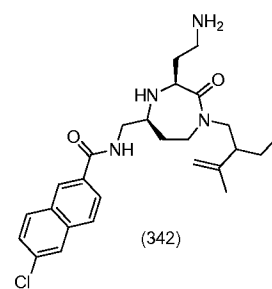
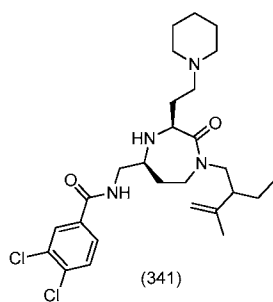
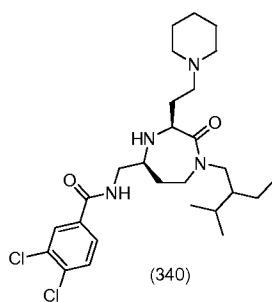
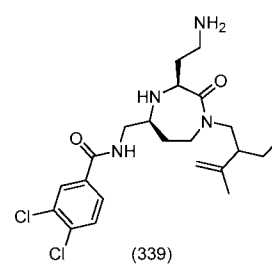
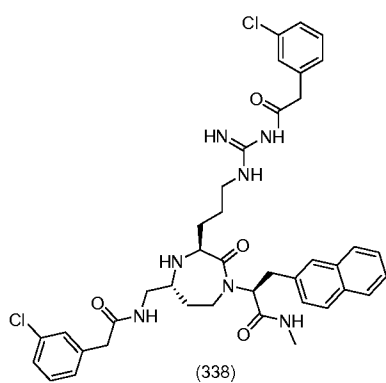
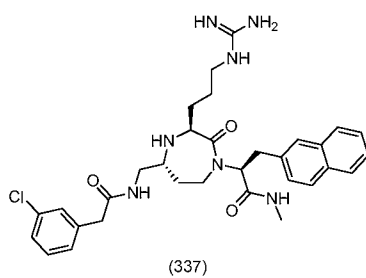
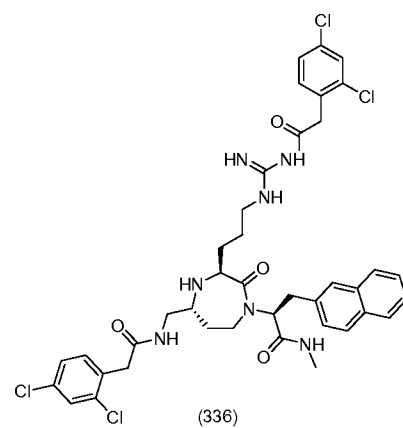
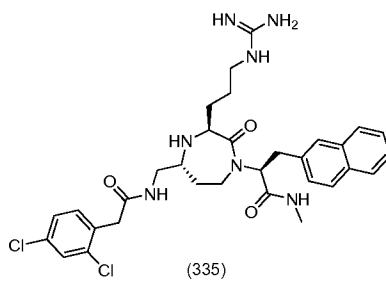
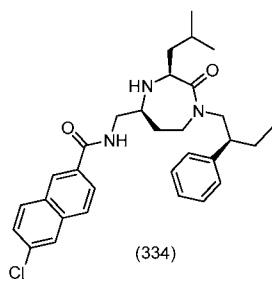


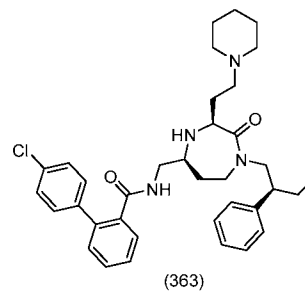
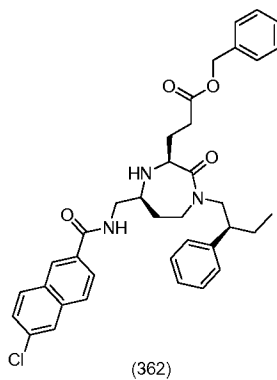
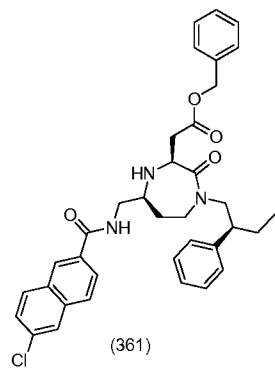
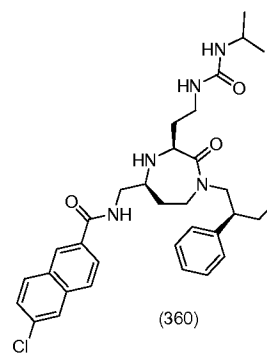
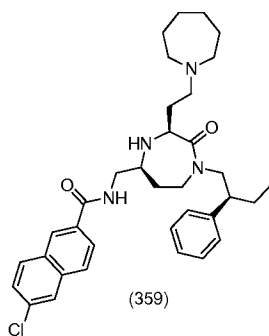
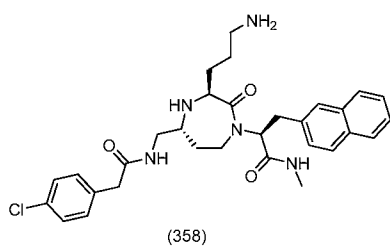
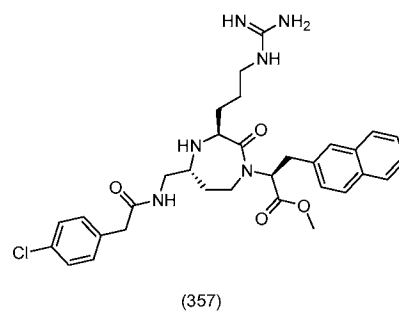
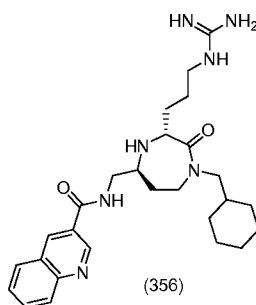
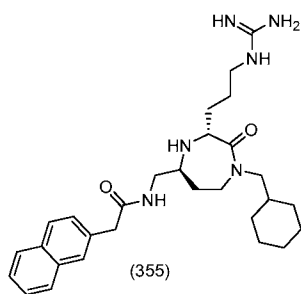
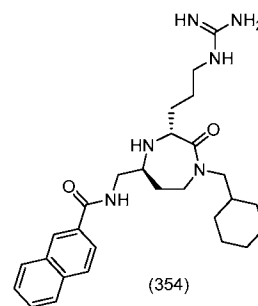
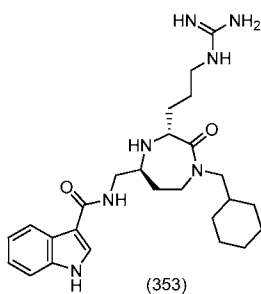
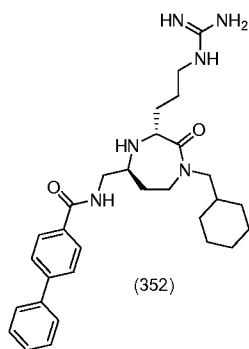
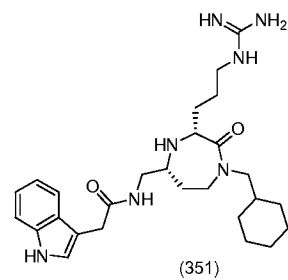
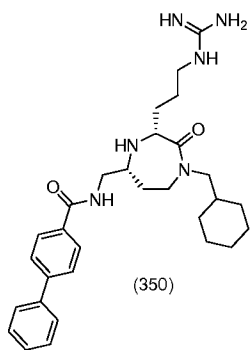
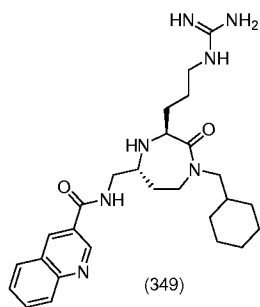
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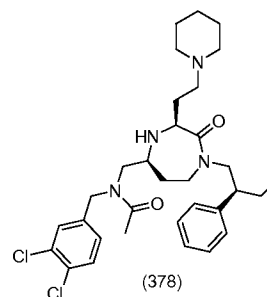
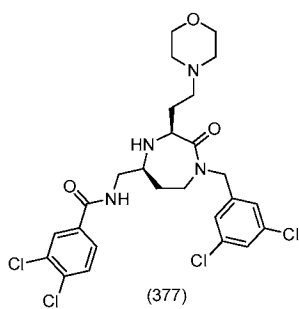
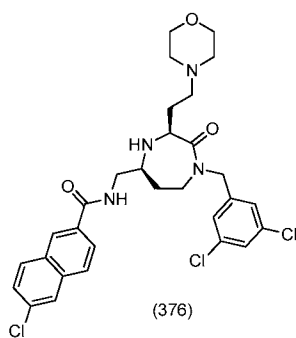
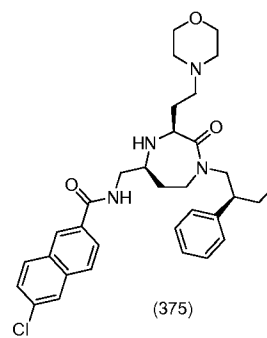
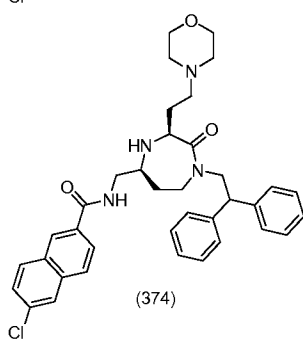
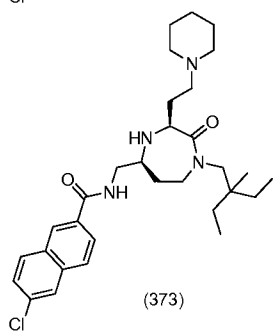
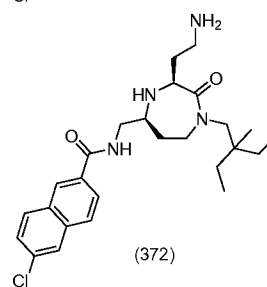
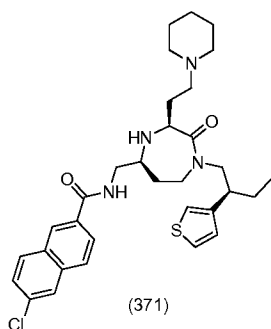
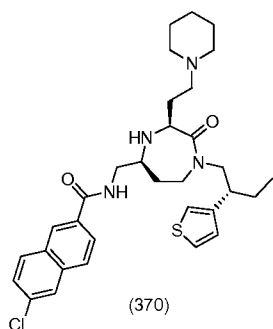
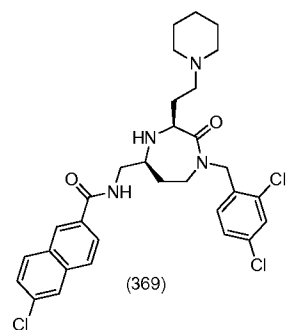
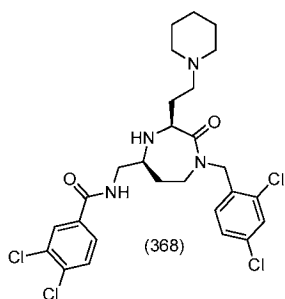
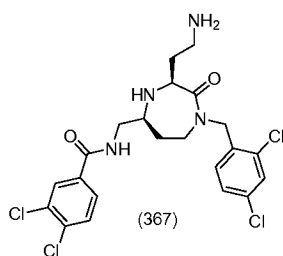
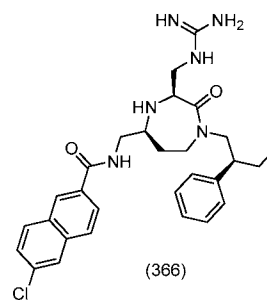
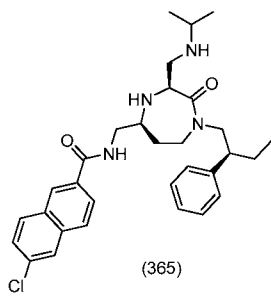
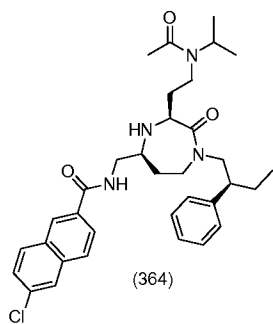


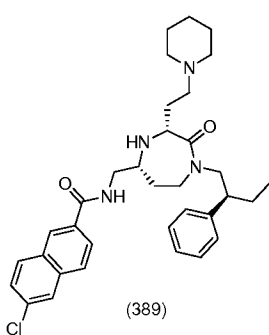
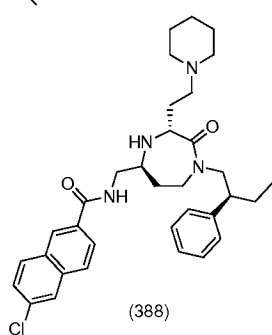
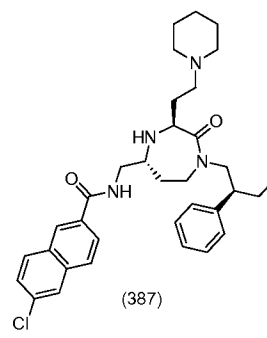
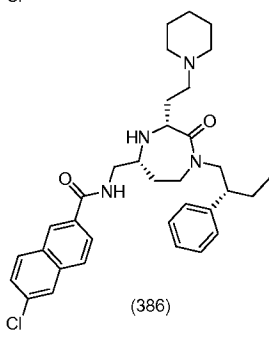
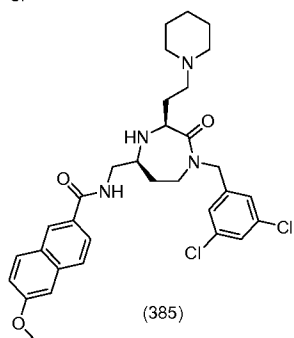
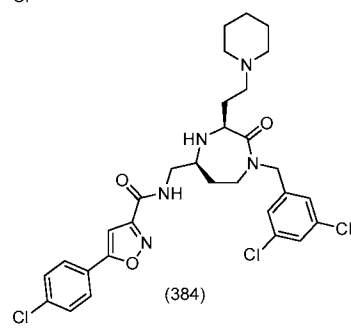
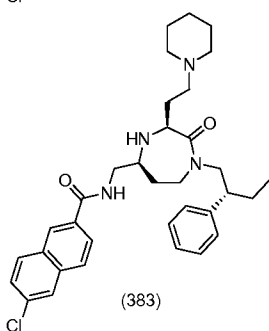
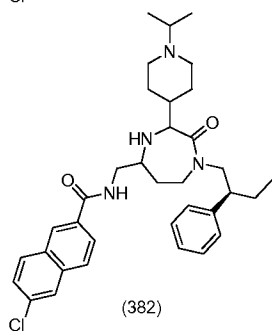
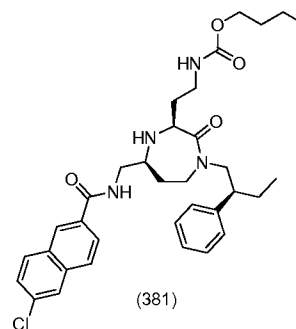
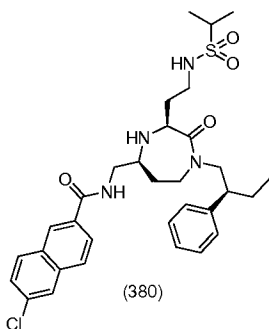
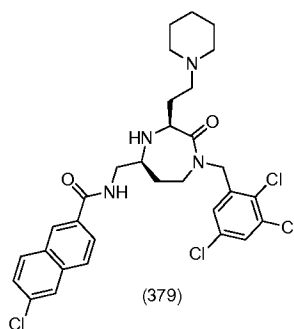












or a pharmaceutically acceptable salt or prodrug thereof.

In order to assist the reader the names of compounds suitable for use in the invention as discussed above are as follows:

(100) N-(((3S,5S)-1-(3,5-dichlorobenzyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide

(101) N-(((3S,5S)-3-(2-aminoethyl)-2-oxo-1-(2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide

- (102) N-(((3S,5S)-3-(2-aminoethyl)-1-(3,5-dichlorobenzyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (103) N-(((3S,5S)-3-(3-aminopropyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-6-bromo-N-methyl-2-naphthamide
- 5 (104) N-(((3S,5S)-3-(3-aminopropyl)-1-(2,2-diphenylethyl)-4-methyl-2-oxo-1,4-diazepan-5-yl)methyl)-6-bromo-2-naphthamide
- (105) N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(3-(3-methylguanidino)propyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (106) (E)-N-(((3S,5S)-3-butyl-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3-(4-chlorophenyl)acrylamide
- 10 (107) N-((S)-1-((3S,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)-2-(naphthalen-2-yl)ethyl)acetamide
- (108) N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)biphenyl-4-carboxamide
- 15 (109) (S)-methyl 2-((3S,5R)-3-(3-guanidinopropyl)-5-((2-(naphthalen-1-yl)acetamido)methyl)-2-oxo-1,4-diazepan-1-yl)-3-(1H-indol-3-yl)propanoate
- (110) N-(((3R,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)biphenyl-4-carboxamide
- (111) N-(((3R,5R)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)biphenyl-4-carboxamide
- 20 (112) N-(((3S,5R)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)biphenyl-4-carboxamide
- (113) N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)quinoline-3-carboxamide
- 25 (114) N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)quinoxaline-2-carboxamide
- (115) N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)isoquinoline-3-carboxamide
- (116) N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)quinoline-2-carboxamide
- 30 (117) (5R,9aS)-5-(4-aminobutyl)-2-(biphenyl-4-ylmethyl)-7-(2-(naphthalen-1-yl)ethyl)tetrahydro-1H-imidazo[1,5-d][1,4]diazepine-3,6(2H,5H)-dione
- (118) N-(((3S,5S)-3-(4-aminobutyl)-1-benzhydryl-2-oxo-1,4-diazepan-5-yl)methyl)biphenyl-4-carboxamide
- 35 (119) N-(((3S,5S)-3-(4-aminobutyl)-1-benzhydryl-2-oxo-1,4-diazepan-5-yl)methyl)-2-(biphenyl-4-yl)acetamide

- (120) (5S,9aS)-5-(4-aminobutyl)-7-benzhydryl-2-(biphenyl-4-ylmethyl)tetrahydro-1H-imidazo[1,5-d][1,4]diazepine-3,6(2H,5H)-dione
- (121) N-(((3S,5S)-3-(4-aminobutyl)-1-benzhydryl-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 5 (122) N-(((3S,5S)-3-(4-aminobutyl)-1-benzhydryl-2-oxo-1,4-diazepan-5-yl)methyl)-2-(naphthalen-2-yl)acetamide
- (123) (5S,9aS)-5-(4-aminobutyl)-7-benzhydryl-2-(naphthalen-2-ylmethyl)tetrahydro-1H-imidazo[1,5-d][1,4]diazepine-3,6(2H,5H)-dione
- (124) N-(((3S,5S)-1-benzhydryl-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-
- 10 (biphenyl-4-yl)acetamide
- (125) 1-(3-(((5S,9aS)-7-benzhydryl-2-(biphenyl-4-ylmethyl)-3,6-dioxooctahydro-1H-imidazo[1,5-d][1,4]diazepin-5-yl)propyl)guanidine
- (126) N-(((3S,5S)-1-benzhydryl-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 15 (127) N-(((3S,5S)-1-benzhydryl-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-(naphthalen-2-yl)acetamide
- (128) N-(((3S,5R)-1-benzhydryl-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)biphenyl-4-carboxamide
- (129) N-(((3S,5R)-1-benzhydryl-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-
- 20 (biphenyl-4-yl)acetamide
- (130) 1-(3-(((5S,9aR)-7-benzhydryl-2-(biphenyl-4-ylmethyl)-3,6-dioxooctahydro-1H-imidazo[1,5-d][1,4]diazepin-5-yl)propyl)guanidine
- (131) N-(((3S,5R)-1-benzhydryl-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-(naphthalen-2-yl)acetamide
- 25 (132) 1-(3-(((5S,9aR)-7-benzhydryl-2-(naphthalen-2-ylmethyl)-3,6-dioxooctahydro-1H-imidazo[1,5-d][1,4]diazepin-5-yl)propyl)guanidine
- (133) N-(((3R,5R)-1-benzhydryl-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)biphenyl-4-carboxamide
- (134) N-(((3R,5R)-1-benzhydryl-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-
- 30 (biphenyl-4-yl)acetamide
- (135) N-(((3R,5R)-1-benzhydryl-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-(naphthalen-2-yl)acetamide
- (136) 1-(3-(((5R,9aR)-7-benzhydryl-2-(naphthalen-2-ylmethyl)-3,6-dioxooctahydro-1H-imidazo[1,5-d][1,4]diazepin-5-yl)propyl)guanidine
- 35 (137) N-(((3S,5R)-3-(4-aminobutyl)-1-(naphthalen-1-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)biphenyl-4-carboxamide

- (138) N-(((3S,5R)-3-(4-aminobutyl)-1-(naphthalen-1-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-(biphenyl-4-yl)acetamide
- (139) (5S,9aR)-5-(4-aminobutyl)-2-(biphenyl-4-ylmethyl)-7-(naphthalen-1-ylmethyl)tetrahydro-1H-imidazo[1,5-d][1,4]diazepine-3,6(2H,5H)-dione
- 5 (140) N-(((3S,5R)-3-(4-aminobutyl)-1-(naphthalen-1-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (141) (5S,9aS)-5-(4-aminobutyl)-2-(biphenyl-4-ylmethyl)-7-(naphthalen-1-ylmethyl)tetrahydro-1H-imidazo[1,5-d][1,4]diazepine-3,6(2H,5H)-dione
- (142) N-(((3S,5S)-3-(4-aminobutyl)-1-(naphthalen-1-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 10 (143) N-(((3S,5S)-3-(4-aminobutyl)-1-(naphthalen-1-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-(naphthalen-2-yl)acetamide
- (144) N-(((3R,5R)-3-(4-aminobutyl)-1-(naphthalen-1-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)biphenyl-4-carboxamide
- 15 (1451) N-(((3R,5R)-3-(4-aminobutyl)-1-(naphthalen-1-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-(biphenyl-4-yl)acetamide
- (146) (5R,9aR)-5-(4-aminobutyl)-2-(biphenyl-4-ylmethyl)-7-(naphthalen-1-ylmethyl)tetrahydro-1H-imidazo[1,5-d][1,4]diazepine-3,6(2H,5H)-dione
- (147) N-(((3R,5S)-3-(4-aminobutyl)-1-(naphthalen-1-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)biphenyl-4-carboxamide
- 20 (148) N-(((3R,5S)-3-(4-aminobutyl)-1-(naphthalen-1-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-(biphenyl-4-yl)acetamide
- (149) (5R,9aS)-5-(4-aminobutyl)-2-(biphenyl-4-ylmethyl)-7-(naphthalen-1-ylmethyl)tetrahydro-1H-imidazo[1,5-d][1,4]diazepine-3,6(2H,5H)-dione
- 25 (150) N-(((3R,5S)-3-(4-aminobutyl)-1-(naphthalen-1-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (151) N-(((3R,5S)-3-(4-aminobutyl)-1-(naphthalen-1-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-(naphthalen-2-yl)acetamide
- (152) N-(((3R,5S)-3-(4-aminobutyl)-1-(naphthalen-1-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-1-naphthamide
- 30 (153) N-(((3R,5S)-3-(4-aminobutyl)-1-(naphthalen-1-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-(naphthalen-1-yl)acetamide
- (154) N-(((3S,5S)-3-(4-aminobutyl)-1-(naphthalen-2-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)biphenyl-4-carboxamide
- 35 (155) N-(((3S,5S)-3-(4-aminobutyl)-1-(naphthalen-2-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-(biphenyl-4-yl)acetamide

- (156) (5S,9aS)-5-(4-aminobutyl)-2-(biphenyl-4-ylmethyl)-7-(naphthalen-2-ylmethyl)tetrahydro-1H-imidazo[1,5-d][1,4]diazepine-3,6(2H,5H)-dione
- (157) N-(((3S,5S)-3-(4-aminobutyl)-1-(naphthalen-2-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 5 (158) N-(((3S,5S)-3-(4-aminobutyl)-1-(naphthalen-2-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-(naphthalen-2-yl)acetamide
- (159) N-(((3S,5R)-3-(4-aminobutyl)-1-(naphthalen-2-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)biphenyl-4-carboxamide
- (160) N-(((3S,5R)-3-(4-aminobutyl)-1-(naphthalen-2-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-(biphenyl-4-yl)acetamide
- 10 (161) (5S,9aR)-5-(4-aminobutyl)-2-(biphenyl-4-ylmethyl)-7-(naphthalen-2-ylmethyl)tetrahydro-1H-imidazo[1,5-d][1,4]diazepine-3,6(2H,5H)-dione
- (1620) N-(((3S,5R)-3-(4-aminobutyl)-1-(naphthalen-1-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 15 (163) N-(((3S,5R)-3-(4-aminobutyl)-1-(naphthalen-2-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-(naphthalen-2-yl)acetamide
- (164) N-(((3S,5R)-3-(4-aminobutyl)-1-(naphthalen-2-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-(naphthalen-1-yl)acetamide
- (165) N-(((3R,5R)-3-(4-aminobutyl)-1-(naphthalen-2-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)biphenyl-4-carboxamide
- 20 (166) N-(((3R,5R)-3-(4-aminobutyl)-1-(naphthalen-2-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-(biphenyl-4-yl)acetamide
- (167) (5R,9aR)-5-(4-aminobutyl)-2-(biphenyl-4-ylmethyl)-7-(naphthalen-2-ylmethyl)tetrahydro-1H-imidazo[1,5-d][1,4]diazepine-3,6(2H,5H)-dione
- 25 (168) N-(((3R,5R)-3-(4-aminobutyl)-1-(naphthalen-2-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (169) N-(((3R,5S)-3-(4-aminobutyl)-1-(naphthalen-2-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)biphenyl-4-carboxamide
- (170) N-(((3R,5S)-3-(4-aminobutyl)-1-(naphthalen-2-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-(biphenyl-4-yl)acetamide
- 30 (171) (5R,9aS)-5-(4-aminobutyl)-2-(biphenyl-4-ylmethyl)-7-(naphthalen-2-ylmethyl)tetrahydro-1H-imidazo[1,5-d][1,4]diazepine-3,6(2H,5H)-dione
- (172) N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)benzamide
- 35 (173) N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)cyclohexanecarboxamide

- (174) N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3-phenoxybenzamide
- (175) N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-4-phenoxybenzamide
- 5 (176) N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-1H-indole-2-carboxamide
- (177) N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3-phenylpropanamide
- (178) N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3,4-dimethylbenzamide
- 10 (179) 4-tert-butyl-N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)benzamide
- (180) N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2,4-dimethoxybenzamide
- 15 (181) 2-cyclohexyl-N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)acetamide
- (182) N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(2-(guanidinoxy)ethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (183) (E)-3-(4-chlorophenyl)-N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)acrylamide
- 20 (184) propyl (R)-1-((3R,5R)-1-(2-(1H-indol-3-yl)ethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)-2-phenylethylcarbamate
- (185) (R)-N-((S)-1-((3S,5S)-1-(2-(1H-indol-3-yl)ethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)-2-phenylethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide
- 25 (186) N-(((3S,5S)-1-(cyclohexylmethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (187) N-(((3S,5S)-3-(3-aminopropyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-6-bromo-2-naphthamide
- (188) (E)-N-(((3S,5S)-3-(3-aminopropyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3-(4-chlorophenyl)acrylamide
- 30 (189) N-(((3S,5S)-3-(3-(3,3-dimethylguanidino)propyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (190) (E)-N-(((3S,5S)-3-(3-aminopropyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3-p-tolylacrylamide
- 35 (191) (E)-N-(((3S,5S)-3-(3-aminopropyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3-(4-fluorophenyl)acrylamide

- (192) N-(((3S,5S)-3-(3-aminopropyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-6-fluoro-2-naphthamide
- (1934) N-(((3S,5S)-3-(3-aminopropyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3,4-dichlorobenzamide
- 5 (194) N-(((3S,5S)-3-(3-(cyclohexylamino)propyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (195) N-(((3S,5S)-3-(3-guanidinopropyl)-1-(naphthalen-2-yl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (196) N-(((3S,5S)-1-((9H-fluoren-9-yl)methyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 10 (197) (E)-N-(((3S,5S)-3-(3-(cyclohexylamino)propyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3-(4-fluorophenyl)acrylamide
- (198) N-(((3S,5S)-3-(3-aminopropyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-5-(4-chlorophenyl)furan-2-carboxamide
- 15 (199) N-(((3S,5S)-3-(3-aminopropyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-4-(1H-pyrrol-1-yl)benzamide
- (200) N-(((3S,5S)-3-(3-aminopropyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-5-(4-chlorophenyl)isoxazole-3-carboxamide
- (201) N-(((3S,5S)-1-(2-cyclohexylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 20 (202) N-(((3S,5S)-1-(2,2-bis(4-fluorophenyl)ethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (203) N-(((3S,5S)-3-(3-guanidinopropyl)-1-(naphthalen-2-yl)methyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 25 (204) 1-(3-(((1R,5S,9aS)-7-(2-(1H-indol-3-yl)ethyl)-1,2-dibenzyl-3,6-dioxooctahydro-1H-imidazo[1,5-d][1,4]diazepin-5-yl)propyl)guanidine
- (205) (E)-N-(((3S,5S)-3-(3-aminopropyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3-(4-fluorophenyl)-N-methylacrylamide
- (206) (E)-N-(((3S,5S)-3-(3-aminopropyl)-1-(2,2-diphenylethyl)-4-methyl-2-oxo-1,4-diazepan-5-yl)methyl)-3-(4-fluorophenyl)acrylamide
- 30 (207) (E)-3-(4-chlorophenyl)-N-(((3S,5S)-1-(2,2-diphenylethyl)-2-oxo-3-(3-(pyrrolidin-1-yl)propyl)-1,4-diazepan-5-yl)methyl)acrylamide
- (208) (E)-3-(4-chlorophenyl)-N-(((3S,5S)-1-(2,2-diphenylethyl)-2-oxo-3-(3-(piperidin-1-yl)propyl)-1,4-diazepan-5-yl)methyl)acrylamide
- 35 (209) N-(((3S,5S)-3-(2-aminoethyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide

- (210) N-(((3S,5S)-3-(3-guanidinopropyl)-1-(naphthalen-1-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (211) N-(((3S,5S)-3-(3-guanidinopropyl)-1-(2-(naphthalen-2-yl)ethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 5 (212) (E)-N-(((3S,5S)-3-(aminomethyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3-(4-chlorophenyl)acrylamide
- (213) N-(((3S,5S)-1-(2,2-diphenylethyl)-2-oxo-3-(piperidin-1-ylmethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (214) (E)-3-(4-chlorophenyl)-N-(((3S,5S)-1-(2,2-diphenylethyl)-2-oxo-3-(piperidin-1-ylmethyl)-1,4-diazepan-5-yl)methyl)acrylamide
- 10 (215) N-(((3S,5S)-3-(2-aminoethyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3,4-dichlorobenzamide
- (216) (E)-N-(((3S,5S)-3-(2-aminoethyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3-(4-chlorophenyl)acrylamide
- 15 (217) 3,4-dichloro-N-(((3S,5S)-1-(2,2-diphenylethyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)benzamide
- (218) N-(((3S,5S)-1-((S)-2-benzamido-2-phenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (219) N-(((3S,5S)-1-(2-(allyloxy)-2-phenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 20 (220) N-(((3S,5S)-1-((R)-2-(allyloxy)-2-phenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (221) (S)-2-amino-N-((R)-1-(((3S,5R)-3-(3-guanidinopropyl)-1-(2-(naphthalen-2-yl)ethyl)-2-oxo-1,4-diazepan-5-yl)-2-phenylethyl)-3-phenylpropanamide
- 25 (222) (S)-2-amino-N-((R)-1-(((3S,5S)-3-(3-guanidinopropyl)-1-(2-(naphthalen-2-yl)ethyl)-2-oxo-1,4-diazepan-5-yl)-2-phenylethyl)-3-phenylpropanamide
- (223) (E)-N-(((3S,5S)-3-butyl-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3-(4-chlorophenyl)acrylamide
- (224) (E)-N-(((3S,5S)-3-(3-amino-3-oxopropyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3-(4-chlorophenyl)acrylamide
- 30 (225) N-(3-((2S,7S)-4-(2,2-diphenylethyl)-3-oxo-7-(((E)-3-p-tolylacrylamido)methyl)-1,4-diazepan-2-yl)propyl)cyclohexanecarboxamide
- (226) N-(((3S,5S)-3-(3-guanidinopropyl)-2-oxo-1-(2-phenoxy-2-phenylethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 35 (227) N-(((3S,5S)-1-(2-ethylbutyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide

- (228) N-(((3S,5S)-1-((3,5-dimethylcyclohexyl)methyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (229) 3,4-dichloro-N-(2-(((3S,5R)-1-(2,2-diphenylethyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)ethyl)benzamide
- 5 (230) N-(((3S,5S)-3-(2-aminoethyl)-1-(3,5-dichlorobenzyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3,4-dichlorobenzamide
- (231) (E)-N-(((3S,5S)-3-(2-aminoethyl)-1-(3,5-dichlorobenzyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3-(4-chlorophenyl)acrylamide
- (232) (S)-2-(((5S,9aS)-2-(4-fluorobenzyl)-5-(3-guanidinopropyl)-3,6-dioxotetrahydro-1H-imidazo[1,5-d][1,4]diazepin-7(8H,9H,9aH)-yl)-N-methyl-3-(naphthalen-2-yl)propanamide
- 10 (233) (S)-2-(((3S,5R)-5-((2-(4-fluorophenyl)acetamido)methyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide
- (234) (S)-2-(((3S,5S)-5-((2-(4-fluorophenyl)acetamido)methyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide
- 15 (235) (S)-2-(((3S,5R)-5-((4-fluorobenzylamino)methyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide
- (236) (S)-2-(((3S,5R)-5-((N-(4-fluorobenzyl)acetamido)methyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide
- (237) N-(((3S,5S)-1-(3-chloro-5-fluorobenzyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 20 (238) N-(((3S,5S)-3-(3-aminopropyl)-2-oxo-1-((1-phenylcyclohexyl)methyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (239) 3,4-dichloro-N-(((3S,5S)-1-(3,5-dichlorobenzyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)benzamide
- 25 (240) N-(((3S,5S)-1-(3,5-dichlorobenzyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (241) (E)-3-(4-chlorophenyl)-N-(((3S,5S)-1-(3,5-dichlorobenzyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)acrylamide
- (242) 4-fluoro-N-(((3R,5R)-3-(3-guanidinopropyl)-1-((S)-1-(methylamino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)-2-oxo-1,4-diazepan-5-yl)methyl)benzamide
- 30 (243) 4-fluoro-N-(((3R,5S)-3-(3-guanidinopropyl)-1-((S)-1-(methylamino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)-2-oxo-1,4-diazepan-5-yl)methyl)benzamide
- (244) (S)-2-(((3R,5R)-5-((2-(4-fluorophenyl)acetamido)methyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide
- 35 (245) (S)-2-(((3R,5R)-5-((2-(4-fluorophenyl)acetamido)propyl)-2-oxo-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide

- (246) (S)-2-((3R,5S)-5-((2-(4-fluorophenyl)acetamido)methyl)-3-(3-(2-(4-fluorophenyl)acetamido)propyl)-2-oxo-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide
- (247) (S)-2-((3R,5S)-5-((2-(4-fluorophenyl)acetamido)methyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide
- 5 (248) 3,4-dichloro-N-(((3S,5S)-1-(2-ethylbutyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)benzamide
- (249) N-(((3S,5S)-1-(2-ethylbutyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 10 (250) (E)-3-(4-chlorophenyl)-N-(((3S,5S)-1-(2-ethylbutyl)-2-oxo-3-(piperidin-1-yl)methyl)-1,4-diazepan-5-yl)methyl)acrylamide
- (251) N-(((3S,5S)-3-(3-guanidinopropyl)-2-oxo-1-(3-oxo-2-phenyl-3-(piperidin-1-yl)propyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (252) N-(((3S,5S)-3-(3-guanidinopropyl)-2-oxo-1-(3-oxo-2-phenyl-3-(phenylamino)propyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 15 (253) N-(((3S,5S)-3-(aminomethyl)-1-(3,5-dichlorobenzyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3,4-dichlorobenzamide
- (254) N-(((3S,5S)-3-(aminomethyl)-1-(3,5-dichlorobenzyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 20 (255) (E)-N-(((3S,5S)-3-(aminomethyl)-1-(3,5-dichlorobenzyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3-(4-chlorophenyl)acrylamide
- (256) 3,4-dichloro-N-(((3S,5S)-1-(3,5-dichlorobenzyl)-2-oxo-3-(piperidin-1-yl)methyl)-1,4-diazepan-5-yl)methyl)benzamide
- (257) (E)-3-(4-chlorophenyl)-N-(((3S,5S)-1-(3,5-dichlorobenzyl)-2-oxo-3-(piperidin-1-yl)methyl)-1,4-diazepan-5-yl)methyl)acrylamide
- 25 (258) N-(((3S,5S)-3-(2-aminoethyl)-2-oxo-1-(2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-3,4-dichlorobenzamide
- (259) (E)-N-(((3S,5S)-3-(2-aminoethyl)-2-oxo-1-(2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-3-(4-chlorophenyl)acrylamide
- 30 (260) 6-chloro-N-(((3S,5S)-1-(2-ethylbutyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (261) 6-chloro-N-(((3S,5S)-1-(2,2-diphenylethyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (262) (E)-N-(((3S,5S)-1-(2,2-diphenylethyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-3-(4-isopropylphenyl)acrylamide
- 35 (263) (E)-N-(((3S,5S)-3-(2-aminoethyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3-(4-isopropylphenyl)acrylamide

- (264) (E)-3-(2,4-dimethylphenyl)-N-(((3S,5S)-1-(2,2-diphenylethyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)acrylamide
- (265) (E)-N-(((3S,5S)-3-(2-aminoethyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3-(2,4-dimethylphenyl)acrylamide
- 5 (266) (E)-3-(2,4-difluorophenyl)-N-(((3S,5S)-1-(2,2-diphenylethyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)acrylamide
- (267) (E)-N-(((3S,5S)-3-(2-aminoethyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3-(2,4-difluorophenyl)acrylamide
- (268) (E)-3-(4-chlorophenyl)-N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(2-morpholinoethyl)-2-oxo-1,4-diazepan-5-yl)methyl)acrylamide
- 10 (269) (E)-3-(4-chlorophenyl)-N-(((3S,5S)-3-(2-(2,5-dimethylpyrrolidin-1-yl)ethyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)acrylamide
- (270) 6-chloro-N-(((3S,5S)-2-oxo-1-((S)-2-phenylbutyl)-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 15 (271) 6-chloro-N-(((3S,5S)-2-oxo-1-((S)-2-phenylbutyl)-3-(2-(pyrrolidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (272) 3,4-dichloro-N-(((3S,5S)-2-oxo-1-((S)-2-phenylbutyl)-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)benzamide
- (273) (E)-3-(4-bromophenyl)-N-(((3S,5S)-1-(2,2-diphenylethyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)acrylamide
- 20 (274) 5-(4-chlorophenyl)-N-(((3S,5S)-1-(2,2-diphenylethyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)isoxazole-3-carboxamide
- (275) 6-chloro-N-(((3S,5S)-2-oxo-3-(3-oxo-3-(piperidin-1-yl)propyl)-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 25 (2768) 6-chloro-N-(((3S,5S)-2-oxo-1-((S)-2-phenylbutyl)-3-(piperidin-1-ylmethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (277) 6-chloro-N-(((3S,5S)-2-oxo-1-((S)-2-phenylbutyl)-3-(3-(piperidin-1-yl)propyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (278) (E)-N-(2-((3S,5S)-3-(2-aminoethyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)propan-2-yl)-3-(4-chlorophenyl)acrylamide
- 30 (279) (E)-3-(4-chlorophenyl)-N-(2-((3S,5S)-1-(2,2-diphenylethyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)propan-2-yl)acrylamide
- (280) 6-chloro-N-(((3S,5S)-1-(3,5-dichlorobenzyl)-3-(2-(isopropylamino)ethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 35 (281) 3,4-dichloro-N-(((3S,5S)-1-(3,5-dichlorobenzyl)-3-(2-(isopropylamino)ethyl)-2-oxo-1,4-diazepan-5-yl)methyl)benzamide

- (282) 6-chloro-N-(((3S,5S)-3-(2-(isopropylamino)ethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (283) N-(((3S,5S)-3-(2-aminoethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-6-chloro-2-naphthamide
- 5 (284) (E)-N-(((3S,5S)-3-((1H-imidazol-1-yl)methyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3-(4-chlorophenyl)acrylamide
- (285) N-(((3S,5S)-3-(2-(benzyl(methyl)amino)ethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-3,4-dichlorobenzamide
- (286) 3,4-dichloro-N-(((3S,5S)-3-(2-(methyl(pentyl)amino)ethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)benzamide
- 10 (287) (S)-6-chloro-N-((2-oxo-1-(2-phenylbutyl)-3-(piperidin-4-yl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (288) (S)-6-chloro-N-(3-(1-isopentylpiperidin-4-yl)-2-oxo-1-(2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 15 (289) 6-chloro-N-(((3S,5S)-3-isopentyl-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (290) 3,4-dichloro-N-(((3S,5S)-3-(2-(3,5-dimethylpiperidin-1-yl)ethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)benzamide
- (291) 3,4-dichloro-N-(((3S,5S)-3-(2-(4-hydroxypiperidin-1-yl)ethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)benzamide
- 20 (292) 1-(2-((2S,7S)-7-((3,4-dichlorobenzamido)methyl)-3-oxo-4-((S)-2-phenylbutyl)-1,4-diazepan-2-yl)ethyl)piperidine-4-carboxylic acid
- (293) N-(((3S,5S)-3-(2-(azepan-1-yl)ethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-3,4-dichlorobenzamide
- 25 (294) 3,4-dichloro-N-(((3S,5S)-3-(2-((S)-2-methylpiperidin-1-yl)ethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)benzamide
- (295) N-(((3S,5S)-3-(3-(butyl(methyl)amino)-3-oxopropyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (296) N-(((3S,5S)-3-(3-(cyclohexylamino)-3-oxopropyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 30 (297) 6-chloro-N-((3-(1-ethylpiperidin-4-yl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (298) (3S,5S)-5-((3,4-dichlorobenzylamino)methyl)-1-(2,2-diphenylethyl)-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-2-one
- 35 (299) 6-chloro-N-(((3S,5S)-3-(2-guanidinoethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide

- (300) 6-chloro-N-(((3S,5S)-3-(2-(3-methylguanidino)ethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (301) (S)-2-amino-3-(4-fluorophenyl)-N-(((3S,5R)-3-(3-guanidinopropyl)-1-((S)-1-(methylamino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)-2-oxo-1,4-diazepan-5-yl)methyl)propanamide
- 5 (302) (S)-2-(((3S,5R)-5-((2-(4-chlorophenyl)acetamido)methyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide
- (303) (R)-2-amino-3-(4-fluorophenyl)-N-(((3S,5R)-3-(3-guanidinopropyl)-1-((S)-1-(methylamino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)-2-oxo-1,4-diazepan-5-yl)methyl)propanamide
- 10 (304) (S)-2-(((3S,5R)-3-(3-guanidinopropyl)-5-((2-(naphthalen-1-yl)acetamido)methyl)-2-oxo-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide
- (305) N-(((3S,5S)-3-(2-aminoethyl)-1-((R)-2-ethyl-3-methylbutyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3,4-dichlorobenzamide
- 15 (306) N-(((3S,5S)-3-(2-aminoethyl)-1-((S)-2-ethyl-3-methylbutyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3,4-dichlorobenzamide
- 307 (E)-3-(4-fluorophenyl)-N-(((3S,5R)-3-(3-guanidinopropyl)-1-((S)-1-(methylamino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)-2-oxo-1,4-diazepan-5-yl)methyl)acrylamide
- (308) 3,4-dichloro-N-(((3S,5S)-1-((R)-2-ethyl-3-methylbutyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)benzamide
- 20 (309) 3,4-dichloro-N-(((3S,5S)-1-((S)-2-ethyl-3-methylbutyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)benzamide
- (310) (S)-2-(((3S,5R)-5-((3-(4-fluorophenyl)propanamido)methyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide
- 25 (311) N-(((3S,5S)-3-(2-amino-2-methylpropyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-6-chloro-2-naphthamide
- (312) N-(((3R,5R)-3-(2-amino-2-methylpropyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-6-chloro-2-naphthamide
- (313) N-(((3S,5S)-3-(2-aminoethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-3,4-dichlorobenzamide
- 30 (314) 3,4-dichloro-N-(((3S,5S)-3-(2-(isopropylamino)ethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)benzamide
- (315) N-(((3S,5S)-3-(2-aminoethyl)-1-(3,5-dichlorobenzyl)-2-oxo-1,4-diazepan-5-yl)methyl)-6-chloro-2-naphthamide
- 35 (316) 6-chloro-N-(((3S,5S)-1-(3,5-dichlorobenzyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide

- (317) 6-chloro-N-(((3S,5S)-3-(2-methyl-2-(piperidin-1-yl)propyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (318) (E)-3-(4-chlorophenyl)-N-(((3S,5R)-3-(3-guanidinopropyl)-1-((S)-1-(methylamino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)-2-oxo-1,4-diazepan-5-yl)methyl)acrylamide
- 5 (319) N-(((3S,5S)-3-(2-aminoethyl)-1-((R)-2-ethyl-3-methylbutyl)-2-oxo-1,4-diazepan-5-yl)methyl)-6-chloro-2-naphthamide
- (320) N-(((3S,5S)-3-(2-aminoethyl)-1-((S)-2-ethyl-3-methylbutyl)-2-oxo-1,4-diazepan-5-yl)methyl)-6-chloro-2-naphthamide
- (321) 6-chloro-N-(((3S,5S)-1-((R)-2-ethyl-3-methylbutyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 10 (322) 6-chloro-N-(((3S,5S)-1-((S)-2-ethyl-3-methylbutyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (323) (S)-2-amino-3-(4-chlorophenyl)-N-(((3S,5R)-3-(3-guanidinopropyl)-1-((S)-1-(methylamino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)-2-oxo-1,4-diazepan-5-yl)methyl)propanamide
- 15 (324) (R)-2-amino-3-(4-chlorophenyl)-N-(((3S,5R)-3-(3-guanidinopropyl)-1-((S)-1-(methylamino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)-2-oxo-1,4-diazepan-5-yl)methyl)propanamide
- (325) (S)-2-(((3S,5R)-3-(3-guanidinopropyl)-5-((2-(4-methoxyphenyl)acetamido)methyl)-2-oxo-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide
- 20 (326) (S)-2-(((3S,5R)-3-(3-guanidinopropyl)-2-oxo-5-((3-phenylpropanamido)methyl)-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide
- (327) (S)-2-(((3S,5R)-5-((3-(4-chlorophenyl)propanamido)methyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide
- 25 (328) (E)-3-(4-chlorophenyl)-N-(((3S,5R)-3-(3-guanidinopropyl)-1-((S)-1-(methylamino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)-2-oxo-1,4-diazepan-5-yl)methyl)acrylamide
- (329) 6-chloro-N-(((3S,5S)-3-hexyl-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (330) 6-chloro-N-(((3S,5S)-3-(2-(3-isopropylguanidino)ethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 30 (331) 6-chloro-N-(((3S,5S)-3-(4-hydroxybutyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (332) 6-chloro-N-(((3S,5S)-3-(2-methoxyethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 35 (333) N-(((3S,5S)-3-(2-(benzyloxy)ethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-6-chloro-2-naphthamide

- (334) 6-chloro-N-(((3S,5S)-3-isobutyl-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (335) (S)-2-(((3S,5R)-5-((2-(2,4-dichlorophenyl)acetamido)methyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide
- 5 (336) (S)-2-(((3S,5R)-5-((2-(2,4-dichlorophenyl)acetamido)methyl)-3-(3-(3-(2-(2,4-dichlorophenyl)acetyl)guanidino)propyl)-2-oxo-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide
- (337) (S)-2-(((3S,5R)-5-((2-(3-chlorophenyl)acetamido)methyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide
- 10 (338) (S)-2-(((3S,5R)-5-((2-(3-chlorophenyl)acetamido)methyl)-3-(3-(3-(2-(3-chlorophenyl)acetyl)guanidino)propyl)-2-oxo-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide
- (339) N-(((3S,5S)-3-(2-aminoethyl)-1-(2-ethyl-3-methylbut-3-enyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3,4-dichlorobenzamide
- 15 (340) 3,4-dichloro-N-(((3S,5S)-1-(2-ethyl-3-methylbut-3-enyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)benzamide
- (341) 3,4-dichloro-N-(((3S,5S)-1-(2-ethyl-3-methylbut-3-enyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)benzamide
- (342) N-(((3S,5S)-3-(2-aminoethyl)-1-(2-ethyl-3-methylbut-3-enyl)-2-oxo-1,4-diazepan-5-yl)methyl)-6-chloro-2-naphthamide
- 20 (343) 6-chloro-N-(((3S,5S)-1-((R)-2-ethyl-3-methylbut-3-enyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (344) 6-chloro-N-(((3S,5S)-1-((S)-2-ethyl-3-methylbut-3-enyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 25 (345) 6-chloro-N-(((3S,5S)-1-(2-ethyl-3-methylbutyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (346) N-(((3S,5S)-1-(cyclohexylmethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)biphenyl-4-carboxamide
- (347) N-(((3S,5S)-1-(cyclohexylmethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)quinoline-3-carboxamide
- 30 (348) N-(((3S,5R)-1-(cyclohexylmethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)biphenyl-4-carboxamide
- (349) N-(((3S,5R)-1-(cyclohexylmethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)quinoline-3-carboxamide
- 35 (350) N-(((3R,5R)-1-(cyclohexylmethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)biphenyl-4-carboxamide

- (351) N-(((3R,5R)-1-(cyclohexylmethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-(1H-indol-3-yl)acetamide
- (352) N-(((3R,5S)-1-(cyclohexylmethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)biphenyl-4-carboxamide
- 5 (353) N-(((3R,5S)-1-(cyclohexylmethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-1H-indole-3-carboxamide
- (354) N-(((3R,5S)-1-(cyclohexylmethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (355) N-(((3R,5S)-1-(cyclohexylmethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-(naphthalen-2-yl)acetamide
- 10 (356) N-(((3R,5S)-1-(cyclohexylmethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)quinoline-3-carboxamide
- (357) (S)-methyl 2-(((3S,5R)-5-((2-(4-chlorophenyl)acetamido)methyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-1-yl)-3-(naphthalen-2-yl)propanoate
- 15 (358) (S)-2-(((3S,5R)-3-(3-aminopropyl)-5-((2-(4-chlorophenyl)acetamido)methyl)-2-oxo-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide
- (359) N-(((3S,5S)-3-(2-(azepan-1-yl)ethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-6-chloro-2-naphthamide
- (360) 6-chloro-N-(((3S,5S)-3-(2-(3-isopropylureido)ethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 20 (361) benzyl 2-(((2S,7S)-7-((6-chloro-2-naphthamido)methyl)-3-oxo-4-((S)-2-phenylbutyl)-1,4-diazepan-2-yl)acetate
- (362) benzyl 3-(((2S,7S)-7-((6-chloro-2-naphthamido)methyl)-3-oxo-4-((S)-2-phenylbutyl)-1,4-diazepan-2-yl)propanoate
- 25 (363) 4'-chloro-N-(((3S,5S)-2-oxo-1-((S)-2-phenylbutyl)-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)biphenyl-2-carboxamide
- (364) 6-chloro-N-(((3S,5S)-3-(2-(N-isopropylacetamido)ethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (365) 6-chloro-N-(((3S,5S)-3-((isopropylamino)methyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 30 (366) 6-chloro-N-(((3S,5S)-3-(guanidinomethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (367) N-(((3S,5S)-3-(2-aminoethyl)-1-(2,4-dichlorobenzyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3,4-dichlorobenzamide
- 35 (368) 3,4-dichloro-N-(((3S,5S)-1-(2,4-dichlorobenzyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)benzamide

- (369) 6-chloro-N-(((3S,5S)-1-(2,4-dichlorobenzyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (370) 6-chloro-N-(((3S,5S)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1-((R)-2-(thiophen-3-yl)butyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 5 (371) 6-chloro-N-(((3S,5S)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1-((S)-2-(thiophen-3-yl)butyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (372) N-(((3S,5S)-3-(2-aminoethyl)-1-(2-ethyl-2-methylbutyl)-2-oxo-1,4-diazepan-5-yl)methyl)-6-chloro-2-naphthamide
- (373) 6-chloro-N-(((3S,5S)-1-(2-ethyl-2-methylbutyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 10 (374) 6-chloro-N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(2-morpholinoethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (375) 6-chloro-N-(((3S,5S)-3-(2-morpholinoethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 15 (376) 6-chloro-N-(((3S,5S)-1-(3,5-dichlorobenzyl)-3-(2-morpholinoethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (377) 3,4-dichloro-N-(((3S,5S)-1-(3,5-dichlorobenzyl)-3-(2-morpholinoethyl)-2-oxo-1,4-diazepan-5-yl)methyl)benzamide
- (378) N-(3,4-dichlorobenzyl)-N-(((3S,5S)-2-oxo-1-((S)-2-phenylbutyl)-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)acetamide
- 20 (379) 6-chloro-N-(((3S,5S)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1-(2,3,5-trichlorobenzyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (380) 6-chloro-N-(((3S,5S)-3-(2-(1-methylethylsulfonamido)ethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 25 (381) butyl 2-((2S,7S)-7-((6-chloro-2-naphthamido)methyl)-3-oxo-4-((S)-2-phenylbutyl)-1,4-diazepan-2-yl)ethylcarbamate
- (382) (S)-6-chloro-N-((3-(1-isopropylpiperidin-4-yl)-2-oxo-1-(2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (383) 6-chloro-N-(((3S,5S)-2-oxo-1-((R)-2-phenylbutyl)-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 30 (384) 5-(4-chlorophenyl)-N-(((3S,5S)-1-(3,5-dichlorobenzyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)isoxazole-3-carboxamide
- (385) N-(((3S,5S)-1-(3,5-dichlorobenzyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-6-methoxy-2-naphthamide
- 35 (386) 6-chloro-N-(((3R,5R)-2-oxo-1-((R)-2-phenylbutyl)-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide

(387) 6-chloro-N-(((3S,5R)-2-oxo-1-((S)-2-phenylbutyl)-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide

(388) 6-chloro-N-(((3R,5S)-2-oxo-1-((S)-2-phenylbutyl)-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide

5 (389) 6-chloro-N-(((3R,5R)-2-oxo-1-((S)-2-phenylbutyl)-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide

As stated previously the compounds of formula (I) are modulators of the MC3R and / or MC4R and therefore may be used to modulate the activity of MC3R and / or MC4R or a
10 fragment or analogue or functional equivalent thereof by exposing MC3R and / or MC4R or a fragment or analogue or functional equivalent thereof to a compound of the invention. This can occur *in vitro* in assays where the modulation of MC3R and / or MC4R activity is desirable, however it is typically more beneficial when utilised in modulation of MC3R and / or MC4R activity in a patient. The amount of modulation provided by the compounds of the
15 invention will vary from compound to compound and will also be affected by the amount of compound administered. The modulation can consist of upregulation or downregulation. In one embodiment the amount of upregulation or downregulation is at least 10%. In another embodiment the amount of upregulation or downregulation is at least 20%. In an even further embodiment the amount of upregulation or downregulation is at least 50%.

20

Accordingly the methods of the present invention may be used in the treatment of any condition in which modulation of the activity of MC3R and / or MC4R or a fragment or analogue or functional equivalent thereof would lead to a beneficial effect on that condition. As such the compounds suitable for use in the present invention may be used in methods of
25 preventing or treating a condition associated either directly or indirectly with the activity of MC3R and / or MC4R or a fragment or analogue or functional equivalent thereof in a mammal wherein an MC3R and / or MC4R modulating amount of the compound of the invention is administered to the mammal. One condition associated with MC3R and / or MC4R activity is metabolic syndromes and conditions related thereto. In one embodiment of the method the
30 condition is selected from the group consisting of obesity, eating disorders, and diabetes. In a more specific embodiment the eating disorder is selected from the group consisting of cachexia, anorexia, weight gain and weight loss. In another specific embodiment the condition is Type II diabetes. Another condition associated with MC3R and / or MC4R activity is sexual dysfunction. In one embodiment the sexual dysfunction is selected from the group
35 consisting of erectile dysfunction and female sexual dysfunction. In one specific embodiment the condition is erectile dysfunction.

The modulation of MC3R and / or MC4R may involve upregulation or downregulation. For example, downregulation of MC4R leads to increased food intake and weight gain and can thus be used in the treatment of cachexia. In another example, upregulation of MC4R leads to weight loss and can thus be used in the treatment of obesity. In another example, upregulation of MC4R leads penile erection and can thus be used in the treatment of erectile dysfunction.

The methods of the invention may also be useful in prevention or treatment of a number of conditions that relate to biological processes controlled by MC3R and / or MC4R, such as diseases related to inflammation, depression, anxiety and addiction.

Due to their impact on metabolism the compounds of formula (I) may also find application in treatments where reduced weight is desirable such as in dieting. The compounds may thus be used in methods of reducing the weight a mammal, the method comprising administering an effective amount of a compound of formula (I).

The compounds of formula (I) may be used in the treatment of conditions in any species in which MC3R and / or MC4R is present, most typically mammals. Examples of species in which MC3R and / or MC4R are found and hence species in which the compounds may be used include humans, rats, mice, dogs, and rhesus monkey. In a specific embodiment the mammal is a human.

Administration of compounds within Formula (I) to a patient such as humans can be by topical administration, by any of the accepted modes for enteral administration such as oral or rectal, or by parenteral administration such as subcutaneous, intramuscular, intravenous and intradermal routes. Injection can be bolus or via constant or intermittent infusion. The active compound is typically included in a pharmaceutically acceptable carrier or diluent and in an amount sufficient to deliver to the patient a therapeutically effective dose.

In using the compounds of formula (I) they can be administered in any form or mode which makes the compound bioavailable. One skilled in the art of preparing formulations can readily select the proper form and mode of administration depending upon the particular characteristics of the compound selected, the condition to be treated, the stage of the condition to be treated and other relevant circumstances. We refer the reader to Remingtons Pharmaceutical Sciences, 19th edition, Mack Publishing Co. (1995) for further information.

The compounds of formula (I) can be administered alone or in the form of a pharmaceutical composition in combination with a pharmaceutically acceptable carrier, diluent or excipient. The compounds of formula (I), while effective themselves, are typically formulated and administered in the form of their pharmaceutically acceptable salts as these forms are typically more stable, more easily crystallised and have increased solubility.

The compounds are, however, typically used in the form of pharmaceutical compositions which are formulated depending on the desired mode of administration. The compositions are prepared in manners well known in the art.

A compound of formula (I) is typically combined with the carrier to produce a dosage form suitable for the particular patient being treated and the particular mode of administration. For example, a formulation intended for the oral administration to humans may contain from about 0.5 mg to about 5 g of the compound of the invention, compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 99.95 percent of the total composition. Representative dosage forms will generally contain between from about 1 mg to about 500 mg of a compound of the invention, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or 1000 mg. Compounds of the present invention may also be formulated for topical delivery in formulations such as solutions, ointments, lotions, gels, creams, microemulsions or transdermal patches. For example, these topical formulations may contain from 0.005 to 5% (wt/wt or wt/vol) of a compound of the invention.

The compounds of formula (I) may be used or administered in combination with one or more additional drug (s), either concurrently or sequentially. The compounds of the present invention may be used in combination with one or more other pharmaceutically-active compounds, such as other metabolism altering, sexual dysfunction, anti-inflammatory, antianxiety, or antiaddiction medications. These components can be administered in the same formulation or in separate formulations. If administered in separate formulations the compounds of the invention may be administered sequentially or simultaneously with the other drug(s).

Pharmaceutical compositions suitable for use in the invention for parenteral injection comprise pharmaceutically acceptable sterile aqueous or non aqueous solutions, dispersions, suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and non aqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol,

propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservative, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of micro-organisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents that delay absorption such as aluminium monostearate and gelatin.

If desired, and for more effective distribution, the compounds can be incorporated into slow release or targeted delivery systems such as polymer matrices, liposomes, and microspheres.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

5 The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding
10 compositions which can be used include polymeric substances and waxes.

 If desired, and for more effective distribution, the compounds can be incorporated into slow release or targeted delivery systems such as polymer matrices, liposomes, and microspheres.

15 The active compounds can also be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients.

 Liquid dosage forms for oral administration include pharmaceutically acceptable
20 emulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide, oils (in particular, cottonseed, groundnut,
25 corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

 Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming
30 agents.

 Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminium metahydroxide, bentonite, agar-agar, and tragacanth,
35 and mixtures thereof.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at room temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

For topical administration, the active agent may be in the form of an ointment, cream, suspension, lotion, powder, solution, paste, gel, spray, aerosol or oil. Alternatively, the composition may be delivered via a liposome, nanosome, rivosome, or nutri-diffuser vehicle. Alternately, a formulation may comprise a transdermal patch or dressing such as a bandage impregnated with an active ingredient and optionally one or more carriers or diluents. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen. Methods for producing formulations for topical administration are known in the art.

The compositions used for topical administration typically contain a pharmaceutically acceptable carrier which may be any vehicle that is toxicologically and pharmaceutically acceptable. Typical pharmaceutically acceptable carriers that can be used in compositions of the present invention include water, ethanol, acetone, isopropyl alcohol, stearyl alcohol, freons, polyvinyl pyrrolidone, propylene glycol, polyethylene glycol, fragrances, gel-producing materials, mineral oil, stearic acid, spermaceti, sorbitan, monoleate, polysorbates, "Tweens," sorbitol, methyl cellulose, petrolatum, a mineral oil (vaseline oil), which may be any petroleum based product; modified or unmodified vegetable oils such as peanut oil, wheatgerm oil, linseed oil, jojoba oil, apricot kernel oil, walnut oil, palm oil, pistachio oil, sesame oil, colza oil, cade oil, corn germ oil, peach kernel oil, poppyseed oil, pine oil, castor oil, soya oil, safflower oil, coconut oil, hazelnut oil, grapeseed oil, avocado oil, soy oil, sweet almond oil, calophyllum oil, castor oil, olive oil, sunflower oil, or animal oils such as whale oil, seal oil, menhaden oil, halibut liver oil, cod liver oil, cod, tuna, turtle tallow, horse's hoof, sheep's foot, mink, otter, marmot oil and the like; synthetic oils such as silicon oil such as dimethylpolysiloxane; alkyl and alkenyl esters of fatty acids, such as isopropyl esters of myristic, palmitic and stearic acids and fatty esters which are solid at room temperature; waxes such as lanolin wax, candelilla wax, spermaceti, cocoa butter, karite butter, silicon waxes, hydrogenated oils which are solid at room temperature, sucro-glycerides, oleates, myristates, linoleates, stearates, paraffin, beeswax, carnauba wax, ozokerite, candelilla wax, microcrystalline wax; fatty alcohols such as lauryl, cetyl, myristyl, stearyl, palmityl and oleyl alcohols; polyoxyethylated fatty alcohols; and wax esters, lanolin and its derivatives, perhydrosqualene and saturated esters, ethyl palmitate, isopropyl palmitate, alkyl myristates such as isopropyl myristate, butyl

myristate and decyl myristate, hexyl stearate, triglyceride esters, triglycerides of octanoic and decanoic acid, cetyl ricinoleate, stearyl octanoate (Purcellin oil), fatty acids, polyhydric alcohols, polyether derivatives, fatty acid monoglycerides, polyethylene glycol, propylene glycol, alkyl ethoxy ether sulfonates, ammonium alkyl sulfates, fatty acid soaps, and
5 hydrogenated polyisobutene, and mixtures of waxes and oils.

The compositions for topical administration may be formulated in numerous forms. However, the composition may often take the form of an aqueous or oily solution or dispersion or emulsion or a gel or a cream. An emulsion may be an oil-in-water emulsion or a
10 water-in-oil emulsion.

The oil phase of water-in-oil or oil-in-water emulsions may comprise for example: a) hydrocarbon oils such as paraffin or mineral oils; b) waxes such as beeswax or paraffin wax; c) natural oils such as sunflower oil, apricot kernel oil, shea butter or jojoba oil; d) silicone oils
15 such as dimethicone, cyclomethicone or cetyldimethicone; e) fatty acid esters such as isopropyl palmitate, isopropyl myristate, dioctylmaleate, glyceryl oleate and cetostearyl isononanoate; f) fatty alcohols such as cetyl alcohol or stearyl alcohol and mixtures thereof (eg cetearyl alcohol); g) polypropylene glycol or polyethylene glycol ethers, eg PPG-14 butyl ether; or h) mixtures thereof.

20

Emulsifiers used may be any emulsifiers known in the art for use in water-in-oil or oil-in-water emulsions. Known cosmetically acceptable emulsifiers include: a) sesquioleates such as sorbitan sesquioleate, available commercially for example under the trade name Arlacel 83 (ICI), or polyglyceryl-2-sesquioleate; b) ethoxylated esters of derivatives of natural
25 oils such as the polyethoxylated ester of hydrogenated castor oil available commercially for example under the trade name Arlacel 989 (ICI); c) silicone emulsifiers such as silicone polyols available commercially for example under the trade name ABIL WS08 (Th. Goldschmidt AG); d) anionic emulsifiers such as fatty acid soaps e.g. potassium stearate and fatty acid sulphates e.g. sodium cetostearyl sulphate available commercially under the trade
30 name Dehydag (Henkel); e) ethoxylated fatty alcohols, for example the emulsifiers available commercially under the trade name Brij (ICI); f) sorbitan esters, for example the emulsifiers available commercially under the trade name Span (ICI); g) ethoxylated sorbitan esters, for example the emulsifiers available commercially under the trade name Tween (ICI); h) ethoxylated fatty acid esters such as ethoxylated stearates, for example the emulsifiers
35 available commercially under the trade name Myrj (ICI); i) ethoxylated mono-, di-, and tri-glycerides, for example the emulsifiers available commercially under the trade name Labrafil (Alfa Chem.); j) non-ionic self-emulsifying waxes, for example the wax available commercially

under the trade name Polawax (Croda); k) ethoxylated fatty acids, for example, the emulsifiers available commercially under the trade name Tefose (Alfa Chem.); l) methylglucose esters such as polyglycerol-3 methyl glucose distearate available commercially under the name Tegocare 450 (Degussa Goldschmidt); or m) mixtures thereof.

5

Gels for topical administration may be aqueous or non-aqueous. Aqueous gels are preferred. The gel will contain a thickening agent or gelling agent in order to give sufficient viscosity to the gel. A variety of thickening agents may be used according to the nature of the liquid carrier and the viscosity required and these are recited hereinafter. A particularly
10 suitable thickener is a copolymer of acryloyl dimethyl tauric acid (or a salt thereof), preferably a copolymer of that monomer with another vinylic monomer. For example, the thickening agent is a copolymer of a salt of acryloyl dimethyl tauric acid with another vinylic monomer. The salt may be a salt of a Group I alkali metal, but is more preferably an ammonium salt. Examples of suitable copolymer thickening agents are: i) Ammonium acryloyl dimethyl taurate
15 l vinyl pyrrolidone copolymer, ie a copolymer of ammonium acryloyl dimethyl taurate and vinyl pyrrolidone (1-vinyl-2-pyrrolidone).

The composition may additionally comprise other components which will be well known to those skilled in the art such as emollients, humectants, emulsion stabilising salts,
20 preservatives, chelating agents or sequestering agents (sequestrants), abrasives, anti-oxidants, stabilisers, pH adjusters, surfactants, thickeners, diluents, perfumes and colourings.

The topical formulations may desirably include a compound that enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of
25 such dermal penetration enhancers include dimethylsulfoxide and related analogues.

The amount of compound administered will preferably treat and reduce or alleviate the condition. A therapeutically effective amount can be readily determined by an attending diagnostician by the use of conventional techniques and by observing results
30 obtained under analogous circumstances. In determining the therapeutically effective amount a number of factors are to be considered including but not limited to, the species of animal, its size, age and general health, sex, diet, the specific condition involved, the severity of the condition, the response of the patient to treatment, the particular compound administered, the mode of administration, the bioavailability of the preparation administered, the dose regime
35 selected, the use of other medications and other relevant circumstances.

A preferred dosage will be a range from about 0.01 to 300 mg per kilogram of body weight per day. A more preferred dosage will be in the range from 0.1 to 100 mg per

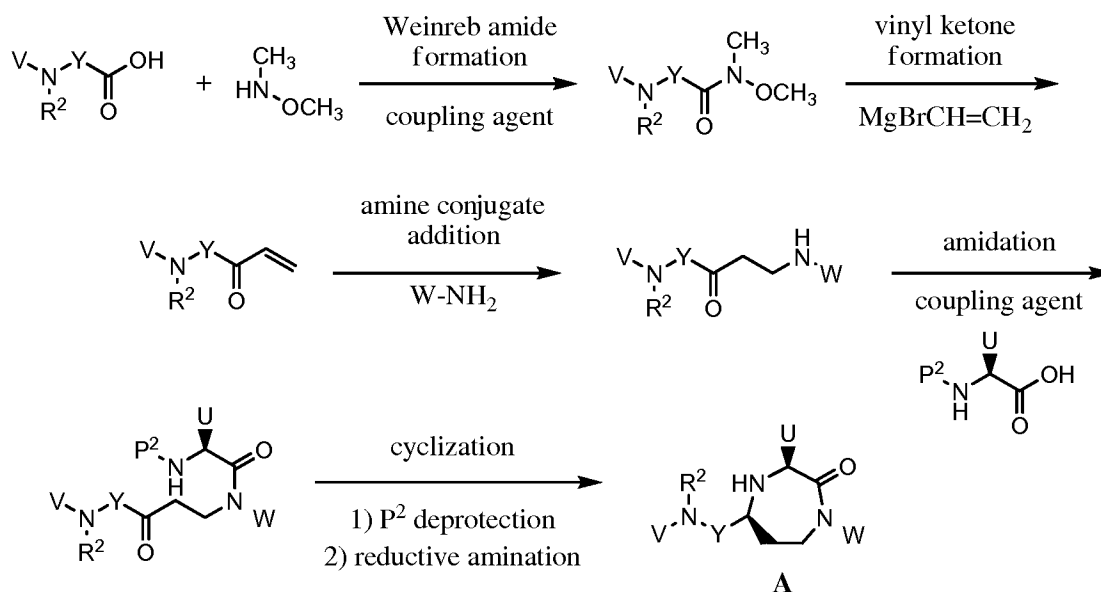
kilogram of body weight per day, more preferably from 0.2 to 80 mg per kilogram of body weight per day, even more preferably 0.2 to 50 mg per kilogram of body weight per day. A suitable dose can be administered in multiple sub-doses per day.

5 SYNTHESIS OF COMPOUNDS FOR USE IN THE INVENTION

The general synthetic route to the compounds for use in the invention proceeds through the key intermediate **A**, produced as outlined in Schemes 1 or 2.

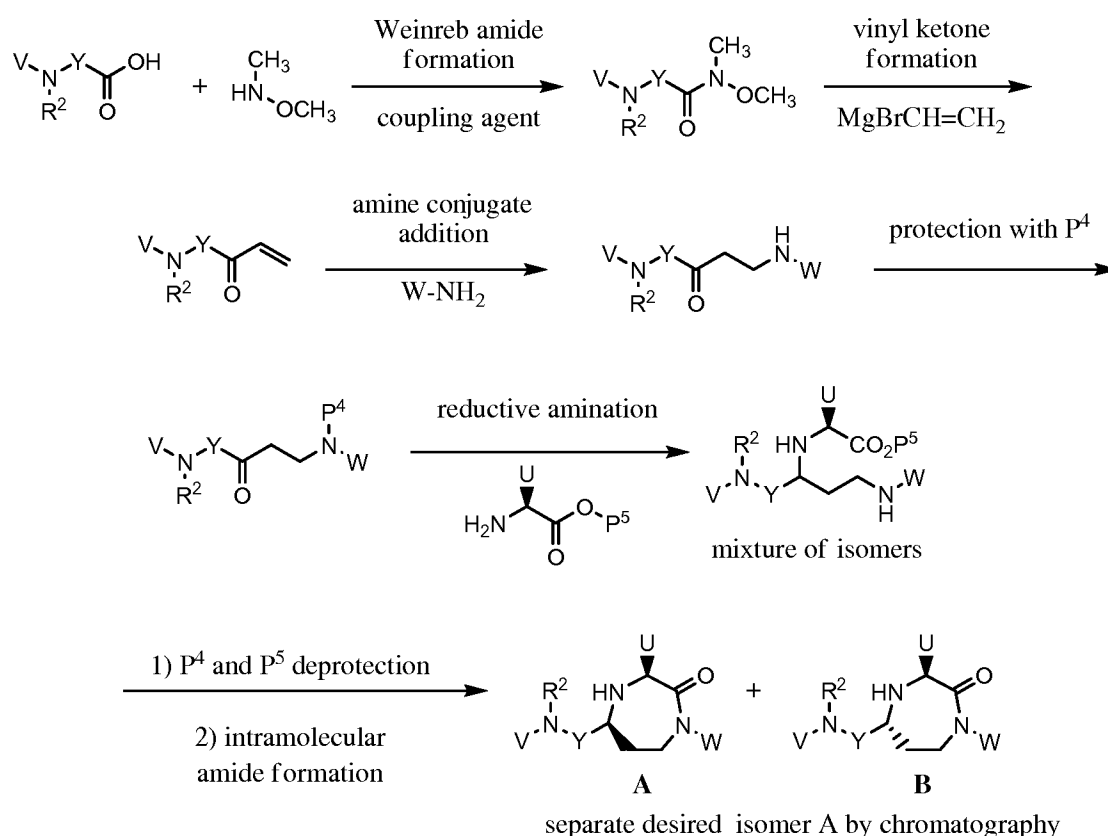
In Scheme 1, an amino acid derivative $V-N(R^2)-Y-CO_2H$ ($V = R^1X$ or an amine protecting group P^1) is converted to a Weinreb amide via activation of the carboxyl group and amidation with *N*-methyl methoxyamine. Addition of a vinyl Grignard reagent produces the aminoalkyl vinyl ketone, which undergoes conjugate addition by the $R^6-(CR^{5a}R^{5b})_rNH_2$ amine component (shown as $W-NH_2$ for simplicity). The resulting secondary amine is acylated under standard peptide coupling conditions with the protected amino acid, $P^2-NHCH(U)-CO_2H$, where U represents either the final R side chain, a protected final side chain $R-P^3$, or a precursor that requires chemical modification to form the final R side chain. Deprotection of the P^2 protecting group is followed by intramolecular reductive amination of the ketone using standard reduction conditions, such as H_2/Pd catalyst, $NaBH_4$, $NaBH_3CN$, or $NaBH(OAc)_3$, forming key intermediate **A**. If $Y = CH_2$ or CH_2CH_2 , **A** is formed as the predominant diastereomer. If $V = R^1X$ and $U = R$, **A** is the final product.

Scheme 1: Synthesis of Intermediate A via Intramolecular Reductive Amination



In Scheme 2, an alternate route to the desired intermediate **A** begins with the same Weinreb amide formation, vinyl Grignard addition, and amine conjugate addition. At this point, the secondary amine is protected with an amine protecting group P^4 . The ketone is then reductively aminated with a protected amino ester, $H_2NCH(U)-CO_2P^5$, producing a mixture of diastereomers that are carried through the next reaction steps. The ring system is generated by deprotection of the P^4 and P^5 protecting groups, followed by amide bond formation using standard peptide coupling reagents. Alternatively, the P^4 protecting group is removed and cyclization achieved by thermal or base-induced cyclization with the P^5 -protected ester. The cyclization produces a mixture of two diastereomers, **A** and **B**, from which the preferred diastereomers **A** can be separated by chromatography.

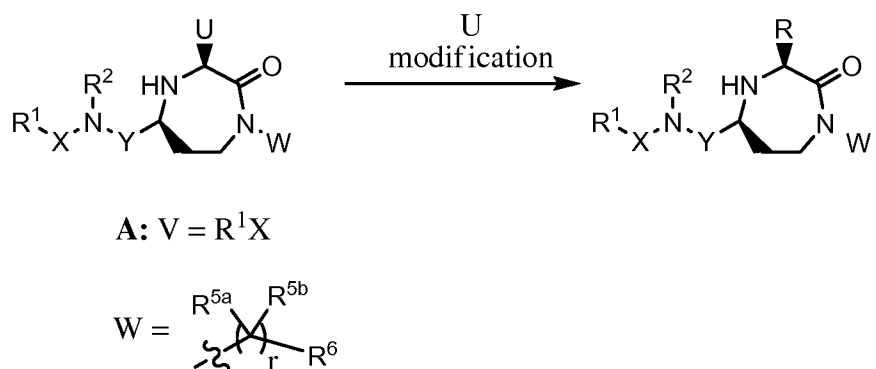
Scheme 2: Synthesis of Intermediate A via Intermolecular Reductive Amination



The key intermediate **A** may be the final product if $U = R$ and $V = R^1X$, but otherwise is converted into the final product as illustrated in Schemes 3, 4 and 5.

In Scheme 3, where $V = R^1X$, the final product is obtained by modification of the U side chain, such as removal of a P^3 protecting group, or removal of a P^3 protecting group followed by further chemical modification.

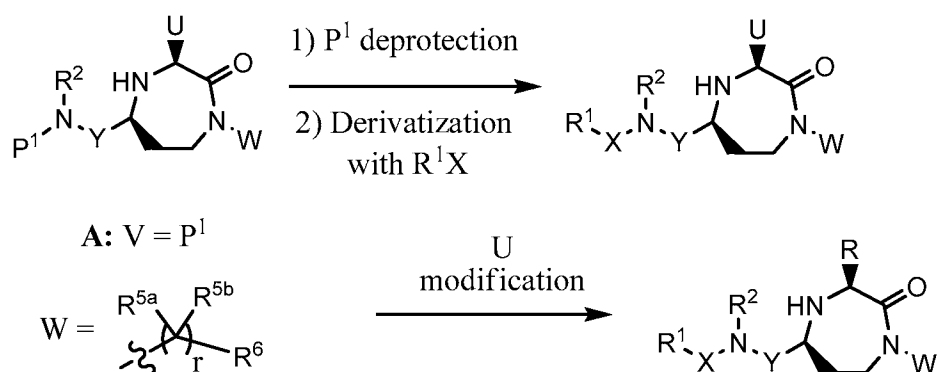
Scheme 3: $V = R^1X$



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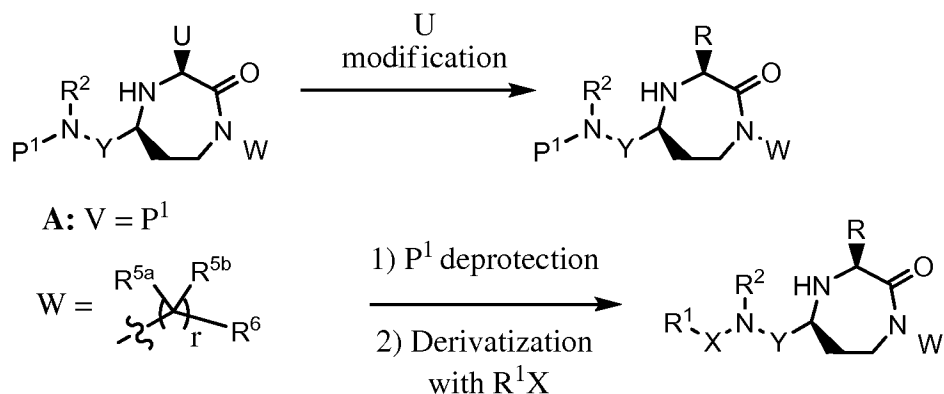
In Scheme 4, where $V = P^1$, the final product is obtained by removal of the P^1 protecting group followed by introduction of the R^1X substituent. If $U = R$, this produces the final product. Alternatively, the U side chain is then modified to produce the final R group as in Scheme 3.

Scheme 4: $V = P^1$



10

In Scheme 5, where $V = P^1$, the final product is obtained by first modifying the U side chain to produce the final R group as in Scheme 3. This is followed by removal of the P^1 protecting group followed by introduction of the R^1X substituent.

Scheme 5: V = P¹

It is also possible to modify the W substituent, if desired, during these reaction sequences.

5 Examples

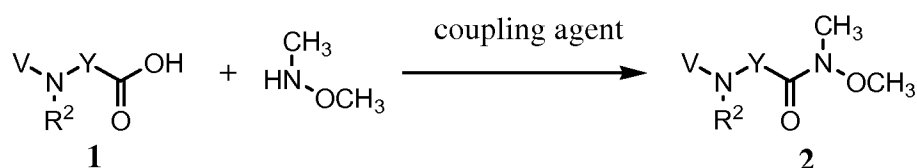
The following examples are intended to illustrate the embodiments disclosed and are not to be construed as being limitations thereto. Additional compounds, other than those described below, may be prepared using the following described reaction schemes as discussed above or appropriate variations or modifications thereof. All starting materials described in the Examples below are commercially available or readily synthesized by those skilled in the art.

Instrumentation

HPLC analyses were carried out on an Agilent 1100 Series Purification System with a Phenomenex Synergi 4 μ Max-RP 80A, 50 x 2.00 mm analytical HPLC column, with peak detection by UV. The standard analysis employed a 1 mL/min flow rate of 0.05% trifluoroacetic acid (TFA) in water (Solvent A) and 0.05% TFA in 90:10 acetonitrile:water (Solvent B), using a gradient of 5% B (initial) to 95% B over 9 min. Mass spectra were run on an Applied Biosystems MDS Sciex API 2000 LC/MS/MS triple quadrupole mass spectrometer and analyzed by ion spray mass spectrometry (ISMS). Preparative scale HPLC was carried out on a Waters Delta Prep 3000 HPLC system with peak detection by UV (Waters model 486 tunable absorbance detector), using Phenomenex Luna 10 μ C5 100A, 250 x 21.20 mm (20 mg scale), Phenomenex Luna 15 μ C8(2) 100A, 250 x 30.00 mm (50 mg scale), or Phenomenex Luna 15 μ C8(2) 100A, 250 x 50.00 mm (100 mg scale) HPLC columns. The solvent system employed various gradients of 0.05% TFA in water (Solvent A) and 0.05% TFA in 90:10 acetonitrile:water (Solvent B).

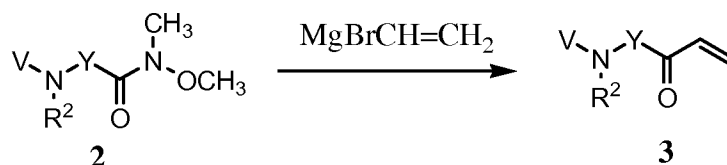
The following examples 1 to 7 provide general synthetic procedures that may be followed in order to carry out the transformations described in schemes 1 to 5. In order to make different end products using these procedures it is necessary to either vary a variable group on the starting material or to vary a variable group on one of the reagents depending upon the nature of the reaction. It will be apparent to a skilled addressee from a reading of the general procedures how to vary either the starting material or the reagents used in the procedure to produce differing end products. In addition depending upon the starting materials and the reagents it may be necessary and/or desirable to make slight modifications to the described general procedures in order to provide the most facile synthesis of the desired end product.

Example 1 – General Procedure - Weinreb Amide Formation



BOP reagent (100 mmol) and diisopropylethylamine (DIPEA) (100 mmol) is added to a stirred solution of the amino acid (**1**) (100 mmol) in dichloromethane (DCM) (100 mL). The solution is then stirred at room temperature for 10 mins, before addition of a premixed solution of *N,O*-dimethylhydroxylamine hydrochloride (100 mmol) and DIPEA (100 mmol) followed by stirring at room temperature overnight. The DCM is then removed by rotary evaporation and the residue taken up in ethyl acetate (EtOAc) (200 mL). The organic phase is then washed with 1N HCl (3 x 100 mL), H₂O (3 x 100 mL), saturated NaHCO₃ aqueous solution (3 x 100 mL) and brine (1 x 10 mL). The organic phase is then dried (MgSO₄) and the EtOAc removed to give the Weinreb amide (**2**) as a white solid or an oil.

Example 2 – General Procedure - Vinyl Grignard Addition to Weinreb Amide to Form α,β -unsaturated ketones of formula (3)

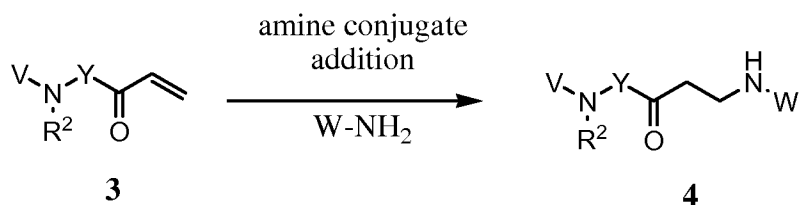


To the Weinreb amide (**2**) (15 mmol) in DCM (10 mL) at 0°C is added vinyl magnesium bromide (45 mmol) in THF (45 mL). The reaction is stirred for 2 hrs and monitored by HPLC. The reaction is then quenched by adding it to a mixture of ice and 1M HCl (200 mL). The aqueous mixture is extracted with DCM (3x 100 mL) and the organic layers combined and washed with 1M HCl (2x 200 mL) and H₂O (3x 100 mL). The organic

phase is dried (MgSO_4) to provide a solution of the α,β -unsaturated ketone (**3**). The α,β -unsaturated ketone (**3**) may be isolated by rotary evaporation or it may be used in solution without further purification. If the intention is to use the α,β -unsaturated ketone (**3**) in solution the volume is reduced to 100 mL by rotary evaporation and stored for later use.

5

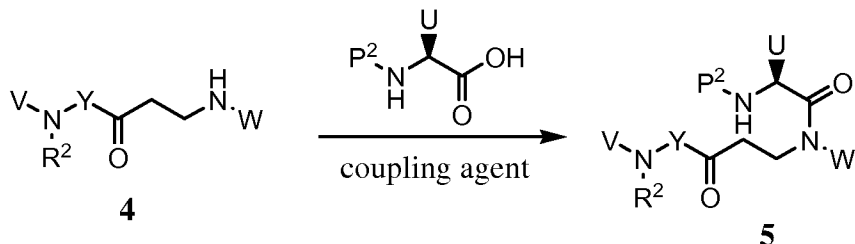
Example 3 General Procedure – Conjugate Addition of Amine to α,β -unsaturated ketones of formula (3) to produce compounds of formula (4)



To the amine $\text{W}-\text{NH}_2$ (7.4 mmol) in DCM (10 mL) is added a solution of the α,β -unsaturated ketone (**3**) (5.7 mmol) in DCM (50 mL). The solution is stirred at room temperature for 15 mins, or until analysis indicates that all of (**3**) has been consumed. The solution of compound (**4**) is immediately used without purification for the subsequent reaction.

10

Example 4 General Procedure – Acylation of Aminoketone (4)



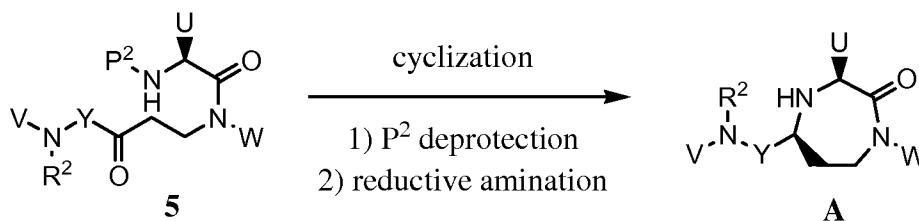
15

The amine acid $\text{P}^2-\text{NHCH}(\text{U})-\text{CO}_2\text{H}$ (15 mmol) and DIC (15 mmol) is added to a solution of DCM containing 10 mmol of the conjugate addition adduct **4**. The reaction is stirred at room temperature overnight. The DCM is removed by rotary evaporation and the residue is then subjected to column chromatography on silica gel using petroleum spirit:EtOAc to give **5**.

20

As an alternative, the DIC may be replaced with HATU (15 mmol) and DIPEA (15 mmol). The reaction is stirred at room temperature overnight. The DCM is removed by rotary evaporation and the residue is taken up in EtOAc (100 mL). The organic layer is washed with saturated sodium bicarbonate solution (2 x 100 mL), saturated ammonium chloride solution (2 x 100 mL) and brine (2 x 100 mL). The organic phase is dried and the solvent removed under reduced pressure. The residue is subjected to column chromatography on silica gel using petroleum ether:EtOAc to give **5**.

25

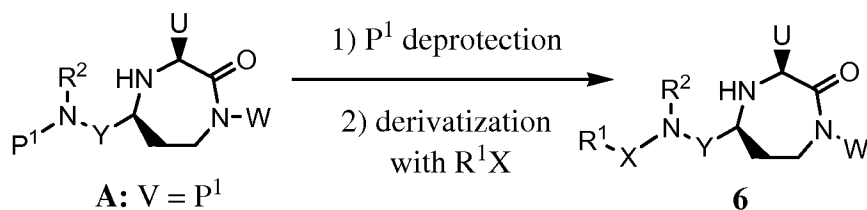
Example 5 General Procedure – P² Deprotection and Cyclization

The procedure adopted for the removal of the P² protecting group will vary depending upon the exact nature of the protecting group. As will be appreciated by a skilled addressee a large number of possible protecting groups may be used and a skilled worker in the art will readily be able to determine an appropriate procedure for the removal of any particular protecting group from procedures known in the art. Nevertheless in order to assist the reader general procedures for the removal of the more common protecting groups are provided.

P² = Fmoc: To compound **5** (2 mmol) in DCM (3 mL) is added diethylamine (20 mmol). The reaction is stirred at room temperature for 1 hr. The DCM and diethylamine is then removed by rotary evaporation. DCM (5 mL) and sodium triacetoxyborohydride (3 mmol) are then added, and the reaction stirred overnight at room temperature. The organic phase is washed with saturated sodium bicarbonate solution (25 mL), dried (MgSO₄) and the DCM removed to give the cyclised product **A**. This may be purified by flash chromatography on silica gel or used without purification.

P² = Boc: To compound **5** (2 mmol) in DCM (3 mL) is added TFA (3 mL) and the reaction stirred at room temperature for 2 hrs. The DCM and TFA are then removed by rotary evaporation. DCM (5 mL) and sodium triacetoxyborohydride (3 mmol) is then added, and the reaction stirred overnight at room temperature. The organic phase is washed with saturated sodium bicarbonate solution (25 mL), dried (MgSO₄) and the DCM removed to give the cyclised product **A**. This may be purified by flash chromatography on silica gel or used without purification.

P² = Cbz: A mixture of crude **5** (1 mmol) and 5% Pd/C (200 mg) in 2-propanol (15 mL) is shaken at room temperature under hydrogen (30 psi) for 24 hrs. The mixture is then filtered through a pad of Celite and the filtrate concentrated under reduced pressure to give a crude product. Purification by flash chromatography on silica gel (100% EtOAc) may be used to give **A**.

Example 6 General Procedure – P¹ Deprotection and Derivatization with R¹X

The procedure adopted for the removal of the P¹ protecting group will vary depending upon the exact nature of the protecting group. As will be appreciated by a skilled addressee a large number of possible protecting groups may be used and a skilled worker in the art will readily be able to determine an appropriate procedure for the removal of any particular protecting group from procedures known in the art. Nevertheless in order to assist the reader general procedures for the removal of the more common protecting groups are provided.

Deprotection, P¹ = Cbz:

To the cyclised product **A** (1 mmol) in methanol (5 mL) is added catalytic Pd/C. The reaction is stirred under a hydrogen atmosphere overnight. The reaction mixture is filtered through Celite and the methanol removed by rotary evaporation to give the free amine. The amine may be used in the next reaction without purification.

Deprotection, P¹ = Boc:

To the cyclised product **A** (1 mmol) in DCM (1 mL) is added TFA (1mL) and the reaction stirred at room temperature for 2 hrs. The solvent is removed by rotary evaporation to give the amine TFA salt, which may be used in the next reaction without purification.

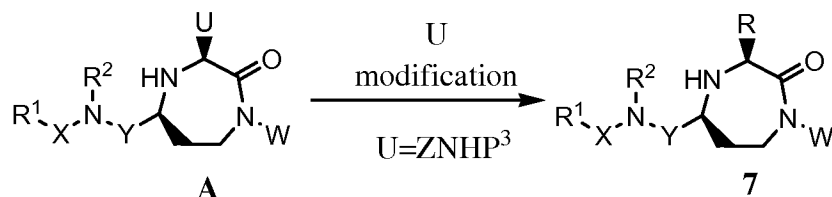
Deprotection, P¹ = Alloc:

To the cyclised product **A** (1 mmol) in DCM (6 mL) is added 1,3-dimethylbarbituric acid (0.2 mmol) and palladium tetrakis triphenylphosphine (10 mg). The reaction is evacuated and stirred at room temperature for 1 hr. The DCM is removed under reduced pressure to give the crude free amine, which may be used in the next reaction without purification.

Derivatisation with R¹X when X = C(=O):

To the free amine (1 mmol) in DCM (5 mL) is added DIPEA (1 mmol), BOP reagent (1.5 mmol) and acid component R¹CO₂H (1.5 mmol). The reaction is stirred at room temperature for 2 hrs. Rotary evaporation and preparative HPLC gives the purified adduct.

Example 7 General Procedure – U Modification via P³ Deprotection and Dialkylation with Dibromide

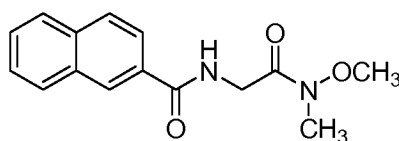


The procedure adopted for modification of U via deprotection and derivatization will vary depending on the exact nature of the U group. As will be appreciated by a skilled addressee a large number of modifications are possible, and a skilled worker in the art will readily be able to determine an appropriate procedure for the conversion into a desired R group. Nevertheless in order to assist the reader, one general modification procedure commonly employed for a number of the following examples is provided.

P³ = Boc:

To the protected amine (1 mmol) in DCM (5 mL) is added TFA (5 mL) and the reaction stirred at room temperature for 2 hrs. DCM (20 mL) is added and the solution is washed with saturated sodium bicarbonate solution (20 mL), dried (MgSO₄) and evaporated to give the crude amine. To the crude amine is added DMF (0.5 mL), potassium carbonate (50 mg) and 1,5-dibromopentane (5 mmol). The reaction mixture is stirred at room temperature for 1.5 hrs, after which DCM (20 mL) is added, the organic layer washed with saturated sodium bicarbonate solution (20 mL) and H₂O (20 mL), dried (MgSO₄) and evaporated. The residue may be purified by preparative HPLC to give the piperidinyll product. The purified product is isolated as the TFA salt, but is readily converted into the free base via neutralisation with aqueous NaHCO₃ and extraction into an organic solvent, or further converted into the HCl salt by acidification with 1N HCl.

Example 8 – Synthesis of Compound 8 N-(2-(methoxy(methyl)amino)-2-oxoethyl)-2-naphthamide



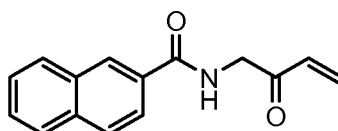
8

N-(2-(methoxy(methyl)amino)-2-oxoethyl)-2-naphthamide

To a mixture of 2-naphthoic acid (5.8 g, 33.7 mmol), 2-amino-*N*-methoxy-*N*-methylacetamide (Gly Weinreb amide; prepared from Boc-Gly Weinreb amide **15** following

the alternative procedure of Example 26) (3.8 g, 32.1 mmol) and DIPEA (12.0 mL, 68.9 mmol) in DCM (70 mL) was added BOP (14.9 g, 33.7 mmol) in one portion at room temperature. The resulting mixture was stirred for 1 hr then saturated NaHCO₃ aqueous solution was added. The organic layer was washed with brine (5 x 60 mL) and 1 N HCl (2 x 30 mL), dried
5 over MgSO₄, filtered and concentrated under reduced pressure to give the crude product, which was used in the next reaction without further purification.

Example 9 – Synthesis of Compound 9 N-(2-(methoxy(methyl)amino)-2-oxoethyl)-2-naphthamide

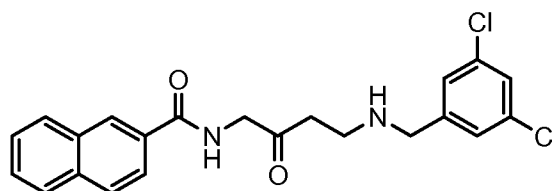


9

N-(2-oxobut-3-enyl)-
2-naphthamide

To a solution of **8** (3.5 g, 12.85 mmol) in dry THF (10 mL) was added a solution of vinylmagnesium bromide in THF (1 M, 31 mL) slowly at 0°C. After addition, the resulting mixture was stirred at room temperature for 1 hr then was poured into an icy 1 N HCl solution (50 mL). The aqueous layer was extracted with DCM (3 x 80 mL) and the combined organic
15 layers were dried over MgSO₄, filtered and concentrated under reduced pressure to give the crude product. **MS (ESI)** 240 (M+1); HPLC *t_R* 5.46 min.

Example 10 – Synthesis of Compound 10 N-(4-(3,5-dichlorobenzylamino)-2-oxobutyl)-2-naphthamide

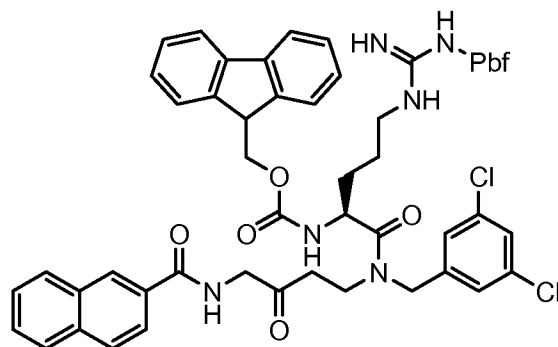


10

N-(4-(3,5-dichlorobenzylamino)-
2-oxobutyl)-2-naphthamide

To a solution of 3,5-dichlorobenzylamine (12 mg, 0.068 mmol) in DCM (0.2 mL) was added a solution of **9** (13 mg, 0.054 mmol) in DCM (0.5 mL) at room temperature. The resulting mixture was stirred until all of the **9** had been consumed (within one hr) and then was used straight in the next reaction. **MS (ESI)** 415 (M+1); HPLC *t_R* 6.00 min.

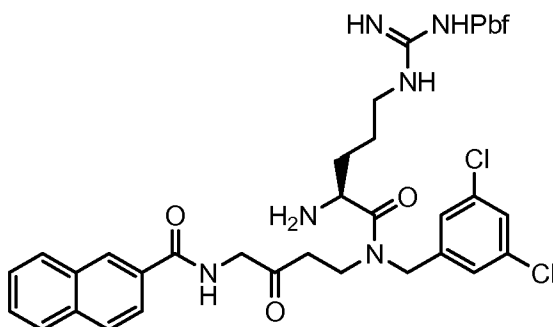
Example 11 – Synthesis of Compound 11 (S)-N-(4-(5-(3-Pbf-guanidino)-2-(Fmoc-amino)-N-(3,5-dichlorobenzyl)pentanamido)-2-oxobutyl)-2-naphthamide

**11**

(S)-N-(4-(5-(3-Pbf-guanidino)-2-(Fmoc-amino)-N-(3,5-dichlorobenzyl)pentanamido)-2-oxobutyl)-2-naphthamide

To a solution of freshly prepared aminoketone **10** in DCM (2 mL) was added Fmoc-L-Arg(Pbf)-OH (53 mg, 0.082 mmol) followed by DIC (12.5 μ L, 0.082 mmol) at room temperature. The resulting mixture was stirred for 2 hrs then the solvent was removed under reduced pressure. The residue was filtered through a short plug of silica gel eluting with DCM followed by EtOAc to give the desired product **11** as a white solid. It was used in the next step without further purification. **MS (ESI)** 1045 (M+1); HPLC t_R 9.99 min.

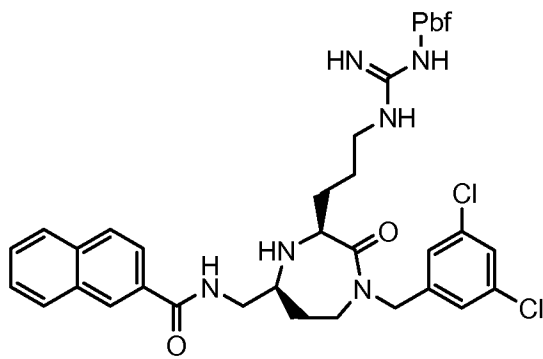
Example 12 – Synthesis of Compound 12 (S)-N-(4-(5-(3-Pbf-guanidino)-2-amino-N-(3,5-dichlorobenzyl)pentanamido)-2-oxobutyl)-2-naphthamide

**12**

(S)-N-(4-(5-(3-Pbf-guanidino)-2-amino-N-(3,5-dichlorobenzyl)pentanamido)-2-oxobutyl)-2-naphthamide

Diethylamine (0.5 mL) was added to Fmoc-protected **11** (56 mg, 0.054 mmol) at room temperature and the resulting mixture was stirred for 30 min. The excess amount of the diethylamine was removed under reduced pressure to give the desired free amine **12**. It was used in the next step without further purification. **MS (ESI)** 823 (M+1); HPLC t_R 7.49 min.

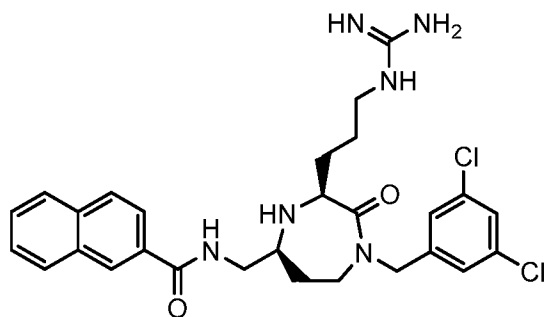
Example 13 – Synthesis of Compound 13 *N*-(((3*S*,5*S*)-3-(3-(3-Pbf-guanidino)propyl)-1-(3,5-dichlorobenzyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide

**13**

N-(((3*S*,5*S*)-3-(3-(3-Pbf-guanidino)propyl)-1-(3,5-dichlorobenzyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide

The amino ketone **12** (44 mg, 0.053 mmol) in DCM (2 mL) was cyclized by addition of NaBH(OAc)₃ (40mg, 0.18 mmol) in one portion at room temperature. The resulting mixture was stirred for 3 hrs, followed by addition of saturated NaHCO₃ aqueous solution (3 mL). The aqueous layer was extracted with DCM (3 x 3 mL) and the combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was filtered through a short plug of silica gel eluting with DCM followed by EtOAc then EtOAc/IPA (9:1) to give the desired product **13** as a white solid. It was used in the next step without further purification. **MS (ESI)** 807 (M+1); HPLC *t*_R 7.75 min.

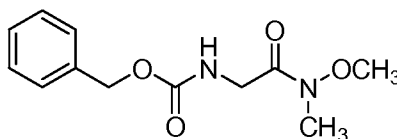
Example 14 – Synthesis of Compound 100 *N*-(((3*S*,5*S*)-1-(3,5-dichlorobenzyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide

**100**

N-(((3*S*,5*S*)-1-(3,5-dichlorobenzyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide

A solution of TFA/DCM (2:1) (1 mL) with 5% H₂O was added to **13** at room temperature and the resulting mixture was stirred for 4 hrs. The solvents were removed under reduced pressure and the residue was purified by prep HPLC (100% H₂O to MeCN/H₂O 9:1, gradient) to give **100** (7.6 mg) as a white solid (TFA salt). The overall yield (from **9**) was ca. 18%. **MS (ESI)** 556.2 (M+1); HPLC *t*_R 5.74 min.

Example 15 – Synthesis of Compound 14 benzyl 2-(methoxy(methyl)amino)-2-oxoethylcarbamate

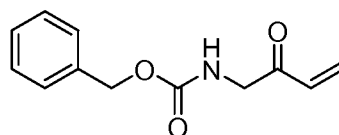


14

benzyl 2-
(methoxy(methyl)amino)-2-
oxoethylcarbamate

To Cbz-glycine (10 g, 47.8 mmol, Aldrich) in DCM (100 mL) was added BOP reagent
5 (21.5 g, 48.6 mmol) and DIPEA (6.5 mL, 46.0 mmol). After stirring at room temperature for
10 mins, N,O-dimethylhydroxylamine hydrochloride (4.9 g, 50.2 mmol) and DIPEA (6.5 mL,
46.0 mmol) were added. The reaction was stirred at room temperature overnight. The DCM
was removed by rotary evaporation and the residue taken up in EtOAc (100 mL). The
organic phase was washed with H₂O (3x 100 mL), saturated sodium bicarbonate solution (3x
10 100 mL), H₂O (3x 100 mL), 1M HCl (3x 100 mL), brine (3x 100 mL). The organic phase was
dried (MgSO₄) and the EtOAc removed to give the Weinreb amide **14** as a white solid (7.78 g,
64%).

Example 16 – Synthesis of Compound 15 benzyl 2-oxobut-3-enylcarbamate

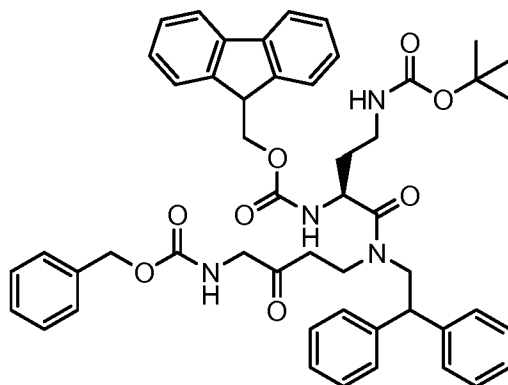


15

benzyl 2-oxobut-3-
enylcarbamate

To the Weinreb amide **14** (3.89 g, 15.42 mmol) in DCM (10mL) at 0°C was added vinyl
magnesium bromide (45 mmol) in THF (45 mL). The reaction was stirred for 2 hrs and
monitored by HPLC. The reaction was added to a mixture of ice and 1M HCl (200 mL). The
aqueous mixture was extracted with DCM (3x 100 mL) and washed with 1M HCl (2x 200mL)
15 and H₂O (3x 100mL). The organic phase was dried (MgSO₄) and the volume reduced to 100
20 mL by rotary evaporation. The α,β -unsaturated ketone **15** was stored and used in solution
without purification.

Example 17 – Synthesis of Compound 16 (S)-9-fluorenylmethyl 10-(2,2-diphenylethyl)-2,2-dimethyl-18-phenyl-4,9,13,16-tetraoxo-3,17-dioxo-5,10,15-triazaoctadecan-8-ylcarbamate



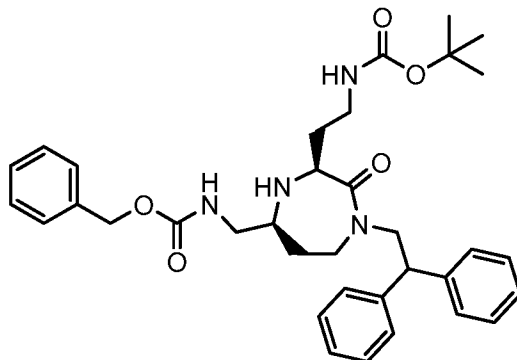
16

(S)-9-fluorenylmethyl 10-(2,2-diphenylethyl)-2,2-dimethyl-18-phenyl-4,9,13,16-tetraoxo-3,17-dioxo-5,10,15-triazaoctadecan-8-ylcarbamate

5 To 2,2-diphenylethylamine (0.95 g, 7.4 mmol) in DCM (10 mL) was added the α,β -unsaturated ketone **15** (5.7 mmol) in DCM (75 mL). After stirring at room temperature for 15 mins, Fmoc-L-2,4-diaminobutyric acid(Boc)-OH (2.4 g, 8.55 mmol) and DIC (0.87 mL, 5.6 mmol) were added. The reaction was stirred at room temperature overnight. The DCM was removed by rotary evaporation and the residue was subjected to column chromatography on
10 silica gel using petroleum spirit:EtOAc (1:1 to 0:1) to give **16** (1.5 g, 31%)

Alternatively, to 2,2-diphenylethylamine (0.97 g, 7.4 mmol) in DCM (20 mL) was added the α,β -unsaturated ketone **15** (5.95 mmol) in DCM (40mL). After stirring at room temperature for 15 mins, Fmoc-L-2,4-diaminobutyric acid(Boc)-OH (2.4 g, 8.55 mmol), DIPEA
15 (2.5 mL) and HATU (2.3 g, 6.0 mmol) were added. The reaction was stirred at room temperature overnight. The DCM was removed by rotary evaporation and the residue was taken up in EtOAc (100 mL). The organic layer was washed with saturated sodium bicarbonate solution (2x 100 mL), saturated ammonium chloride solution (2x 100 mL) and brine (2x 100 mL). The organic phase was dried and the solvent removed under reduced
20 pressure. The residue was subjected to column chromatography on silica gel using petroleum spirit:EtOAc (3:1 to 1:1 to 0:1) to give **16** (0.86 g, 17%).

Example 18 – Synthesis of Compound 17 (3*S*,5*S*)-3-(2-*tert*-butoxycarbonylaminoethyl)-5-(benzyloxycarbonylaminomethyl)-1-(2,2-diphenylethyl)-1,4-diazepan-2-one

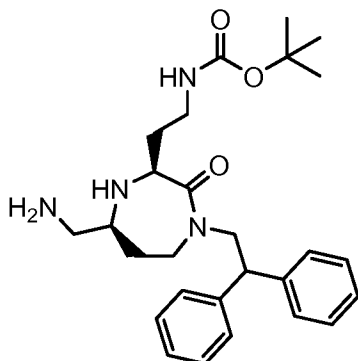


17

(3*S*,5*S*)-3-(2-*tert*-butoxycarbonylaminoethyl)-5-(benzyloxycarbonylaminomethyl)-1-(2,2-diphenylethyl)-1,4-diazepan-2-one

To Compound **16** (1.5 g, 1.8 mmol) in DCM (3 mL) was added diethylamine (1.5 mL, 14.5 mmol). The reaction was stirred at room temperature for 1hr. The DCM and diethylamine was removed by rotary evaporation. DCM (5 mL), sodium triacetoxyborohydride (0.4 g, 1.9 mmol) was added, and the reaction was stirred overnight at room temperature. The organic phase was washed with saturated sodium bicarbonate solution (25 mL), dried (MgSO₄) and the DCM removed to give the cyclised product **17**, which was used in the next step without purification.

Example 19 – Synthesis of Compound 18 (3*S*,5*S*)-3-(2-*tert*-butoxycarbonylaminoethyl)-5-aminomethyl-1-(2,2-diphenylethyl)-1,4-diazepan-2-one



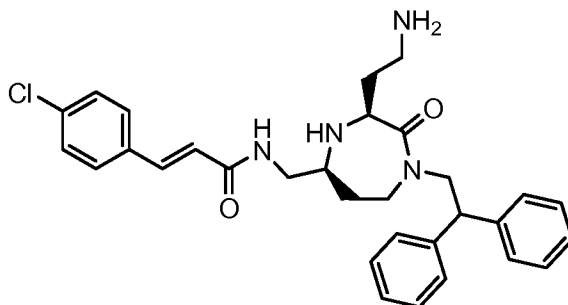
18

(3*S*,5*S*)-3-(2-*tert*-butoxycarbonylaminoethyl)-5-aminomethyl-1-(2,2-diphenylethyl)-1,4-diazepan-2-one

To the cyclised product **17** in methanol (5 mL) was added catalytic Pd/C. The reaction was stirred under a hydrogen atmosphere overnight. The reaction mixture was filtered

through Celite and the methanol removed by rotary evaporation to give the amine **18** (0.7 g, 83% from **16**).

Example 20 – Synthesis of Compound 216 (*E*)-*N*-(((3*S*,5*S*)-3-(2-aminoethyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3-(4-chlorophenyl)acrylamide

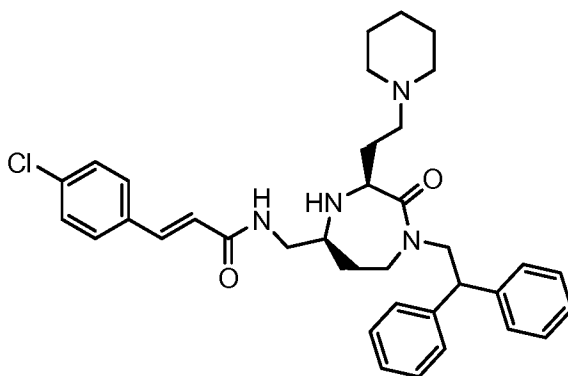


216

(*E*)-*N*-(((3*S*,5*S*)-3-(2-aminoethyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3-(4-chlorophenyl)acrylamide

To the amine **18** (0.06 g, 0.13 mmol) in DCM (5 mL) was added DIPEA (0.10 mL), BOP reagent (0.06 g, 0.13 mmol) and 4-chlorocinnamic acid (0.03 g, 0.16 mmol). The reaction was stirred at room temperature overnight. TFA (1mL) was added and the reaction stirred at room temperature for 1 hrs. Rotary evaporation and preparative HPLC gave **216** (0.058 g, 84%). **MS (ESI)** 531.4 ($M+1$); HPLC t_R min 5.89

Example 21 – Synthesis of Compound 19 (*E*)-3-(4-chlorophenyl)-*N*-(((3*S*,5*S*)-1-(2,2-diphenylethyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)acrylamide



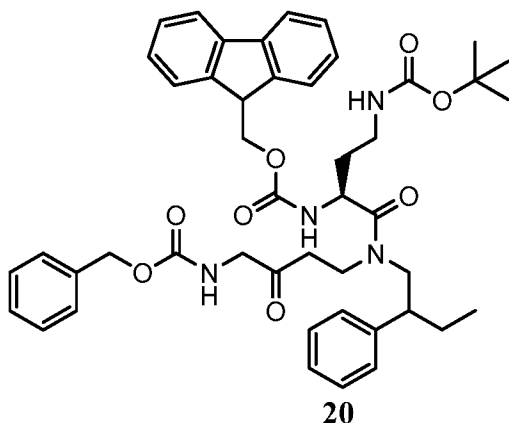
19

(*E*)-3-(4-chlorophenyl)-*N*-(((3*S*,5*S*)-1-(2,2-diphenylethyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)acrylamide

To the amine **216** (*E*)-3-(4-chlorophenyl)-*N*-(((3*S*,5*S*)-1-(2,2-diphenylethyl)-2-oxo-3-(2-aminoethyl)-1,4-diazepan-5-yl)methyl)acrylamide (21 mg, 0.05 mmol) in DMF (0.25 mL) was added K_2CO_3 (5 mg) and 1,5-dibromopropane (0.066 mL, 0.5 mmol). The reaction mixture

was left at room temperature for 4 hrs. The solvent was removed under high vacuum, and the residue purified by preparative HPLC to give 8 mg (~30%) of **19** as the TFA salt. **MS** (ESI) 599.4 (M+1); HPLC t_R min 6.31

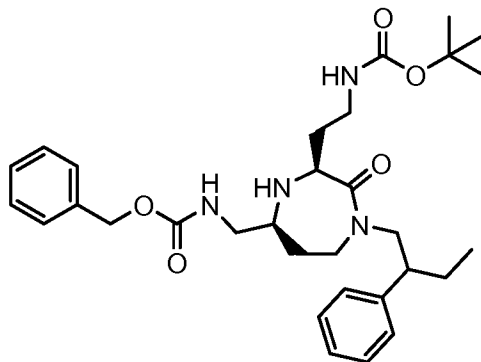
5 **Example 22 – Synthesis of Compound 20 (S)-9-fluorenylmethyl 10-(2-phenylbutyl)-2,2-dimethyl-18-phenyl-4,9,13,16-tetraoxo-3,17-dioxo-5,10,15-triazaoctadecan-8-ylcarbamate**



(S)-9-fluorenylmethyl 10-(2-phenylbutyl)-2,2-dimethyl-18-phenyl-4,9,13,16-tetraoxo-3,17-dioxo-5,10,15-triazaoctadecan-8-ylcarbamate

To 2-phenylbutylamine hydrochloride (0.26 g, 1.4 mmol) in DCM (10 mL) and DIPEA (0.25 mL, 1.8 mmol) was added the α,β -unsaturated ketone **15** (1.06 mmol) in DCM (20 mL). After stirring at room temperature for 15 mins, Fmoc-diaminobutyric acid(Boc)-OH (0.7 g, 1.56 mmol) and DIC (0.25 mL, 1.61 mmol) were added. The reaction was stirred at room temperature overnight. The DCM was removed by rotary evaporation and the residue was subjected to column chromatography on silica gel using petroleum spirit:EtOAc (1:1 to 0:1), providing Compound **20** as a mixture of diastereomers (0.17 g, 21%).

Example 23 – Synthesis of Compound 21 (3*S*,5*S*)-3-(2-*tert*-butoxycarbonylaminoethyl)-5-(benzyloxycarbonylaminomethyl)-1-(2-phenylbutyl)-1,4-diazepan-2-one

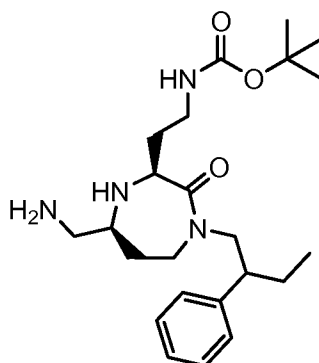
**21**

(3*S*,5*S*)-3-(2-*tert*-butoxycarbonylaminoethyl)-5-(benzyloxycarbonylaminomethyl)-1-(2-phenylbutyl)-1,4-diazepan-2-one

To Compound **20** (0.17 g, 0.2 mmol) in DCM (3 mL) was added diethylamine (1.5 mL).

- 5 The reaction was stirred at room temperature for 1hr. The DCM and diethylamine was removed by rotary evaporation. DCM (5 mL) and sodium triacetoxyborohydride (0.1 g, 0.47 mmol) were added and the reaction was stirred overnight at room temperature. The organic phase was washed with saturated sodium bicarbonate solution (25 mL), dried (MgSO₄) and the DCM removed to give the cyclised product **21** as a mixture of diastereomers (0.11 g, 100%).
- 10

Example 24 – Synthesis of Compound 22 (3*S*,5*S*)-3-(2-*tert*-butoxycarbonylaminoethyl)-5-(aminomethyl)-1-(2-phenylbutyl)-1,4-diazepan-2-one

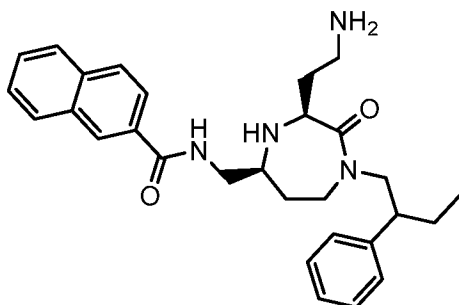
**22**

(3*S*,5*S*)-3-(2-*tert*-butoxycarbonylaminoethyl)-5-(aminomethyl)-1-(2-phenylbutyl)-1,4-diazepan-2-one

- 15 To the cyclised product **21** (0.11 g) in methanol (5 mL) was added catalytic Pd/C. The reaction was stirred under a hydrogen atmosphere overnight. The reaction mixture was

filtered through Celite and the methanol removed by rotary evaporation to give the amine **22** as a mixture of diastereomers (0.11 g, 100%).

Example 25 – Synthesis of Compound 101 (3*S*,5*S*)-3-(2-aminoethyl)-5-(*N*-2-naphthamidomethyl)-1-(2-phenylbutyl)-1,4-diazepan-2-one

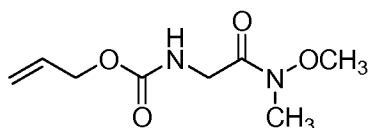


101

(3*S*,5*S*)-3-(2-aminoethyl)-5-(2-naphthamidomethyl)-1-(2-phenylbutyl)-1,4-diazepan-2-one

To the amine **22** (0.02 mg, 0.05 mmol) in DCM (1mL) was added DIPEA (0.1 mL, 0.7 mmol), BOP reagent (0.02 mg, 0.045 mmol) and 2-naphthoic acid (0.015 mg, 0.09 mmol). The reaction was stirred at room temperature for 2 hrs. TFA (1 mL) was added and the reaction stirred at room temperature for 2 hrs. Rotary evaporation and preparative HPLC gave **101** as a mixture of diastereomers (13.4 mg, 57%). **MS (ESI)** 473.4 (M+1); HPLC *t_R* 5.59 min

Example 26 – Synthesis of Compound 23 allyl 2-(methoxy(methyl)amino)-2-oxoethylcarbamate



23

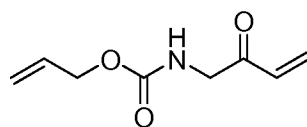
allyl 2-(methoxy(methyl)-amino)-2-oxoethylcarbamate

To Alloc-glycine (1.45 g, 9.1 mmol) in DCM (20 mL) was added BOP reagent (3.3 g, 7.46 mmol) and DIPEA (1.5 mL, 10.7 mmol). After stirring at room temperature for 10 mins, N,O-dimethylhydroxylamine hydrochloride (0.8 g, 8.2 mmol) and DIPEA (1.5 mL, 10.7 mmol) were added. The reaction was stirred at room temperature overnight. The DCM was removed by rotary evaporation and the residue taken up in EtOAc (100 mL). The organic phase was washed with H₂O (3x 100 mL), saturated sodium bicarbonate solution (3x 50 mL), H₂O (3x 50 mL), 1M HCl (3x 50 mL), brine (3x 50 mL). The organic phase was dried

(MgSO₄) and the EtOAc removed to give the Weinreb amide **23** as a white solid (0.43 g, 23%).

Alternatively, *tert*-butyl 2-(methoxy(methyl)amino)-2-oxoethylcarbamate **34** (Boc-Gly Weinreb amide, 1.4 g, 6.4 mmol) in DCM (5 mL) and TFA (3 mL) were stirred at room temperature 1 hr. The solvent was removed under reduced pressure, followed by addition of DCM (20 mL) and then DIPEA until basic. The solution of 2-amino-*N*-methoxy-*N*-methylacetamide (Gly Weinreb amide) was cooled to 0° C and allyl chloroformate added (1.4 mL, 13.2 mmol). The reaction was stirred at room temperature overnight. The reaction mixture was neutralised with 1M HCl and extracted with EtOAc. The EtOAc was removed by rotary evaporation and the residue was subjected to column chromatography on silica gel using petroleum spirit:EtOAc (1:1 to 0:1), providing **23** (0.86 g, 66%).

Example 27 – Synthesis of Compound 24 allyl 2-oxobut-3-enylcarbamate



24

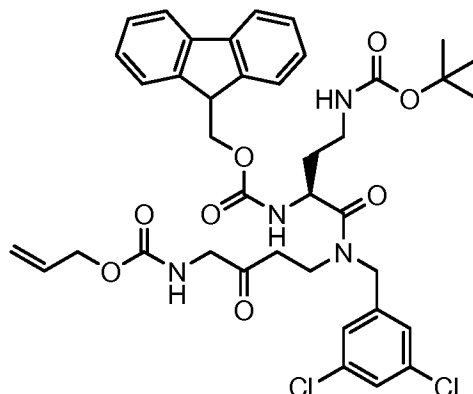
allyl 2-oxobut-3-enylcarbamate

15

To the Weinreb amide **23** (0.43 g, 2.1 mmol) in DCM (5 mL) at 0° C was added vinyl magnesium bromide (10 mmol) in THF (10 mL). The reaction was stirred for 2 hrs and monitored by HPLC. The reaction was added to a mixture of ice and 1M HCl (100 mL). The aqueous mixture was extracted with DCM (3x 50 mL) and washed with 1M HCl (2x 100 mL) and H₂O (3x 50 mL). The organic phase was dried (MgSO₄) and the volume reduced to 50 mL by rotary evaporation. The α,β -unsaturated ketone **24** was stored and used in solution without further purification.

20

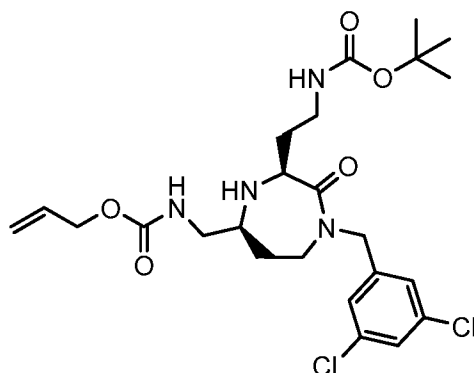
Example 28 – Synthesis of Compound 25 (*S*)-9-fluorenylmethyl 10-(3,5-dichlorobenzyl)-2,2-dimethyl-4,9,13,16-tetraoxo-3,17-dioxa-5,10,15-triazaiscos-19-en-8-ylcarbamate

**25**

(*S*)-9-fluorenylmethyl 10-(3,5-dichlorobenzyl)-2,2-dimethyl-4,9,13,16-tetraoxo-3,17-dioxa-5,10,15-triazaiscos-19-en-8-ylcarbamate

To 3,5-dichlorobenzylamine (0.49 g, 2.8 mmol) in DCM (5 mL) was added the α,β -unsaturated ketone **24** (2.12 mmol) in DCM (10 mL). After stirring at room temperature for 15 mins, Fmoc-diaminobutyric acid(Boc)-OH (1.35 g, 3.1 mmol) and DIC (0.5 mL, 3.2 mmol) was added. The reaction was stirred at room temperature overnight. The DCM was removed by rotary evaporation and the residue was subjected to column chromatography on silica gel using petroleum spirit:EtOAc (1:1 to 0:1), providing compound **25** (0.48 g, 22%).

Example 29 – Synthesis of Compound 26 (3*S*,5*S*)-3-(2-*tert*-butoxycarbonylaminoethyl)-5-(allyloxycarbonylaminomethyl)-1-(3,5-dichlorobenzyl)-1,4-diazepan-2-one

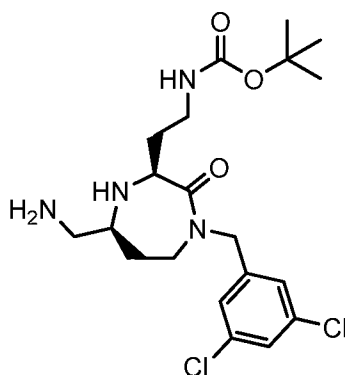
**26**

(3*S*,5*S*)-3-(2-*tert*-butoxycarbonylaminoethyl)-5-(allyloxycarbonylaminomethyl)-1-(3,5-dichlorobenzyl)-1,4-diazepan-2-one

To Compound **25** (0.48 g, 0.63 mmol) in DCM (3 mL) was added diethylamine (1.5 mL). The reaction was stirred at room temperature for 1hr. The DCM and diethylamine was removed by rotary evaporation. DCM (5 mL), sodium triacetoxyborohydride (0.2 g, 0.94

mmol) was added, and the reaction was stirred overnight at room temperature. The organic phase was washed with saturated sodium bicarbonate solution (25 mL), dried (MgSO₄) and the DCM removed to give the cyclised product **26** (0.24 g, 72%).

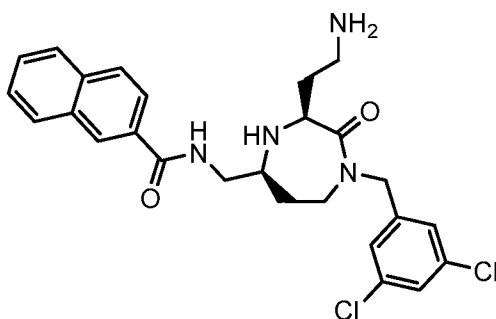
5 **Example 30 – Synthesis of Compound 27 (3*S*,5*S*)-3-(2-*tert*-butoxycarbonylaminoethyl)-5-aminomethyl-1-(3,5-dichlorobenzyl)-1,4-diazepan-2-one**

**27**

(3*S*,5*S*)-3-(2-*tert*-butoxycarbonylaminoethyl)-5-aminomethyl-1-(3,5-dichlorobenzyl)-1,4-diazepan-2-one

To the cyclised product **26** (0.24 g, 0.45 mmol) in DCM (3 mL) was added 1,3-dimethylbarbituric acid (13 mg, 0.08 mmol) and palladium tetrakis triphenylphosphine (5 mg). The reaction was evacuated and stirred at room temperature for 1 hr. The DCM was removed under reduced pressure to give the crude product **27** (0.15 g, 75%) which was used in the next reaction without purification.

15 **Example 31 – Synthesis of Compound 102 (3*S*,5*S*)-3-(2-aminoethyl)-5-(2-naphthoylaminoethyl)-1-(3,5-dichlorobenzyl)-1,4-diazepan-2-one**

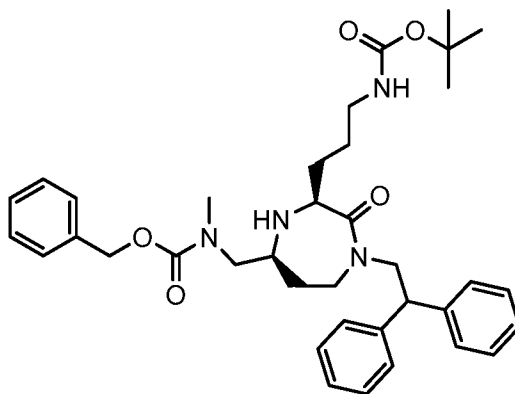
**102**

(3*S*,5*S*)-3-(2-aminoethyl)-5-(2-naphthoylaminoethyl)-1-(3,5-dichlorobenzyl)-1,4-diazepan-2-one

To the amine **27** (0.05 mg, 0.11 mmol) in DCM (1 mL) was added DIPEA (0.1 mL, 0.7 mmol), BOP reagent (0.05 mg, 0.11 mmol) and 2-naphthoic acid (0.04 mg, 0.23 mmol). The

reaction was stirred at room temperature for 2 hrs. TFA (1 mL) was added and the reaction stirred at room temperature for 2 hrs. Rotary evaporation and preparative HPLC gave **102** (48 mg, 90%). **MS (ESI)** 499.3 (M+1); HPLC t_R 5.77 min

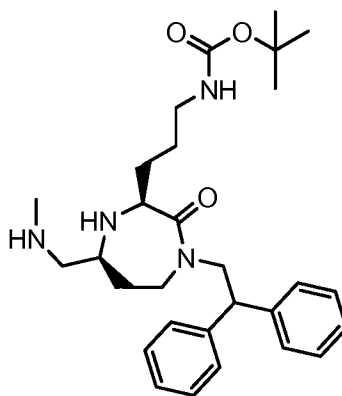
5 **Example 32** – Synthesis of Compound 28 (3*S*,5*S*)-3-(2-*tert*-butoxycarbonylamino)propyl)-5-[benzyloxycarbonyl(methylamino)methyl]-1-(2,2-diphenylethyl)-1,4-diazepan-2-one

**28**

(3*S*,5*S*)-3-(2-*tert*-butoxycarbonylamino)propyl)-
5-[benzyloxycarbonyl(methylamino)methyl]-
1-(2,2-diphenylethyl)-1,4-diazepan-2-one

Prepared from Cbz-Sar, 2,2-diphenylethylamine and Fmoc-L-Orn(Boc) according to
10 the procedures of Examples 15-18.

Example 33 – Synthesis of Compound 29 (3*S*,5*S*)-3-(2-*tert*-butoxycarbonylamino)propyl)-5-(methylamino)methyl-1-(2,2-diphenylethyl)-1,4-diazepan-2-one

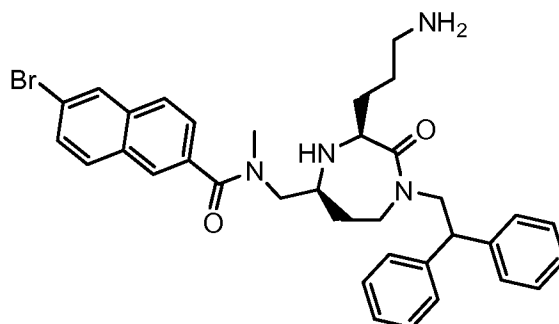
**29**

(3*S*,5*S*)-3-(2-*tert*-butoxycarbonylamino)propyl)-
5-(methylamino)methyl-
1-(2,2-diphenylethyl)-1,4-diazepan-2-one

The cyclised product **28** (1.9 g) was dissolved in methanol (10 mL) with catalytic Pd/C and hydrogenated under a hydrogen atmosphere (40 psi) overnight. The reaction mixture was filtered through Celite and the methanol removed by rotary evaporation to give the amine **29** (1.86 g, 97%).

5

Example 34– Synthesis of Compound 103 N-(((3*S*,5*S*)-3-(3-aminopropyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-6-bromo-N-methyl-2-naphthamide

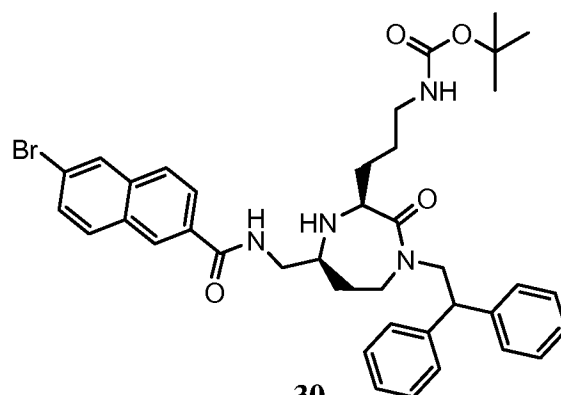
**103**

N-(((3*S*,5*S*)-3-(3-aminopropyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-6-bromo-*N*-methyl-2-naphthamide

The amine **29** was coupled with 6-bromo-2-naphthoic acid then deprotected with TFA according to Example 20. Rotary evaporation and preparative HPLC gave **103** (7.8 mg). **MS** (ESI) 629.4 (M+1); HPLC *t_R* 6.27 min.

10

Example 35 – Synthesis of Compound 30 (3*S*,5*S*)-3-(*tert*-butoxycarbonylaminopropyl)-5-(6-bromo-2-naphthamidomethyl)-1-(2,2-diphenylethyl)-1,4-diazepan-2-one

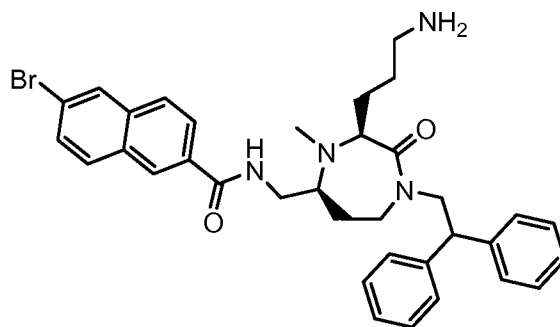
**30**

(3*S*,5*S*)-3-(*tert*-butoxycarbonylaminopropyl)-5-(6-bromo-2-naphthamidomethyl)-1-(2,2-diphenylethyl)-1,4-diazepan-2-one

15

Prepared from 2,2-diphenylethylamine, Fmoc-L-Orn(Boc) and 6-bromo-2-naphthoic acid according to the procedures of Examples 17-20, without the TFA deprotection step of Example 20.

Example 36 – Synthesis of Compound 104 *N*-(((3*S*,5*S*)-3-(3-aminopropyl)-1-(2,2-diphenylethyl)-4-methyl-2-oxo-1,4-diazepan-5-yl)methyl)-6-bromo-2-naphthamide

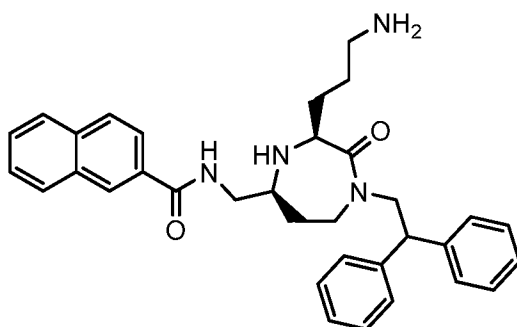


104

N-(((3*S*,5*S*)-3-(3-aminopropyl)-1-(2,2-diphenylethyl)-4-methyl-2-oxo-1,4-diazepan-5-yl)methyl)-6-bromo-2-naphthamide

- 5 Compound **30** (20.8 mg) was dissolved in DMF (1 mL) and treated with methyl iodide (6 μ L) at room temperature for 1 week. Additional methyl iodide (0.5 mL) and K_2CO_3 were added and the reaction left at room temperature for an additional 2 days. TFA (2 mL) was added and the reaction stirred at room temperature for 2h. Rotary evaporation followed by evaporation under high vacuum then preparative HPLC gave **104** (8.5 mg). **MS (ESI)** 629.3 (M+1); HPLC t_R 6.22 min.
- 10

Example 37 - Synthesis of Compound 31 *N*-(((3*S*,5*S*)-3-(3-aminopropyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide

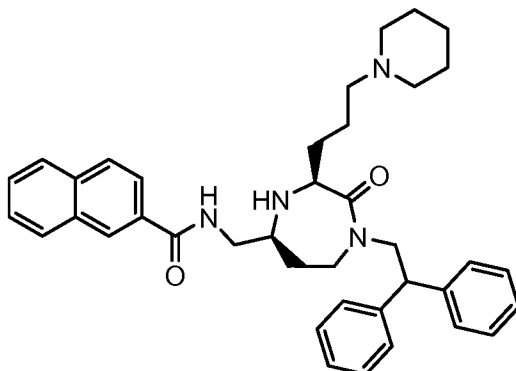


31

N-(((3*S*,5*S*)-3-(3-aminopropyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide

- 15 Obtained from **9**, 2,2-diphenylethylamine and Fmoc-L-Orn(Boc) according to Examples 10-13. The Boc group was removed under standard conditions to give the free amine. **MS(ESI)** 535 (M+1); HPLC t_R 5.78 min

Example 38 - Synthesis of Compound **32** *N*-(((3*S*,5*S*)-1-(2,2-diphenylethyl)-2-oxo-3-(3-(piperidin-1-yl)propyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide

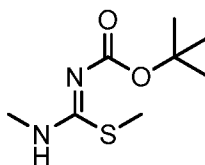
**32**

N-(((3*S*,5*S*)-1-(2,2-diphenylethyl)-2-oxo-3-(3-(piperidin-1-yl)propyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide

5 The amine **31** (0.79 g, 1.48 mmol), 1,5-dibromopentane (0.2 mL, 1.48 mmol) and K_2CO_3 (0.79 g) in DMF (11 mL) was stirred at room temperature for 4 h. The resulting mixture was diluted with ethylacetate (30 mL), washed with H_2O (5 x 30 mL), brine (10 mL) and dried over $MgSO_4$. Purification by preparative HPLC yielded **32** (0.23 g, 25%) **MS(ESI)** 603.3 ($M+1$); HPLC t_R 6.04 min

10

Example 39 - Synthesis of Compound **33** *tert*-butyl (methylamino)(methylthio)methylenecarbamate

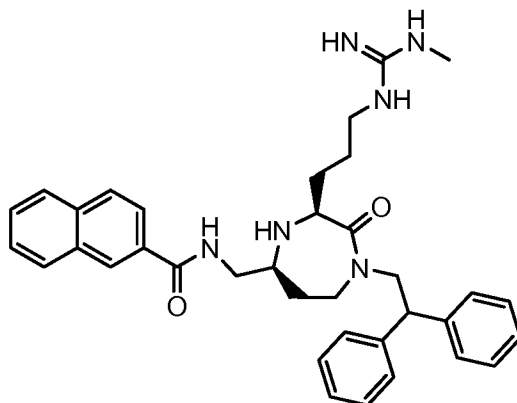
**33**

tert-butyl (methylamino)(methylthio)-methylenecarbamate

15 DIAD (2.7 mL, 13.8 mmol) was added to a stirred mixture of thiopseudourea (2.0 g, 6.9 mmol), PPh_3 (3.6g, 13.8 mmol), and MeOH (0.55 mL, 13.8 mmol) in dry THF (5 mL) at $0^\circ C$ under nitrogen. Stirring continued at $0^\circ C$ for 3 h then at room temperature for 16 h. The solvent was removed under reduced pressure and the resulting residue was re-dissolved in EtOAc, washed with saturated aqueous $NaHCO_3$ solution (20 mL) and brine (20 mL), and dried over $MgSO_4$. Purification by silica gel chromatography using 20% EtOAc in petroleum ether as eluent gave **33** (1.63 g, 78%) as a colourless oil. **MS(ESI)** 305 ($M+1$); HPLC t_R 7.97 min.

20

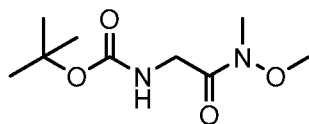
Example 40 - Synthesis of Compound 105 *N*-(((3*S*,5*S*)-1-(2,2-diphenylethyl)-3-(3-(3-methylguanidino)propyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide

**105**

N-(((3*S*,5*S*)-1-(2,2-diphenylethyl)-3-(3-(3-methylguanidino)propyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide

A mixture of Compound **31** (10 mg, 0.019 mmol), guanylation agent **33** (56.9 mg, 0.19 mmol) and DIPEA (6.6 μ L, 0.038 mmol) in DCM (5 mL) was stirred at room temperature for 16 h. TFA (5 mL) was added, and the resulting mixture was stirred at room temperature for 30 min. Solvent was removed under reduced pressure, and the crude product was purified by preparative HPLC to give **105** (0.53 mg, 4.7%) as a white solid. **MS(ESI)** 591.3 ($M+1$); HPLC t_R 5.94 min

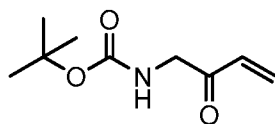
Example 41 - Synthesis of Compound 34 *tert*-butyl 2-(methoxy(methyl)amino)-2-oxoethylcarbamate (Boc-Gly Weinreb amide)

**34**

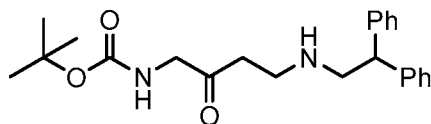
tert-butyl 2-(methoxy(methyl)amino)-2-oxoethylcarbamate

To a stirred mixture of Boc-Gly-OH (20 g, 114.1 mmol), DIPEA (19.8 mL, 114.1 mmol) and BOP (50.5 g, 114.1 mmol) in DCM (20 mL) was added a pre-mixed solution of *N,O*-dimethylhydroxylamine hydrochloride (11.2 g, 114.1 mmol) and DIPEA (19.8 mL, 114.1 mmol) in DCM (20 mL) at room temperature. The resulting mixture was stirred for 16 h then washed with 1N HCl (3 x 120 mL), H₂O (3 x 120 mL), saturated NaHCO₃ aqueous solution (3 x 120 mL) and brine (40 mL), dried over MgSO₄, filtered and concentrated under reduced pressure to give **34** as a white solid (20 g, 80%), which was used in the next step without further purification.

MS(ESI) 219 ($M+1$); HPLC t_R 4.12 min.

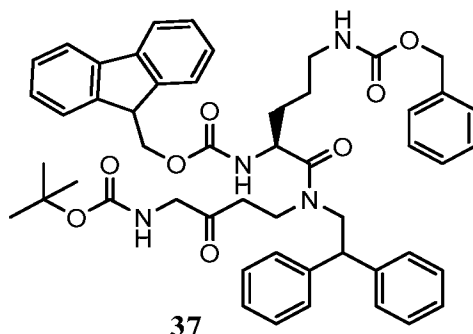
Example 42 – Synthesis of Compound 35 tert-butyl 2-oxobut-3-enylcarbamate**35***tert*-butyl 2-oxobut-3-enylcarbamate

At 0°C a solution of vinylmagnesium bromide in THF (184 mL, 1 M) was added in one portion to Weinreb amide **34** (20 g, 91.6 mmol) under nitrogen with stirring. The resulting mixture was allowed to stir for 2 h, and poured into a 1N HCl/ice mixture (400 mL). The aqueous mixture was extracted with DCM (5 x 100 mL), the combined DCM extract was washed with 1N HCl (2 x 100 mL), saturated NaHCO₃ aqueous solution (100 mL) and brine (100 mL), then dried over MgSO₄. Solvent was removed under reduced pressure gave the ketone **35** (12.9 g, 76%) as a pale yellow oil, which was used in the next step without further purification. **MS(ESI)** 186 (M+1); HPLC *t_R* 4.19 min.

Example 43 – Synthesis of Compound 36 tert-butyl 4-(2,2-diphenylethylamino)-2-oxobutylcarbamate**36***tert*-butyl 4-(2,2-diphenylethylamino)-2-oxobutylcarbamate

To a stirred solution of 2,2-diphenylethylamine (0.33 g, 1.66 mmol) in DCM (10 mL) was added α,β -unsaturated ketone **35** (0.31 g, 1.66 mmol) at room temperature. Stirring continued for 2 h; the crude reaction mixture of **36** was used in the next step without purification. **MS(ESI)** 383 (M+1); HPLC *t_R* 5.98 min

Example 44 - Synthesis of Compound 37 (S)-9-fluorenylmethyl 1-phenyl-10-(2,2-diphenylethyl)-18,18-dimethyl-4,9,13,16-tetraoxo-2,17-dioxa-4,10,15-triazanonadecan-8-ylcarbamate

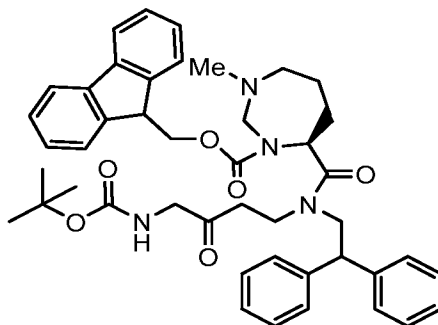


37

(S)-9-fluorenylmethyl 1-phenyl-10-(2,2-diphenylethyl)-18,18-dimethyl-4,9,13,16-tetraoxo-2,17-dioxa-4,10,15-triazanonadecan-8-ylcarbamate

- 5 To a stirred mixture of Fmoc-L-Orn(Cbz)-OH (1.78 g, 3.65 mmol), DIPEA (0.64 mL, 3.65 mmol) and HATU (1.39 g, 3.65 mmol) in DCM (10 mL) was added a solution of amine **36** at room temperature. Stirring continued for 3 h, the reaction mixture was washed with saturated NaHCO₃ aqueous solution (20 mL) and brine (20 mL), and dried over MgSO₄. The solvent was removed under reduced pressure, with the crude **37** used in the next step without
10 further purification. **MS(ESI)** 853 (M+1); HPLC *t_R* 9.90 min.

Example 45 - Synthesis of Compound 38 (S)-(9H-fluoren-9-yl)methyl 7-((4-(tert-butoxycarbonylamino)-3-oxobutyl)(2,2-diphenylethyl)carbamoyl)-3-methyl-1,3-diazepane-1-carboxylate



38

(S)-(9H-fluoren-9-yl)methyl 7-((4-(tert-butoxycarbonylamino)-3-oxobutyl)(2,2-diphenylethyl)carbamoyl)-3-methyl-1,3-diazepane-1-carboxylate

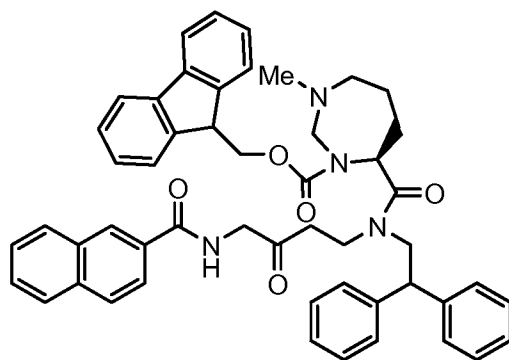
15

A mixture of **37** (136 mg, 0.159 mmol) and Pd/C (20 mg) in ethanol (5 mL) was shaken under H₂ at 30 psi for 16 h, then filtered, concentrated under reduced pressure to give the crude amine (90 mg, 78%). The amine (90 mg, 0.125 mmol) was treated with excess

formaldehyde solution in H₂O (37 mmol) in MeOH (5 mL) followed by sodium triacetoxyborohydride (23.5 mg, 0.375 mmol). After 1 h, the reaction mixture was washed with saturated NaHCO₃ aqueous solution (10 mL) and brine (10 mL), dried over MgSO₄, filtered and concentrated. The crude material was used in the next step without further purification.

5 **MS(ESI)** 745 (M+1); HPLC ; HPLC *t_R* 7.83 min.

Example 46 - Synthesis of Compound 39 (S)-(9H-fluoren-9-yl)methyl 7-((4-(2-naphthamido)-3-oxobutyl)(2,2-diphenylethyl)-carbamoyl)-3-methyl-1,3-diazepane-1-carboxylate



39

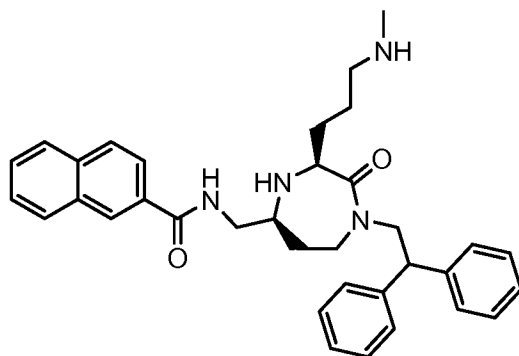
(S)-(9H-fluoren-9-yl)methyl 7-((4-(2-naphthamido)-3-oxobutyl)(2,2-diphenylethyl)carbamoyl)-3-methyl-1,3-diazepane-1-carboxylate

10

Compound **38** (8 mg, 0.011 mmol) was treated with 1:1 v/v trifluoacetic acid/DCM mixture (2 mL) for 30 min at room temperature. The mixture was concentrated under reduced pressure, re-dissolved in DCM (5 mL), washed with saturated NaHCO₃ aqueous solution (5 mL) and brine (5 mL), dried over MgSO₄ and filtered. The filtrate was then treated with a mixture of 2-naphthoic acid (1.8 mg, 0.011 mmol), DIPEA (5.7 μL, 0.033 mmol) and BOP (4.8 mg, 0.011 mmol) in DCM (1 mL) with stirring at room temperature. After 3 h, the reaction mixture was washed with saturated NaHCO₃ aqueous solution (10 mL) and brine (10 mL), dried over MgSO₄, filtered and concentrated. The crude material was used in the next step without further purification. **MS(ESI)** 799 (M+1); HPLC *t_R* 7.90 min.

20

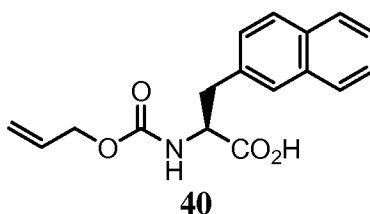
Example 47 - Synthesis of Compound 106 *N*-(((3*S*,5*S*)-1-(2,2-diphenylethyl)-3-(3-(methylamino)propyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide

**106**

N-(((3*S*,5*S*)-1-(2,2-diphenylethyl)-3-(3-(methylamino)propyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide

To a stirred solution of **39** (0.011 mmol) in DCM (5 mL) was added diethylamine (5 mL) at room temperature. The reaction was stirred for 1 h, then concentrated under reduced pressure. The residue was re-dissolved in DCM (5 mL) followed by addition sodium triacetoxyborohydride (5 mg, 0.08 mmol) at room temperature. Stirring continued for 1 h, with the resulting mixture washed with saturated NaHCO₃ aqueous solution (10 mL) and brine (10 mL), dried over MgSO₄, filtered and concentrated. Purification by preparative HPLC yielded **106** (0.21 mg) as a white solid. **MS(ESI)** 549.3 (M+1); HPLC *t_R* 5.93 min

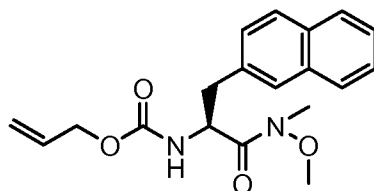
Example 48 - Synthesis of Compound 40 (*S*)-2-(allyloxycarbonylamino)-3-(naphthalen-2-yl)propanoic acid

**40**

((*S*)-2-(allyloxycarbonylamino)-3-(naphthalen-2-yl)propanoic acid

To a stirred mixture of L-3-(2-naphthyl)alanine hydrochloride (5.0 g, 19.8 mmol), Na₂CO₃ (7.3 g, 69.3 mmol) and 1,4-dioxane (30 mL) in H₂O (50 mL) was added allylchloroformate (2.1 mL, 19.8 mmol) at 0°C. The resulting mixture was stirred for 16 h then concentrated under reduced pressure. The residue was diluted with ethylacetate (50 mL), and at 0°C acidified to pH 2. The aqueous phase was extracted with ethylacetate (3 x 20 mL), the combined organic phase was washed with H₂O (50 mL) and brine (20 mL), dried over MgSO₄, filtered and concentrated under reduced pressure to give **40** as a colourless oil (5.8 g, 97%), which was used in the next step without further purification. HPLC *t_R* 6.60 min.

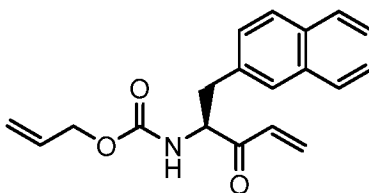
Example 49 - Synthesis of Compound 41 (*S*)-allyl 1-(methoxy(methyl)amino)-3-(naphthalen-2-yl)-1-oxopropan-2-ylcarbamate

**41**

(*S*)-allyl 1-(methoxy(methyl)amino)-3-(naphthalen-2-yl)-1-oxopropan-2-ylcarbamate

To a stirred mixture of the acid **40** (5.84 g, 19.5 mmol), DIPEA (3.7 mL, 2.09 mmol) and BOP (8.63 g, 19.5 mmol) in DCM (10 mL) was added a pre-mixed solution of *N,O*-dimethylhydroxylamine hydrochloride (1.9 g, 19.5 mmol) and DIPEA (7.3 mL, 41.6 mmol) in DCM (10 mL) at room temperature. Stirring continued for 16 h the reaction mixture was washed with 1N HCl (3 x 60 mL), H₂O (3 x 60 mL), saturated NaHCO₃ aqueous solution (3 x 60 mL) and brine (60 mL), dried over MgSO₄. Purification by silica gel chromatography using 20% ethylacetate in petroleum ether as eluent gave **41** (4.83 g, 71%) as a colourless oil. **MS (ESI)** 343 (M+1); HPLC *t_R* 7.07 min.

Example 50 - Synthesis of Compound 42 (*S*)-allyl 1-(naphthalen-2-yl)-3-oxopent-4-en-2-ylcarbamate

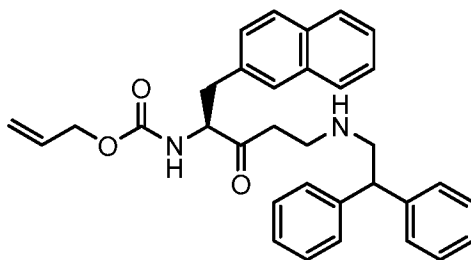
**42**

(*S*)-allyl 1-(naphthalen-2-yl)-3-oxopent-4-en-2-ylcarbamate

15

At 0° C a solution of vinylmagnesium bromide in THF (11.5 mL, 1 M) was added in one portion to Weinreb amide **41** (1.58 g, 4.62 mmol) under nitrogen with stirring. The resulting mixture was allowed to stir for 2 h, and poured into a 1N HCl/ice mixture (50 mL). The aqueous mixture was extracted with DCM (3x 20 mL), the combined DCM extract was washed with 1N HCl (50 mL), saturated NaHCO₃ aqueous solution (50 mL) and brine (20 mL), dried over MgSO₄. Solvent was removed under reduced pressure producing the product **42** (1.14 g, 80%), which was used in the next step without further purification. **MS(ESI)** 310 (M+1); HPLC *t_R* 7.51 min.

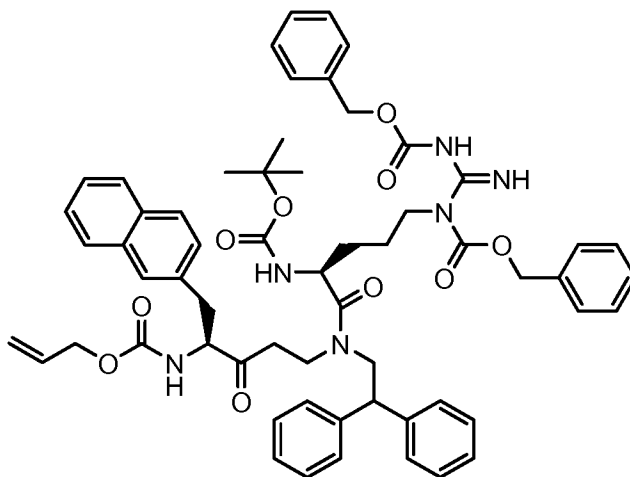
Example 51 - Synthesis of Compound 43 (S)-allyl 5-(2,2-diphenylethylamino)-1-(naphthalen-2-yl)-3-oxopentan-2-ylcarbamate

**43**

(S)-allyl 5-(2,2-diphenylethylamino)-1-(naphthalen-2-yl)-3-oxopentan-2-ylcarbamate

To a stirred solution of 2,2-diphenylethylamine (0.45 g, 2.3 mmol) in DCM (55 mL) was added the vinyl ketone **42** (0.71 g, 2.3 mmol) in one portion. Stirring continued for 2 h, with the reaction mixture used in the next step without purification. **MS(ESI)** 507 (M+1); HPLC t_R 7.22 min.

Example 52 - Synthesis of Compound 44 (S)-allyl 5-(N-(Boc-L-Arg(Cbz)₂) 2,2-diphenylethylamino)-1-(naphthalen-2-yl)-3-oxopentan-2-ylcarbamate

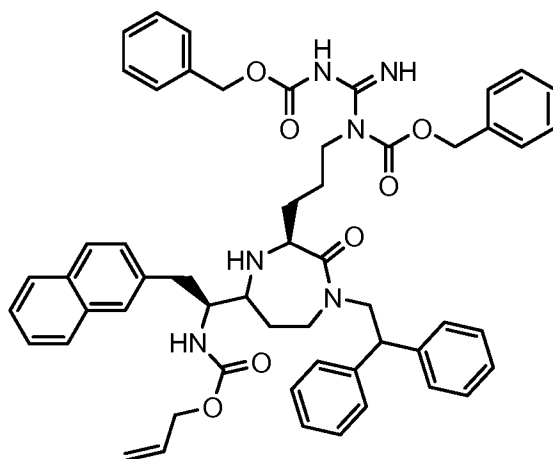
**44**

(S)-allyl 5-(N-(Boc-L-Arg(Cbz)₂) 2,2-diphenylethylamino)-1-(naphthalen-2-yl)-3-oxopentan-2-ylcarbamate

To a stirred solution of the amine adduct **43** (2.3 mmol) was added a mixture of Boc-Arg(Cbz)₂-OH (1.25 g, 2.3 mmol), DIPEA (0.8 mL, 4.6 mmol) and HATU (0.87 g, 2.3 mmol) in DCM (15 mL) at room temperature. Stirring continued for 16 h, after which the reaction mixture was washed with saturated NaHCO₃ aqueous solution (3x 20 mL) and brine (10 mL) then dried over MgSO₄. Purification by silica gel chromatography using 20% ethylacetate in

petroleum ether as eluent gave **44** as a colourless oil (708 mg, 30% over 3 steps). **MS(ESI)** 1031 (M+1); HPLC t_R 10.80 min.

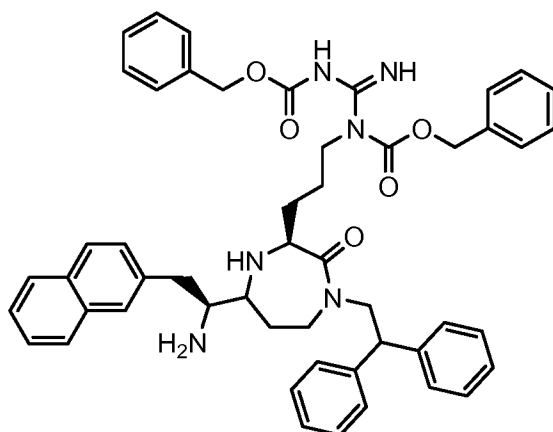
Example 53 - Synthesis of Compound 45 allyl (S)-1-((3S,5RS)-1-(2,2-diphenylethyl)-3-(bis Cbz 3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)-2-(naphthalen-2-yl)ethylcarbamate

**45**

allyl (S)-1-((3S,5RS)-1-(2,2-diphenylethyl)-3-(bis Cbz 3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)-2-(naphthalen-2-yl)ethylcarbamate

To a stirred solution of acyclic intermediate **44** (0.48 g, 0.47 mmol) in DCM (5 mL) was added TFA (5 mL) at room temperature. Stirring continued for 30 min, after which the mixture was diluted with DCM (20 mL) then washed with saturated NaHCO₃ aqueous solution (3 x 20 mL) and brine (10 mL), and dried over MgSO₄. To the resulting solution was added sodium triacetoxyborohydride (0.2 g, 0.94 mmol) with stirring at room temperature, after 30 min the mixture was washed with saturated NaHCO₃ aqueous solution (3 x 20 mL) and brine (10 mL), then dried over MgSO₄. The crude **45**, a mixture of diastereomers at the diazepan-2-one C5, was used in the next step without further purification. **MS(ESI)** 915 (M+1)

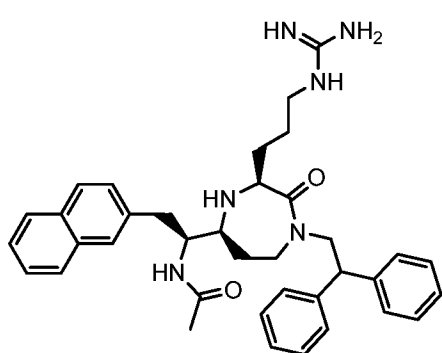
Example 54 - Synthesis of Compound **46** bis (Cbz) 1-(3-((2*S*,7*RS*)-7-((*S*)-1-amino-2-(naphthalen-2-yl)ethyl)-4-(2,2-diphenylethyl)-3-oxo-1,4-diazepan-2-yl)propyl)guanidine

**46**

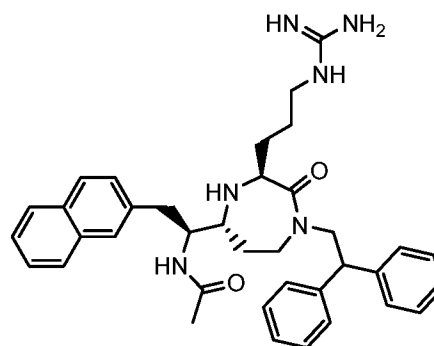
bis (Cbz) 1-(3-((2*S*,7*RS*)-7-((*S*)-1-amino-2-(naphthalen-2-yl)ethyl)-4-(2,2-diphenylethyl)-3-oxo-1,4-diazepan-2-yl)propyl)guanidine

A mixture of compound **45** (36 mg, 0.039 mmol), 1,3-dimethylbarbituric acid (7.4 mg, 0.047 mmol) and Pd(PPh₃)₄ in DCM (5 mL) was stirred at room temperature under vacuum for 4 h. The resulting mixture was used in the next step without further purification. **MS(ESI)** 832 (M+1)

Example 55 - Synthesis of Compounds **107** and **47** N-((*S*)-1-((3*S*,5*S*)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)-2-(naphthalen-2-yl)ethyl)acetamide and N-((*S*)-1-((3*S*,5*R*)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)-2-(naphthalen-2-yl)ethyl)acetamide

**107**

N-((*S*)-1-((3*S*,5*S*)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)-2-(naphthalen-2-yl)ethyl)acetamide

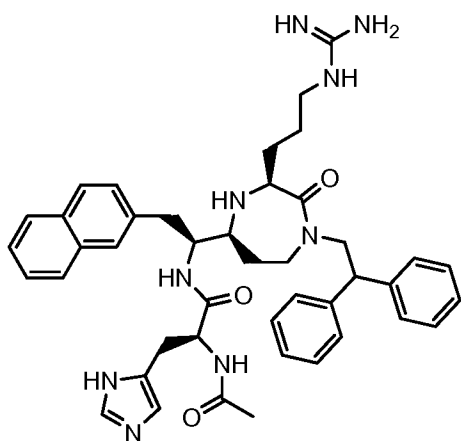
**47**

N-((*S*)-1-((3*S*,5*R*)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)-2-(naphthalen-2-yl)ethyl)acetamide

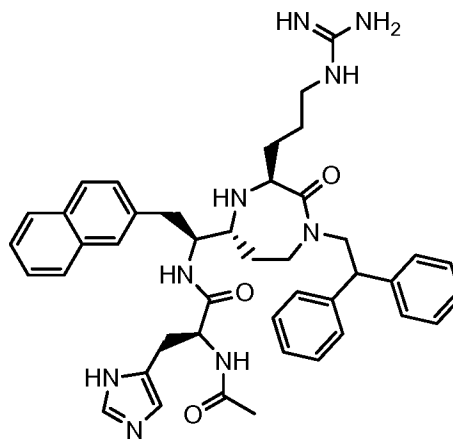
A solution of the amine **46** (0.09 mmol) in DCM (5 mL) was treated with acetic anhydride (8.6 μL, 0.09 mmol) with stirring at room temperature. After 3 h the mixture was

concentrated, re-dissolved in EtOAc, washed with saturated NaHCO₃ aqueous solution (10 mL) and brine (10 mL), dried over MgSO₄, then concentrated under reduced pressure. The residue was dissolved in MeOH (10 mL), Pd/C (5 mg) was added, and the solution shaken under H₂ at 20 psi for 16 h. The reaction was filtered, concentrated and purified by preparative HPLC to give the minor diastereomer **107** (3 mg) and the major diastereomer **47** (6 mg) as white solids. **107**: MS(ESI) 606.4 (M+1); HPLC *t_R* 6.033 min, **47**: MS(ESI) 606.3 (M+1); HPLC *t_R* 6.046 min

Example 56 - Synthesis of Compounds 48 and 49 (S)-2-acetamido-N-((S)-1-((3S,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)-2-(naphthalen-2-yl)ethyl)-3-(1H-imidazol-5-yl)propanamide and (S)-2-acetamido-N-((S)-1-((3S,5R)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)-2-(naphthalen-2-yl)ethyl)-3-(1H-imidazol-5-yl)propanamide



48
(S)-2-acetamido-N-((S)-1-((3S,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)-2-(naphthalen-2-yl)ethyl)-3-(1H-imidazol-5-yl)propanamide

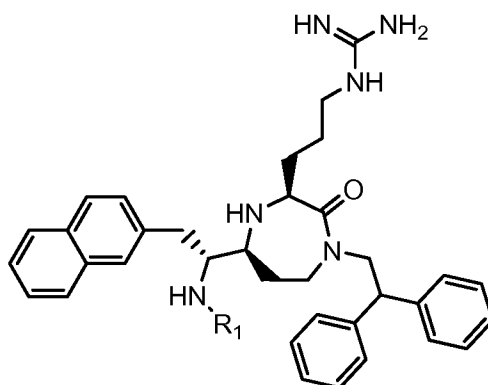


49
(S)-2-acetamido-N-((S)-1-((3S,5R)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)-2-(naphthalen-2-yl)ethyl)-3-(1H-imidazol-5-yl)propanamide

To a stirred mixture of Ac-L-His-OH (33.6 mg, 0.156 mmol), DIPEA (112.5 μL, 0.312 mmol) and BOP (68.8 mg, 0.156 mmol) in DMF (1 mL) was added the amine **46** (0.039 mmol) at room temperature. Stirring continued for 16 h, then the reaction mixture was diluted with DCM/H₂O mixture (10 mL, 1:1 v/v), and the aqueous phase was extracted with DCM (3 x 5 mL). The combined DCM extracts were washed with saturated NaHCO₃ aqueous solution (3 x 20 mL) and brine (10 mL), dried over MgSO₄, and concentrated under reduced pressure. The residue was re-dissolved in MeOH (5 mL), and Pd/C (20 mg) was added. The resulting mixture was shaken under H₂ at 30 psi for 16 h, then was filtered, concentrated and purified by preparative HPLC to give the minor diastereomer **48** (1.9 mg) and the major diastereomer **49** (0.9 mg) as white solids.

48: MS(ESI) 743.4 (M+1); HPLC *t_R* 5.489 min **49**: MS(ESI) 743.4 (M+1); HPLC *t_R* 5.555 min

Example 57 - Synthesis of Compounds 50 and 51 1-(3-((2*S*,7*S*)-7-(*N*-R₁ (*R*)-1-amino-2-(naphthalen-2-yl)ethyl)-4-(2,2-diphenylethyl)-3-oxo-1,4-diazepan-2-yl)propyl)guanidine



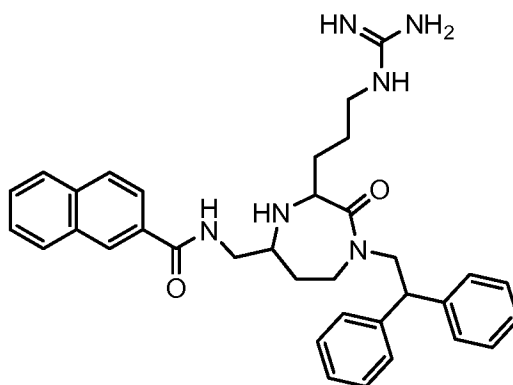
50, 51

1-(3-((2*S*,7*S*)-7-(*N*-R₁ (*R*)-1-amino-2-(naphthalen-2-yl)ethyl)-4-(2,2-diphenylethyl)-3-oxo-1,4-diazepan-2-yl)propyl)guanidine

Compounds **50** and **51** were prepared in the same fashion as Compounds **107** and **48** using the procedures described in Examples 48-56, but with D-(2-naphthyl)alanine hydrochloride as the starting material.

Compound	R ₁ group	MS (M+1)	t _R (min)
50	Ac	606.2	6.01
51	Ac-His	743.5	5.41

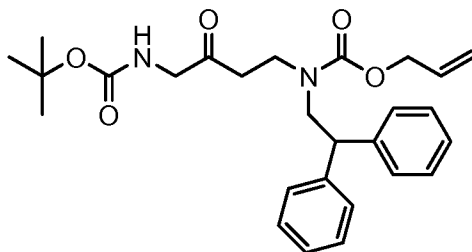
Examples 58-66: Synthesis via Scheme 2: Preparation of all Four Diastereomers of N-((1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide 52



52

N-((1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide

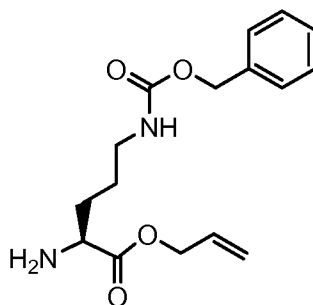
Example 58 – Synthesis of Compound 53 2,2-dimethyl-10-(2,2-diphenylethyl)-4,7,11-trioxo-3,12-dioxo-5,10-diazapentadec-14-ene

**53**

2,2-dimethyl-10-(2,2-diphenylethyl)-4,7,11-trioxo-3,12-dioxo-5,10-diazapentadec-14-ene

2,2-diphenylethylamine (3g) was added to Boc-vinylketone **35** (2.8g) as in Example 43. To the crude adduct **36** was added Alloc-Cl (1.6 mL) and the reaction stirred until TLC indicated consumption of the secondary amine. THE solvent was evaporated and the residue purified by column chromatography (SiO₂ gel, pet. ether/EtOAc) to give 3.2 g (57%) of **53**.

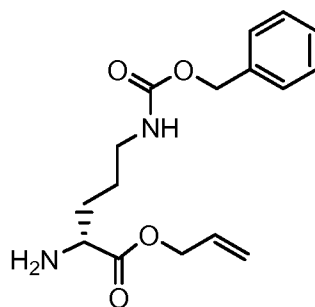
Example 59 – Synthesis of Compound 54 (S)-allyl 2-amino-5-(benzyloxycarbonylamino)pentanoate L-H-Orn(Cbz)-Oallyl

**54**

(S)-allyl 2-amino-5-(benzyloxycarbonylamino)pentanoate

H-L-Orn(Cbz)-OH (6.66g, 25 mmol), allyl alcohol (17.56 mL, 25 mmol) and p-TsOH (5.7g, 30 mmol) were dissolved in benzene (200 mL) and refluxed under Dean-Stark conditions for 5h. The majority of the solvent was then distilled off, with the remainder removed under vacuum. The resulting solid was recrystallized from DCM, filtered and dried to give 11.19g (94%) of the tosylate salt. To obtain the free amine the solid was dissolved in DCM, washed with sat. NaHCO₃, the aqueous layer washed with DCM (3x), and the organic layers dried over MgSO₄ and evaporated to dryness.

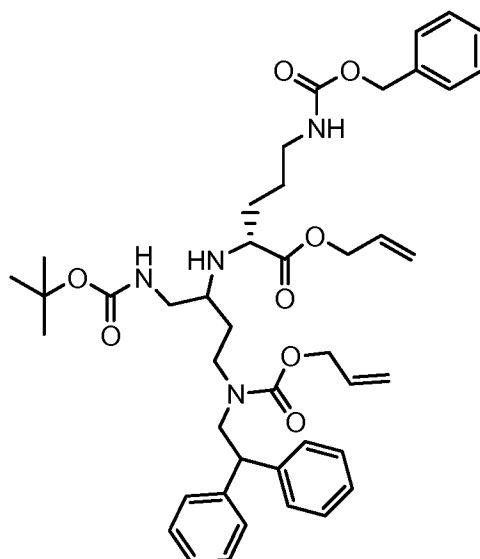
Example 60 – Synthesis of Compound 55 (R)-allyl 2-amino-5-(benzyloxycarbonylamino)pentanoate

**55**

(*R*)-allyl 2-amino-5-(benzyloxycarbonylamino)pentanoate

H-D-Orn(Cbz)-OH (6.66g, 25 mmol) was converted into 10.93 g (91%) of the tosylate salt of **55** as in Example 59, then converted into the free amine.

Example 61 – Synthesis of Compound 56 (2*R*)-allyl 5-(benzyloxycarbonylamino)-2-(10-(2,2-diphenylethyl)-2,2-dimethyl-4,11-dioxo-3,12-dioxo-5,10-diazapentadec-14-en-7-ylamino)pentanoate

**56**

(2*R*)-allyl 5-(benzyloxycarbonylamino)-2-(10-(2,2-diphenylethyl)-2,2-dimethyl-4,11-dioxo-3,12-dioxo-5,10-diazapentadec-14-en-7-ylamino)pentanoate

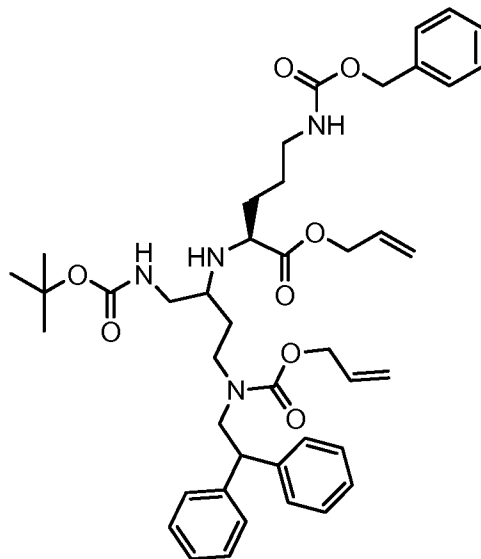
10

The protected aminoketone **53** (746 mg, 1.6 mmol), D-Orn(Cbz)-Oallyl **55** (538 mg, 1.76 mmol) and NaBH(OAc)₃ (678 mg, 3.2 mmol) in a minimum volume of DCM were stirred for 24 h. A drop of AcOH was added just before workup, at which point saturated NaHCO₃ was added, extracted with DCM (3x), and the organic extracts combined and washed with saturated NaHCO₃ and H₂O, dried over MgSO₄, and evaporated to dryness. The product was

15

purified by column chromatography (SiO₂ gel, pet. ether/EtOAc) to give 890 mg (74%) of **56** as a mixture of diastereoisomers.

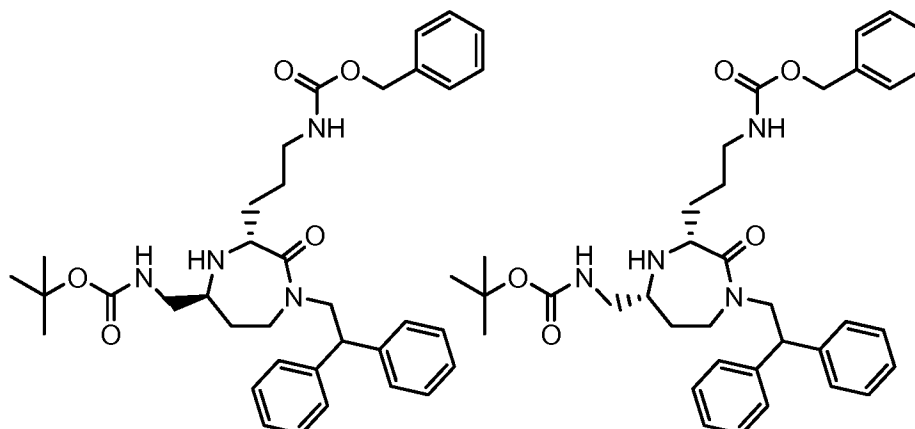
Example 62 – Synthesis of Compound **57** (2*S*)-allyl 5-(benzyloxycarbonylamino)-2-(10-(2,2-diphenylethyl)-2,2-dimethyl-4,11-dioxo-3,12-dioxo-5,10-diazapentadec-14-en-7-ylamino)pentanoate

**57**

(2*S*)-allyl 5-(benzyloxycarbonylamino)-2-(10-(2,2-diphenylethyl)-2,2-dimethyl-4,11-dioxo-3,12-dioxo-5,10-diazapentadec-14-en-7-ylamino)pentanoate

Protected aminoketone **53** and L-Orn(Cbz)-Oallyl **54** (592 mg, 1.93 mmol) were converted into a mixture of the set of diastereomers **57** (925 mg, 76%) following the procedures of Example 61.

Example 63 – Synthesis of Compounds **58** and **59** (3*R*,5*S*)-5-(*N*-Boc aminomethyl)-3-(*N*-Cbz 3-aminopropyl)-1-(2,2-diphenylethyl)-1,4-diazepan-2-one and (3*R*,5*R*)-5-(*N*-Boc aminomethyl)-3-(*N*-Cbz 3-aminopropyl)-1-(2,2-diphenylethyl)-1,4-diazepan-2-one

**58**

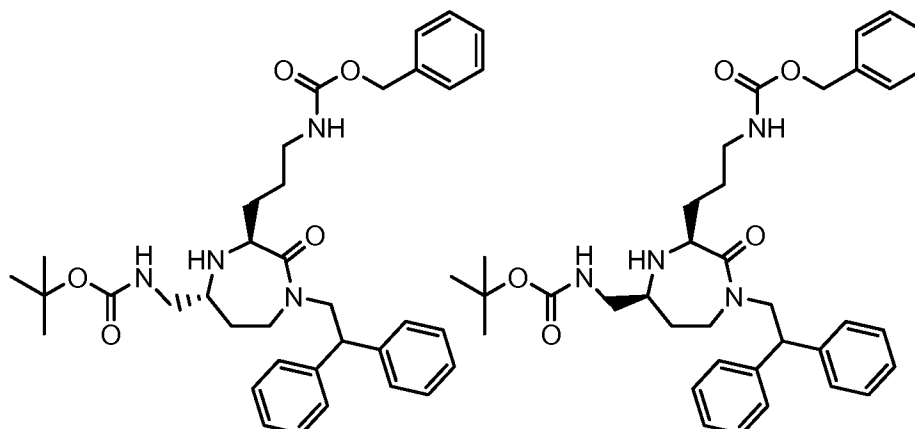
(3*R*,5*S*)-5-(*N*-Boc aminomethyl)-3-(*N*-Cbz 3-aminopropyl)-1-(2,2-diphenylethyl)-1,4-diazepan-2-one

59

(3*R*,5*R*)-5-(*N*-Boc aminomethyl)-3-(*N*-Cbz 3-aminopropyl)-1-(2,2-diphenylethyl)-1,4-diazepan-2-one

- 5 The Alloc/allyl protected derivative **56** (840 mg, 1.11 mmol) was dissolved in a minimum of DCM. 1,3-Dimethylbarbituric acid (346 mg, 2.22 mmol) and catalytic Pd(PPh₃)₄ were added, and the reaction degassed under vacuum, sealed and stirred overnight. The reaction was diluted to 50 mL with DCM, DIPEA (430 mg, 3.33 mmol) and BOP (540 mg, 1.22 mmol) were added, and the reaction stirred for 30 min. The DCM was removed under vacuum and the residue taken up in EtOAc, washed (saturated NaHCO₃, H₂O, saturated NaCl), dried (MgSO₄) and evaporated to dryness (TLC: EtOAc, 2 spots, R_f 0.33 and 0.57).
 10 The two diastomeric products were separated by column chromatography (SiO₂ gel, pet. ether/EtOAc) to give 362 mg of the earlier eluting (3*R*,5*S*) isomer **58**, and 342 mg of the later eluting (3*R*,5*R*) isomer **59**.

Example 64 – Synthesis of Compounds 96 and 97 (3*S*,5*R*)-5-(*N*-Boc aminomethyl)-3-(*N*-Cbz 3-aminopropyl)-1-(2,2-diphenylethyl)-1,4-diazepan-2-one and (3*S*,5*S*)-5-(*N*-Boc aminomethyl)-3-(*N*-Cbz 3-aminopropyl)-1-(2,2-diphenylethyl)-1,4-diazepan-2-one

**60**

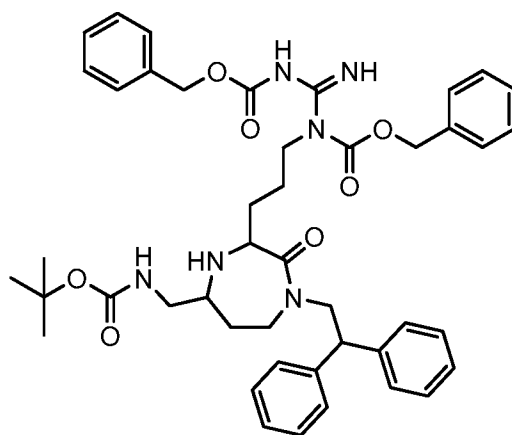
(3*R*,5*S*)-5-(*N*-Boc aminomethyl)-3-(*N*-Cbz 3-aminopropyl)-1-(2,2-diphenylethyl)-1,4-diazepan-2-one

61

(3*R*,5*R*)-5-(*N*-Boc aminomethyl)-3-(*N*-Cbz 3-aminopropyl)-1-(2,2-diphenylethyl)-1,4-diazepan-2-one

5 The (3*S*,5*R*) (312 mg) and (3*S*,5*S*) (331 mg) isomers were obtained from the L-Orn-derived acyclic material **57** (870 mg) following the procedure of Example 63.

Example 65 – Synthesis of Compounds 62-65 5-(*N*-Boc aminomethyl)-3-(*N,N'*-Cbz₂ 3-guanidinopropyl)-1-(2,2-diphenylethyl)-1,4-diazepan-2-one

**62-65**

10

The Orn Cbz group of **58** was removed by hydrogenation (H₂, 30 psi) over catalytic Pd/C in methanol overnight. The solution was filtered through Celite and evaporated to give a solid. A solution of the resulting amine (187 mg, 0.39 mmol) in DCM was mixed with a solution of the guanylating reagent CbzNHC(=NCbz)NHTf (196 mg, 0.43 mmol) in DCM. TEA (43 mg, 0.43 mmol) was added, and the reaction stirred overnight. The solution was diluted with DCM, washed (KHSO₄, sat. NaHCO₃, brine), dried (MgSO₄) and evaporated to dryness,

15

then purified by flash chromatography over SiO₂ using hexanes/EtOAc as eluent, to give (3R,5S) **62** (182 mg, 59%). The other isomers **59-61** were converted in a similar manner to give: **63** (3R,5R): 171mg (68%) from 148 mg of amine, **64** (3S,5S): 80 mg (65%) from 72 mg of amine, **65** (3S,5R): 142 mg (58%) from 144 mg of amine

5

Example 66 – Synthesis of Compounds 66-69

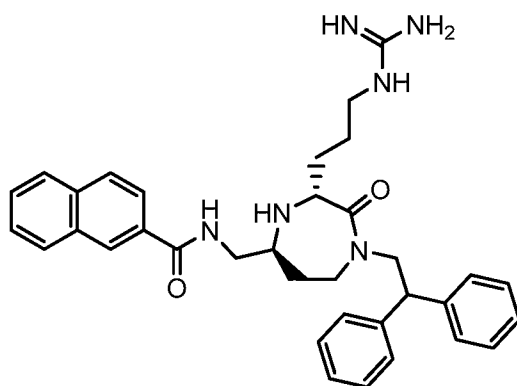
66 N-(((3R,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide

67 N-(((3R,5R)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide

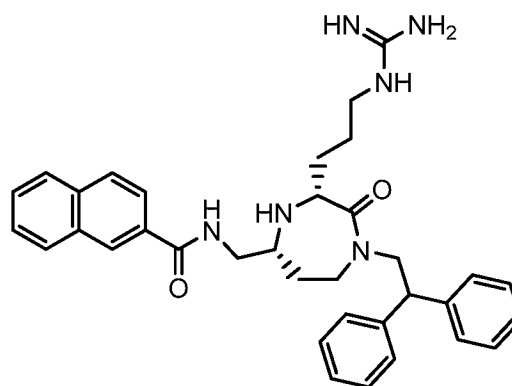
10

68 N-(((3S,5R)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide

69 N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide

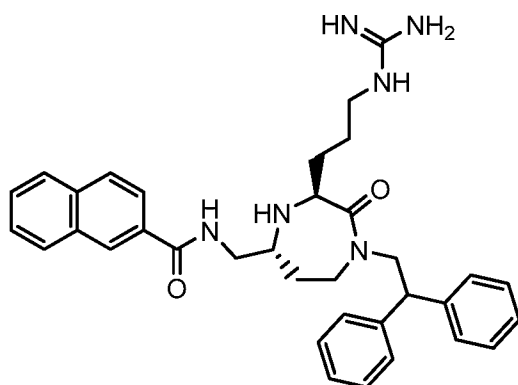
**66**

N-(((3*R*,5*S*)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide

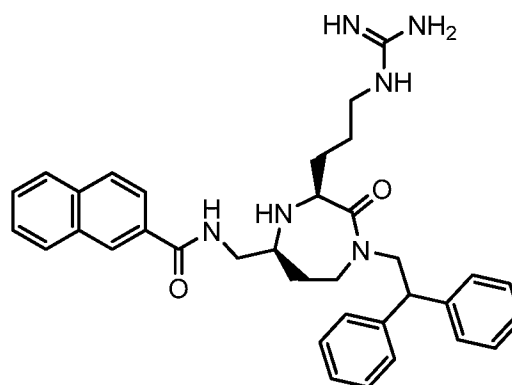
**67**

N-(((3*R*,5*R*)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide

15

**68**

N-(((3*S*,5*R*)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide

**69**

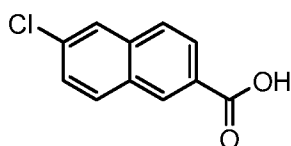
N-(((3*S*,5*S*)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide

The Boc derivative **63** (180 mg) in DCM (1 mL) was treated with TFA (1 mL) for 20 mL. The solvent was removed by evaporation, a solution of NaHCO₃ was added, and extracted 3x with DCM. The dichloromethane solution was dried over MgSO₄, filtered and evaporated to dryness. A portion (56 mg, 0.086 mmol) of the crude deprotected amine in DCM was stirred with 2-naphthoic acid (16 mg), DIPEA (60 μ L) and BOP (42 mg) for 30 min. MeOH was added and the reaction stirred overnight. The reaction was filtered, then purified by flash chromatography over SiO₂ using petroleum ether/EtOAc as eluent, to give the (3R,5R) isomer (43 mg, 94%). The other isomers were converted in a similar manner to give the protected derivatives: (3R,5S): 41 mg (85%) from 60 mg **62**, (3S,5R): 27 mg (70%) from 40 mg **65**, and (3S,5S): 13 mg (74%) from 20 mg **64**

Each compound was dissolved in dioxane:MeOH and hydrogenated over catalytic Pd/C under 30 psi H₂ overnight. The solution was filtered through Celite and evaporated to give a solid. **66** (3R,5S): 27mg (96%) from 41 mg, **67** (3R,5R): 25mg (85%) from 43 mg, **68** (3S,5R): 11 mg (quantitative) from 13 mg, and **69** (3S,5S): 3 mg (73%) from 6 mg.

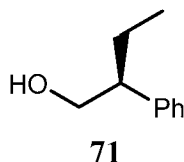
Compound	stereochemistry	MS (M+1)	t _R (min)
66	(3R,5S)	577.4	5.775
67	(3R,5R)	577.5	5.750
68	(3S,5R)	577.5	5.783
69	(3S,5S)	577.3	5.787

Example 67 – Synthesis of Compound 70 6-chloro-2-naphthoic acid

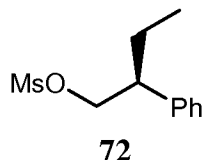


70
6-chloro-2-naphthoic acid

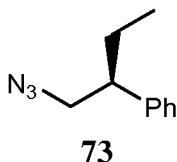
A suspension of 6-bromo-2-naphthoic acid (3.0 g, 11.47 mmol), CuCl (11.7 g, 114.64 mmol) and CuI (2.19 g, 11.50 mmol) in degassed DMF (45 mL) was heated to reflux under argon in dark for 4 hrs. After cooling to room temperature, the solution was decanted into H₂O (200 mL) and the resulting mixture was extracted with EtOAc (2 x 500 mL). The combined organic layers were then washed with H₂O (4 x 500 mL) followed by brine (1 x 500 mL), dried over MgSO₄, filtered and concentrated under reduced pressure to dryness. The residue was triturated with CH₃CN and the solid obtained was then re-crystallized from EtOAc to give the pure product **70** (2.2 g, 93%) as a off-white solid. HPLC t_R 6.47 min.

Example 68 – Synthesis of Compound 71 (*S*)-2-phenylbutanol

To a suspension of sodium borohydride (2.36 g, 62.4 mmol) in THF (50 mL) was added a solution of (*S*)-2-phenylbutyric acid (4.27 g, 26.0 mmol) in THF (40 mL) slowly at 0°C. The mixture was stirred until the evolution of gas ceased. A solution of iodine (6.60 g, 26.0 mmol) in THF (40 mL) was then added slowly at 0 °C. After addition, the resulting mixture was allowed to warm to room temperature and stirred for 1 hr. The reaction solution was then slowly poured into a 1 N HCl solution (280 mL) and the resulting mixture was diluted with EtOAc (250 mL). The aqueous layer was extracted with EtOAc (150 mL x 3) and the combined organic layers were then washed with saturated NaHCO₃ (aq), 0.5 M Na₂S₂O₃ (aq) and brine. This organic solution was dried over MgSO₄, filtered and concentrated under reduced pressure to give the crude product. Purification by flash chromatography on silica gel (Petroleum ether:EtOAc 4:1) gave the desired product **71** as a colorless oil in quantitative yield. HPLC *t_R* 5.24 min.

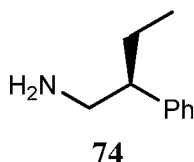
Example 69 – Synthesis of Compound 72 (*S*)-1-mesyloxy-2-phenylbutane

To a mixture of **71** (3.9 g, 26.0 mmol) and triethylamine (5.5 mL, 39.5 mmol) in DCM (90 mL) was added a solution of methanesulfonyl chloride (4.47 g, 39.0 mmol) in DCM (30 mL) slowly at 0°C. After addition, the resulting mixture was allowed to warm to room temperature and stirred for 2 hrs. 1 N HCl (70 mL) was then added to the above mixture and the aqueous layer was extracted with DCM (1 x 70 mL). The combined organic layers were washed with brine (150 mL), dried over MgSO₄, filtered and concentrated under reduced pressure to give the crude product **72** as a colorless oil. This crude product was used in the next step without further purification. HPLC *t_R* 6.48 min.

Example 70 – Synthesis of Compound 73 (*S*)-1-azido-2-phenylbutane

A suspension of **72** (5.93 g, 26.0 mmol) and sodium azide (5.7 g, 78.0 mmol) in DMF (60 mL) was heated at 85°C for 3 hrs. After cooling to room temperature, the mixture was diluted with H₂O (200 mL) and extracted with EtOAc (250 mL). The organic layer was then washed with H₂O (4 x 150 mL) followed by brine (150 mL), dried over MgSO₄, filtered and concentrated under reduced pressure to give the crude product. Purification by flash chromatography on silica gel (100% petroleum ether as the eluent) gave the pure product **73** (4.03 g, 88%) as a colorless oil. HPLC *t_R* 7.67 min.

Example 71 – Synthesis of Compound 74 (S)-2-phenylbutylamine



A mixture of **73** (4.0 g, 22.8 mmol) and Lindlar's catalyst (1.5 g) in EtOAc (50 mL) was shaken at room temperature under H₂ (40 psi) over-night. The mixture was then filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to give the crude product **74** (3.4 g, 100%) as a light yellowish oil. This crude product was used for the conjugate addition reactions without further purification. **MS (ESI)** 150 (M+1); HPLC *t_R* 1.84 min.

Example 72 – Synthesis of Compounds 75, 76, 270, 383, 386-389

270 6-chloro-N-(((3S,5S)-2-oxo-1-((S)-2-phenylbutyl)-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide

383 6-chloro-N-(((3S,5S)-2-oxo-1-((R)-2-phenylbutyl)-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide

386 6-chloro-N-(((3R,5R)-2-oxo-1-((R)-2-phenylbutyl)-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide

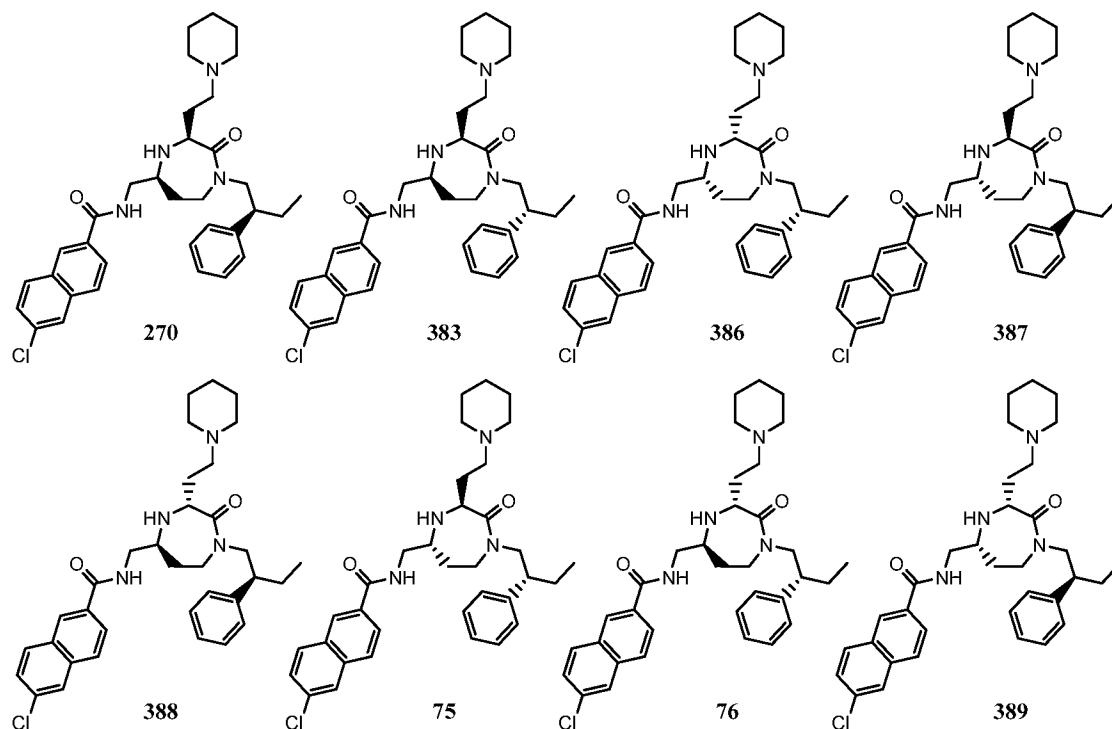
387 6-chloro-N-(((3S,5R)-2-oxo-1-((S)-2-phenylbutyl)-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide

388 6-chloro-N-(((3R,5S)-2-oxo-1-((S)-2-phenylbutyl)-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide

75 6-chloro-N-(((3S,5R)-2-oxo-1-((R)-2-phenylbutyl)-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide

76 6-chloro-N-(((3R,5S)-2-oxo-1-((R)-2-phenylbutyl)-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide

389 6-chloro-N-(((3R,5R)-2-oxo-1-((S)-2-phenylbutyl)-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide



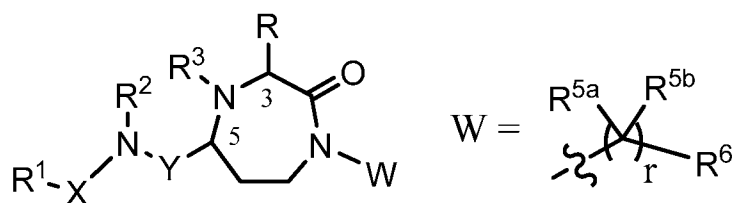
Compounds **75**, **76**, **270**, **383**, and **386-389** were prepared following similar procedures as used to prepare Compounds 102-104 (Scheme 2 route). In addition, compounds **270**, **383**, **386** and **389** were prepared according to the Scheme 1 route.

Compound	stereochemistry	MS (M+1)	t _R (min)
270	(3S,5S,2'S)	575.3	6.269
383	(3S,5S,2'R)	574.8	6.265
386	(3R,5R,2'R)	575.4	6.404
387	(3S,5R,2'S)	575.2	6.262
388	(3R,5S,2'S)	575.2	6.110
75	(3S,5R,2'R)	575.1	6.211
76	(3R,5S,2'R)	575.2	6.253
389	(3R,5R,2'S)	575.4	6.274

Example 73 – Syntheses of Compounds 100-389.

Compounds **100-389**, with substituents as identified in Table 2, were prepared as in the previous examples according to the routes identified in Schemes 1-5, as summarized in Table 3, with experimental properties summarized in Table 4.

Table 2: Identity of Compounds



Cpd	R^1X	R^2	R^3	Y	R	W	3,5-conf
100	2-naphthoyl	H	H	CH_2	$(CH_2)_3NHC(=NH)NH_2$	3,5-dichlorobenzyl	S,S
101	2-naphthoyl	H	H	CH_2	$CH_2CH_2NH_2$	2-phenylbutyl	S,S
102	2-naphthoyl	H	H	CH_2	$CH_2CH_2NH_2$	3,5-dichlorobenzyl	S,S
103	6-bromo-2-naphthoyl	Me	H	CH_2	$CH_2CH_2CH_2NH_2$	2,2-diphenylethyl	S,S
104	6-bromo-2-naphthoyl	H	Me	CH_2	$CH_2CH_2CH_2NH_2$	2,2-diphenylethyl	S,S
105	2-naphthoyl	H	H	CH_2	$CH_2CH_2CH_2NHC(=NH)NH(Me)$	2,2-diphenylethyl	S,S
106	2-naphthoyl	H	H	CH_2	$CH_2CH_2CH_2NHMe$	2,2-diphenylethyl	S,S
107	Ac	H	H	(S)- $CHCH_2$ (2-naphthyl)	$(CH_2)_3NHC(=NH)NH_2$	2,2-diphenylethyl	S,S
108	4-biphenylcarbonyl	H	H	CH_2	$(CH_2)_3NHC(=NH)NH_2$	2,2-diphenylethyl	SS
109	1-naphthylacetyl	H	H	CH_2	$(CH_2)_3NHC(=NH)NH_2$	(S)- $CH(CO_2Me)CH_2$ (indol-3-yl)	S,R
110	4-biphenylcarbonyl	H	H	CH_2	$(CH_2)_3NHC(=NH)NH_2$	2,2-diphenylethyl	R,S
111	4-biphenylcarbonyl	H	H	CH_2	$(CH_2)_3NHC(=NH)NH_2$	2,2-diphenylethyl	R,R
112	4-biphenylcarbonyl	H	H	CH_2	$(CH_2)_3NHC(=NH)NH_2$	2,2-diphenylethyl	S,R
113	3-quinoline carbonyl	H	H	CH_2	$(CH_2)_3NHC(=NH)NH_2$	2,2-diphenylethyl	S,S
114	2-quinoxaline carbonyl	H	H	CH_2	$(CH_2)_3NHC(=NH)NH_2$	2,2-diphenylethyl	S,S
115	3-isoquinoline carbonyl	H	H	CH_2	$(CH_2)_3NHC(=NH)NH_2$	2,2-diphenylethyl	S,S
116	quinaldic	H	H	CH_2	$(CH_2)_3NHC(=NH)NH_2$	2,2-diphenylethyl	S,S
117	4-biphenylmethyl	$R^2 = R^3 = -CO-$	$R^2 = R^3 = -CO-$	CH_2	$(CH_2)_4NH_2$	1-naphthylethyl	RS
118	4-biphenylcarbonyl	H	H	CH_2	$(CH_2)_4NH_2$	diphenylmethyl	S,S
119	4-biphenylacetyl	H	H	CH_2	$(CH_2)_4NH_2$	diphenylmethyl	S,S
120	4-biphenylmethyl	$R^2 = R^3 = -CO-$	$R^2 = R^3 = -CO-$	CH_2	$(CH_2)_4NH_2$	diphenylmethyl	S,S
121	2-naphthoyl	H	H	CH_2	$(CH_2)_4NH_2$	diphenylmethyl	S,S
122	2-naphthylacetyl	H	H	CH_2	$((CH_2)_4NH_2)$	diphenylmethyl	S,S
123	2-naphthylmethyl	$R^2 = R^3 = -CO-$	$R^2 = R^3 = -CO-$	CH_2	$(CH_2)_4NH_2$	diphenylmethyl	S,S
124	4-biphenylacetyl	H	H	CH_2	$(CH_2)_3NHC(=NH)NH_2$	diphenylmethyl	S,S
125	4-biphenylmethyl	$R^2 = R^3 = -CO-$	$R^2 = R^3 = -CO-$	CH_2	$(CH_2)_3NHC(=NH)NH_2$	diphenylmethyl	S,S
126	2-naphthoyl	H	H	CH_2	$(CH_2)_3NHC(=NH)NH_2$	diphenylmethyl	S,S

Cpd	R ¹ X	R ²	R ³	Y	R	W	3,5-conf
127	2-naphthylacetyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	diphenylmethyl	S,S
128	4-biphenylcarbonyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	diphenylmethyl	S,R
129	4-biphenylacetyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	diphenylmethyl	S,R
130	4-biphenylmethyl	R ² = R ³ = -CO-	R ² = R ³ = -CO-	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	diphenylmethyl	S,R
131	2-naphthylacetyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	diphenylmethyl	S,R
132	2-naphthylmethyl	R ² = R ³ = -CO-	R ² = R ³ = -CO-	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	diphenylmethyl	S,R
133	4-biphenylcarbonyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	diphenylmethyl	R,R
134	4-biphenylacetyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	diphenylmethyl	R,R
135	2-naphthylacetyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	diphenylmethyl	R,R
136	2-naphthylmethyl	R ² = R ³ = -CO-	R ² = R ³ = -CO-	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	diphenylmethyl	R,R
137	4-biphenylcarbonyl	H	H	CH ₂	(CH ₂) ₄ NH ₂	1-naphthylmethyl	S,R
138	4-biphenylacetyl	H	H	CH ₂	(CH ₂) ₄ NH ₂	1-naphthylmethyl	S,R
139	4-biphenylmethyl	R ² = R ³ = -CO-	R ² = R ³ = -CO-	CH ₂	(CH ₂) ₄ NH ₂	1-naphthylmethyl	S,R
140	2-naphthoyl	H	H	CH ₂	(CH ₂) ₄ NH ₂	1-naphthylmethyl	S,R
141	4-biphenylmethyl	R ² = R ³ = -CO-	R ² = R ³ = -CO-	CH ₂	(CH ₂) ₄ NH ₂	1-naphthylmethyl	S,S
142	2-naphthoyl	H	H	CH ₂	(CH ₂) ₄ NH ₂	1-naphthylmethyl	S,S
143	2-naphthylacetyl	H	H	CH ₂	(CH ₂) ₄ NH ₂	1-naphthylmethyl	S,S
144	4-biphenylcarbonyl	H	H	CH ₂	(CH ₂) ₄ NH ₂	1-naphthylmethyl	R,R
145	4-biphenylacetyl	H	H	CH ₂	(CH ₂) ₄ NH ₂	1-naphthylmethyl	R,R
146	4-biphenylmethyl	R ² = R ³ = -CO-	R ² = R ³ = -CO-	CH ₂	(CH ₂) ₄ NH ₂	1-naphthylmethyl	R,R
147	4-biphenylcarbonyl	H	H	CH ₂	(CH ₂) ₄ NH ₂	1-naphthylmethyl	R,S
148	4-biphenylacetyl	H	H	CH ₂	(CH ₂) ₄ NH ₂	1-naphthylmethyl	R,S
149	4-biphenylmethyl	R ² = R ³ = -CO-	R ² = R ³ = -CO-	CH ₂	(CH ₂) ₄ NH ₂	1-naphthylmethyl	R,S
150	2-naphthoyl	H	H	CH ₂	(CH ₂) ₄ NH ₂	1-naphthylmethyl	R,S
151	2-naphthylacetyl	H	H	CH ₂	(CH ₂) ₄ NH ₂	1-naphthylmethyl	R,S
152	1-naphthoyl	H	H	CH ₂	((CH ₂) ₄ NH ₂	1-naphthylmethyl	R,S
153	1-naphthylacetyl	H	H	CH ₂	(CH ₂) ₄ NH ₂	1-naphthylmethyl	R,S
154	4-biphenylcarbonyl	H	H	CH ₂	(CH ₂) ₄ NH ₂	2-naphthylmethyl	S,S
155	4-biphenylacetyl	H	H	CH ₂	(CH ₂) ₄ NH ₂	2-naphthylmethyl	S,S
156	4-biphenylmethyl	R ² = R ³ = -CO-	R ² = R ³ = -CO-	CH ₂	(CH ₂) ₄ NH ₂	2-naphthylmethyl	S,S
157	2-naphthoyl	H	H	CH ₂	(CH ₂) ₄ NH ₂	2-naphthylmethyl	S,S

Cpd	R ¹ X	R ²	R ³	Y	R	W	3,5-conf
158	2-naphthylacetyl	H	H	CH ₂	(CH ₂) ₄ NH ₂	2-naphthylmethyl	S,S
159	4-biphenylcarbonyl	H	H	CH ₂	(CH ₂) ₄ NH ₂	2-naphthylmethyl	S,R
160	4-biphenylacetyl	H	H	CH ₂	((CH ₂) ₄ NH ₂	2-naphthylmethyl	S,R
161	4-biphenylmethyl	R ² = R ³ = -CO-	R ² = R ³ = -CO-	CH ₂	(CH ₂) ₄ NH ₂	2-naphthylmethyl	S,R
162	2-naphthoyl	H	H	CH ₂	(CH ₂) ₄ NH ₂	2-naphthylmethyl	S,R
163	2-naphthylacetyl	H	H	CH ₂	(CH ₂) ₄ NH ₂	2-naphthylmethyl	S,R
164	1-naphthylacetyl	H	H	CH ₂	(CH ₂) ₄ NH ₂	2-naphthylmethyl	S,R
165	4-biphenylcarbonyl	H	H	CH ₂	(CH ₂) ₄ NH ₂	2-naphthylmethyl	R,R
166	4-biphenylacetyl	H	H	CH ₂	(CH ₂) ₄ NH ₂	2-naphthylmethyl	R,R
167	4-biphenylmethyl	R ² = R ³ = -CO-	R ² = R ³ = -CO-	CH ₂	(CH ₂) ₄ NH ₂	2-naphthylmethyl	R,R
168	2-naphthoyl	H	H	CH ₂	(CH ₂) ₄ NH ₂	2-naphthylmethyl	R,R
169	4-biphenylcarbonyl	H	H	CH ₂	(CH ₂) ₄ NH ₂	2-naphthylmethyl	R,S
170	4-biphenylacetyl	H	H	CH ₂	(CH ₂) ₄ NH ₂	2-naphthylmethyl	R,S
171	4-biphenylmethyl	R ² = R ³ = -CO-	R ² = R ³ = -CO-	CH ₂	(CH ₂) ₄ NH ₂	2-naphthylmethyl	R,S
172	benzoyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	2,2-diphenylethyl	S,S
173	cyclohexanoyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	2,2-diphenylethyl	S,S
174	3-phenoxybenzoyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	2,2-diphenylethyl	S,S
175	4-phenoxybenzoyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	2,2-diphenylethyl	S,S
176	indole-2-carboxyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	2,2-diphenylethyl	S,S
177	3-Ph-propionyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	2,2-diphenylethyl	S,S
178	3,4-dimethylbenzoyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	2,2-diphenylethyl	S,S
179	4-tert-butylbenzoyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	2,2-diphenylethyl	S,S
180	2,4-dimethoxybenzoyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	2,2-diphenylethyl	S,S
181	cyclohexylacetyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	2,2-diphenylethyl	S,S
182	2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ CONHC(=NH)NH ₂	2,2-diphenylethyl	S,S
183	4-chlorocinnamoyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	2,2-diphenylethyl	S,S
184	iPrO(O)C	H	H	(R)-CH(Bn)	(CH ₂) ₃ NHC(=NH)NH ₂	2-(indol-3-yl)ethyl	R,R
185	H-D-Tic	H	H	(S)-CH(Bn)	(CH ₂) ₃ NHC(=NH)NH ₂	2-(indol-3-yl)ethyl	S,S
186	2-naphthoyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	cyclohexanemethyl	S,S
187	6-bromonaphthoyl	H	H	CH ₂	CH ₂ CH ₂ CH ₂ NH ₂	2,2-diphenylethyl	S,S
188	4-chlorocinnamoyl	H	H	CH ₂	CH ₂ CH ₂ CH ₂ NH ₂	2,2-diphenylethyl	S,S
189	2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ CH ₂ NHC(=NH)N(Me) ₂	2,2-diphenylethyl	S,S
190	4-Me cinnamoyl	H	H	CH ₂	CH ₂ CH ₂ CH ₂ NH ₂	2,2-diphenylethyl	S,S
191	4-fluoro cinnamoyl	H	H	CH ₂	CH ₂ CH ₂ CH ₂ NH ₂	2,2-diphenylethyl	S,S

Cpd	R ¹ X	R ²	R ³	Y	R	W	3,5-conf
192	6-fluoro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ CH ₂ NH ₂	2,2-diphenylethyl	S,S
193	3,4-dichlorobenzoyl	H	H	CH ₂	CH ₂ CH ₂ CH ₂ NH ₂	2,2-diphenylethyl	S,S
194	2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ CH ₂ NHcHex	2,2-Diphenylethyl	S,S
195	2-naphthoyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	2-naphthyl	S,S
196	2-naphthoyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	(9-fluorenyl)methyl	S,S
197	4-fluorocinnamoyl	H	H	CH ₂	CH ₂ CH ₂ CH ₂ NH(cHex)	2,2-diphenylethyl	S,S
198	5-(4-chlorophenyl)-2-furoyl	H	H	CH ₂	CH ₂ CH ₂ CH ₂ NH ₂	2,2-diphenylethyl	S,S
199	4-(pyrrol-1-yl)-benzoyl	H	H	CH ₂	CH ₂ CH ₂ CH ₂ NH ₂	2,2-diphenylethyl	S,S
200	5-(4-chlorophenyl)-3-isoxazole	H	H	CH ₂	CH ₂ CH ₂ CH ₂ NH ₂	2,2-diphenylethyl	S,S
201	2-naphthoyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	cyclohexaneethyl	S,S
202	2-naphthoyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	2,2-bis(4-fluorophenyl)ethyl	S,S
203	2-naphthoyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	2-naphthalenemethyl	S,S
204	phenylacetyl	H	H	(R)-CH(Bn)	(CH ₂) ₃ NHC(=NH)NH ₂	2-(indol-3-yl)ethyl	S,S
205	4-fluorocinnamoyl	Me	H	CH ₂	CH ₂ CH ₂ CH ₂ NH ₂	2,2-diphenylethyl	S,S
206	4-fluorocinnamoyl	H	Me	CH ₂	CH ₂ CH ₂ CH ₂ NH ₂	2,2-diphenylethyl	S,S
207	4-chlorocinnamoyl	H	H	CH ₂	(CH ₂) ₃ (1-pyrrolidinyl)	2,2-diphenylethyl	S,S
208	4-chlorocinnamoyl	H	H	CH ₂	(CH ₂) ₃ (1-piperidinyl)	2,2-diphenylethyl	S,S
209	2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ NH ₂	2,2-diphenylethyl	S,S
210	2-naphthoyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	1-naphthalenemethyl	S,S
211	2-naphthoyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	2-(2-naphthyl)ethyl	S,S
212	4-chlorocinnamoyl	H	H	CH ₂	CH ₂ NH ₂	2,2-diphenylethyl	S,S
213	2-naphthoyl	H	H	CH ₂	CH ₂ (1-piperidinyl)	2,2-diphenylethyl	S,S
214	4-chlorocinnamoyl	H	H	CH ₂	CH ₂ (1-piperidinyl)	2,2-diphenylethyl	S,S
215	3,4-dichlorobenzoyl	H	H	CH ₂	CH ₂ CH ₂ NH ₂	2,2-diphenylethyl	S,S
216	4-chlorocinnamoyl	H	H	CH ₂	CH ₂ CH ₂ NH ₂	2,2-diphenylethyl	S,S
217	3,4-dichlorobenzoyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidinyl)	2,2-diphenylethyl	S,S
218	2-naphthoyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	(S)-CH ₂ CH(Ph)NHCOPh	S,S
219	2-naphthoyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	CH ₂ CH(Ph)OCH ₂ CH=CH ₂	S,S
220	2-naphthoyl	H	H	(R)-CH(Bn)	(CH ₂) ₃ NHC(=NH)NH ₂	(S)-CH ₂ CH(Ph)OCH ₂ CH=CH ₂	S,S
221	H-L-Phe	H	H	(R)-CH(Bn)	(CH ₂) ₃ NHC(=NH)NH ₂	2-(2-naphthyl)ethyl	S,R
222	H-L-Phe	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	2-(2-naphthyl)ethyl	S,S
223	4-chlorocinnamoyl	H	H	CH ₂	nBu	2,2-diphenylethyl	S,S
224	4-chlorocinnamoyl	H	H	CH ₂	CH ₂ CH ₂ CONH ₂	2,2-diphenylethyl	S,S
225	4-methylcinnamoyl	H	H	CH ₂	(CH ₂) ₃ NHCOcHex	2,2-diphenylethyl	S,S
226	2-naphthoyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	CH ₂ CH(Ph)OPh	S,S

Cpd	R ¹ X	R ²	R ³	Y	R	W	3,5-conf
227	2-naphthoyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	2-ethylbutyl	S,S
228	2-naphthoyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	3,5-dimethyl-cyclohexylmethyl	S,S
229	3,4-dichlorobenzoyl	H	H	(CH ₂) ₂	CH ₂ CH ₂ (1-piperidinyl)	2,2-diphenylethyl	S,S
230	3,4-dichlorobenzoyl	H	H	CH ₂	CH ₂ CH ₂ NH ₂	3,5-dichlorobenzyl	S,S
231	4-chlorocinnamoyl	H	H	CH ₂	CH ₂ CH ₂ NH ₂	3,5-dichlorobenzyl	S,S
232	4-fluorobenzyl	R ² = R ³ = -CO-	R ² = R ³ = -CO-	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	(S)-CH(CONHMe)-CH ₂ (2-naphthyl)	S,S
233	4-fluoro-phenylacetyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	(S)-CH(CONHMe)-CH ₂ (2-naphthyl)	S,R
234	4-fluoro-phenylacetyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	(S)-CH(CONHMe)-CH ₂ (2-naphthyl)	S,S
235	4-fluorobenzyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	(S)-CH(CONHMe)-CH ₂ (2-naphthyl)	S,R
236	4-fluorobenzyl	Ac	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	(S)-CH(CONHMe)-CH ₂ (2-naphthyl)	S,R
237	2-naphthoyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	3-chloro-5-fluorobenzyl	S,S
238	2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ CH ₂ NH ₂	1-(1-phenyl-cyclohexyl)methyl	S,S
239	3,4-dichlorobenzoyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidinyl)	3,5-dichlorobenzyl	S,S
240	2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidinyl)	3,5-dichlorobenzyl	S,S
241	4-chlorocinnamoyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidinyl)	3,5-dichlorobenzyl	S,S
242	4-fluoro-benzoyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	(S)-CH(CONHMe)-CH ₂ (2-naphthyl)	R,R
243	4-fluoro-benzoyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	(S)-CH(CONHMe)-CH ₂ (2-naphthyl)	R,S
244	4-fluoro-phenylacetyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	(S)-CH(CONHMe)-CH ₂ (2-naphthyl)	R,R
245	4-fluoro-phenylacetyl	H	H	CH ₂	(CH ₂) ₃ NHCOCH ₂ (4-F-Ph)	(S)-CH(CONHMe)-CH ₂ (2-naphthyl)	R,R
246	4-fluoro-phenylacetyl	H	H	CH ₂	(CH ₂) ₃ NHCOCH ₂ (4-F-Ph)	(S)-CH(CONHMe)-CH ₂ (2-naphthyl)	R,S
247	4-fluoro-phenylacetyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	(S)-CH(CONHMe)-CH ₂ (2-naphthyl)	R,S
248	3,4-dichlorobenzoyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidinyl)	2-ethylbutyl	S,S
249	2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidinyl)	2-ethylbutyl	S,S
250	4-chlorocinnamoyl	H	H	CH ₂	CH ₂ (1-piperidinyl)	2-ethylbutyl	S,S
251	2-naphthoyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	CH ₂ CH(Ph)CON[-(CH ₂) ₅ -]	S,S
252	2-naphthoyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	CH ₂ CH(Ph)CONHPh	S,S
253	3,4-dichlorobenzoyl	H	H	CH ₂	CH ₂ NH ₂	3,5-dichlorobenzyl	S,S
254	2-naphthoyl	H	H	CH ₂	CH ₂ NH ₂	3,5-dichlorobenzyl	S,S
255	4-chlorocinnamoyl	H	H	CH ₂	CH ₂ NH ₂	3,5-dichlorobenzyl	S,S
256	3,4-dichlorobenzoyl	H	H	CH ₂	CH ₂ (1-piperidinyl)	3,5-dichlorobenzyl	S,S
257	4-chlorocinnamoyl	H	H	CH ₂	CH ₂ (1-piperidinyl)	3,5-dichlorobenzyl	S,S
258	3,4-dichlorobenzoyl	H	H	CH ₂	CH ₂ CH ₂ NH ₂	2-phenylbutyl	S,S
259	4-chlorocinnamoyl	H	H	CH ₂	CH ₂ CH ₂ NH ₂	2-phenylbutyl	S,S
260	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidinyl)	2-ethylbutyl	S,S

Cpd	R ¹ X	R ²	R ³	Y	R	W	3,5-conf
261	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidinyl)	2,2-diphenylethyl	S,S
262	4-isopropylcinnamoyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidinyl)	2,2-diphenylethyl	S,S
263	4-isopropylcinnamoyl	H	H	CH ₂	CH ₂ CH ₂ NH ₂	2,2-diphenylethyl	S,S
264	2,4-dimethylcinnamoyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidinyl)	2,2-diphenylethyl	S,S
265	2,4-dimethylcinnamoyl	H	H	CH ₂	CH ₂ CH ₂ NH ₂	2,2-diphenylethyl	S,S
266	2,4-difluorocinnamoyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidinyl)	2,2-diphenylethyl	S,S
267	2,4-difluorocinnamoyl	H	H	CH ₂	CH ₂ CH ₂ NH ₂	2,2-diphenylethyl	S,S
268	4-chlorocinnamoyl	H	H	CH ₂	CH ₂ CH ₂ (4-morpholinyl)	2,2-diphenylethyl	S,S
269	4-chlorocinnamoyl	H	H	CH ₂	CH ₂ CH ₂ (2,5-Me ₂ -pyrrolidin-1-yl)	2,2-diphenylethyl	S,S
270	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidinyl)	(S)-2-phenylbutyl	S,S
271	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidinyl)	(S)-2-phenylbutyl	S,S
272	3,4-dichlorobenzoyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidinyl)	(S)-2-phenylbutyl	S,S
273	4-bromocinnamoyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidinyl)	2,2-diphenylethyl	S,S
274	5-(4-chlorophenyl)-3-isoxazole	H	H	CH ₂	CH ₂ CH ₂ (1-piperidinyl)	2,2-diphenylethyl	S,S
275	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ CO(1-piperidinyl)	(S)-2-phenylbutyl	S,S
276	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ (1-piperidinyl)	(S)-2-phenylbutyl	S,S
277	6-chloro-2-naphthoyl	H	H	CH ₂	(CH ₂) ₃ (1-piperidinyl)	(S)-2-phenylbutyl	S,S
278	4-chlorocinnamoyl	H	H	C(Me) ₂	CH ₂ CH ₂ NH ₂	2,2-diphenylethyl	S,S
279	4-chlorocinnamoyl	H	H	C(Me) ₂	CH ₂ CH ₂ (1-piperidinyl)	2,2-diphenylethyl	S,S
280	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ NHiPr	3,5-dichlorobenzyl	S,S
281	3,4-dichlorobenzoyl	H	H	CH ₂	CH ₂ CH ₂ NHiPr	3,5-dichlorobenzyl	S,S
282	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ NHiPr	(S)-2-phenylbutyl	S,S
283	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ NH ₂	(S)-2-phenylbutyl	S,S
284	4-chlorocinnamoyl	H	H	CH ₂	CH ₂ C(imidazol-1-yl)	2,2-diphenylethyl	S,S
285	3,4-dichlorobenzoyl	H	H	CH ₂	CH ₂ CH ₂ N(Bn)Me	(S)-2-phenylbutyl	S,S
286	3,4-dichlorobenzoyl	H	H	CH ₂	CH ₂ CH ₂ N(nPent)Me	(S)-2-phenylbutyl	S,S
287	6-chloro-2-naphthoyl	H	H	CH ₂	4-piperidinyl	(S)-2-phenylbutyl	S,S/ R,R
288	6-chloro-2-naphthoyl	H	H	CH ₂	1-isopentyl-4-piperidinyl	(S)-2-phenylbutyl	S,S/ R,R
289	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ iPr	(S)-2-phenylbutyl	S,S
290	3,4-dichlorobenzoyl	H	H	CH ₂	CH ₂ CH ₂ (3,5-Me ₂ -piperidin-1-yl)	(S)-2-phenylbutyl	S,S
291	3,4-dichlorobenzoyl	H	H	CH ₂	CH ₂ CH ₂ (4-OH-piperidin-1-yl)	(S)-2-phenylbutyl	S,S
292	3,4-dichlorobenzoyl	H	H	CH ₂	CH ₂ CH ₂ (4-CO ₂ H-piperidin-1-yl)	(S)-2-phenylbutyl	S,S
293	3,4-dichlorobenzoyl	H	H	CH ₂	CH ₂ CH ₂ NH[-(CH ₂) ₆ -]	(S)-2-phenylbutyl	S,S
294	3,4-dichlorobenzoyl	H	H	CH ₂	CH ₂ CH ₂ [(S)-2-Me-piperidin-1-yl]	(S)-2-phenylbutyl	S,S
295	2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ CON(Me)nBu	(S)-2-phenylbutyl	S,S

Cpd	R ¹ X	R ²	R ³	Y	R	W	3,5-conf
296	2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ CONHcHex	(S)-2-phenylbutyl	S,S
297	6-chloro-2-naphthoyl	H	H	CH ₂	1-ethyl-piperidin-4-yl	(S)-2-phenylbutyl	S,S/ R,R
298	3,4-dichlorobenzyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidinyl)	2,2-diphenylethyl	S,S
299	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ NHC(=NH)N H ₂	(S)-2-phenylbutyl	S,S
300	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ NHC(=NH)N HMe	(S)-2-phenylbutyl	S,S
301	H-L-(4-F)Phe	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	(S)-CH(CONHMe)- CH ₂ (2-naphthyl)	S,R
302	4-chloro- phenylacetyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	(S)- CH(CONHMe)CH ₂ (2- naphthyl)	S,R
303	H-D-(4-F)Phe	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	(S)-CH(CONHMe)- CH ₂ (2-naphthyl)	S,R
304	1-naphthylacetyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	(S)-CH(CONHMe)- CH ₂ (2-naphthyl)	S,R
305	3,4-dichlorobenzoyl	H	H	CH ₂	CH ₂ CH ₂ NH ₂	(R)-2-isopropylbutyl	S,S
306	3,4-dichlorobenzoyl	H	H	CH ₂	CH ₂ CH ₂ NH ₂	(S)-2-isopropylbutyl	S,S
307	4-fluorocinnamoyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	(S)-CH(CONHMe)- CH ₂ (2-naphthyl)	S,R
308	3,4-dichlorobenzoyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidinyl)	(R)-2-isopropylbutyl	S,S
309	3,4-dichlorobenzoyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidinyl)	(S)-2-isopropylbutyl	S,S
310	4-fluorocinnamoyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	(S)-CH(CONHMe)- CH ₂ (2-naphthyl)	S,R
311	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ C(Me ₂)NH ₂	(S)-2-phenylbutyl	S,S
312	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ C(Me ₂)NH ₂	(S)-2-phenylbutyl	R,R
313	3,4-dichlorobenzoyl	H	H	CH ₂	CH ₂ CH ₂ NH ₂	(S)-2-phenylbutyl	S,S
314	3,4-dichlorobenzoyl	H	H	CH ₂	CH ₂ CH ₂ NHiPr	(S)-2-phenylbutyl	S,S
315	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ NH ₂	3,5-dichlorobenzyl	S,S
316	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidinyl)	3,5-dichlorobenzyl	S,S
317	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ C(Me ₂)(1- piperidinyl)	(S)-2-phenylbutyl	S,S
318	4-chlorocinnamoyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	(S)-CH(CONHMe)- CH ₂ (2-naphthyl)	S,R
319	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ NH ₂	(R)-2-isopropylbutyl	S,S
320	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ NH ₂	(S)-2-isopropylbutyl	S,S
321	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidinyl)	(R)-2-isopropylbutyl	S,S
322	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidinyl)	(S)-2-isopropylbutyl	S,S
323	NH ₂ -L-(4-Cl)Phe	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	(S)-CH(CONHMe)- CH ₂ (2-naphthyl)	S,R
324	NH ₂ -D-(4-Cl)Phe	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	(S)-CH(CONHMe)- CH ₂ (2-naphthyl)	S,R
325	4-methoxy- phenylacetyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	(S)-CH(CONHMe)- CH ₂ (2-naphthyl)	S,R
326	phenylpropanoyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	(S)-CH(CONHMe)- CH ₂ (2-naphthyl)	S,R
327	4-chloro- phenylpropanoyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	(S)-CH(CONHMe)- CH ₂ (2-naphthyl)	S,R
328	4-chlorocinnamoyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	(S)-CH(CONHMe)- CH ₂ (2-naphthyl)	S,R
329	6-chloro-2-naphthoyl	H	H	CH ₂	nHex	(S)-2-phenylbutyl	S,S

Cpd	R ¹ X	R ²	R ³	Y	R	W	3,5-conf
330	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ NHC(=NH)NHiPr]	(S)-2-phenylbutyl	S,S
331	6-chloro-2-naphthoyl	H	H	CH ₂	(CH ₂) ₄ OH	(S)-2-phenylbutyl	S,S
332	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ OMe	(S)-2-phenylbutyl	S,S
333	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ OBn	(S)-2-phenylbutyl	S,S
334	6-chloro-2-naphthoyl	H	H	CH ₂	iBu	(S)-2-phenylbutyl	S,S
335	2,4-dichlorophenylacetyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	(S)-CH(CONHMe)-CH ₂ (2-naphthyl)	S,R
336	2,4-dichlorophenylacetyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NHCOCH ₂ (2,4-Cl ₂ -Ph)	(S)-CH(CONHMe)-CH ₂ (2-naphthyl)	S,R
337	3-chlorophenylacetyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	(S)-CH(CONHMe)-CH ₂ (2-naphthyl)	S,R
338	3-chlorophenylacetyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NHCOCH ₂ (3-Cl-Ph)	(S)-CH(CONHMe)-CH ₂ (2-naphthyl)	S,R
339	3,4-dichlorobenzoyl	H	H	CH ₂	CH ₂ CH ₂ NH ₂	2-ethyl-3-methyl-but-3-enyl	S,S
340	3,4-dichlorobenzoyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidiny)	2-isopropylbutyl	S,S
341	3,4-dichlorobenzoyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidiny)	2-ethyl-3-methyl-but-3-enyl	S,S
342	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ NH ₂	2-ethyl-3-methyl-but-3-enyl	S,S
343	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidiny)	(R)-2-ethyl-3-methyl-but-3-enyl	S,S
344	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidiny)	(S)-2-ethyl-3-methyl-but-3-enyl	S,S
345	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidiny)	2-isopropylbutyl	S,S
346	4-biphenylcarboxyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	cyclohexanemethyl	S,S
347	quinoline-3-carboxyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	cyclohexanemethyl	S,S
348	4-biphenylcarbonyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	cyclohexanemethyl	S,R
349	quinoline-3-carbonyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	cyclohexanemethyl	S,R
350	4-biphenylcarbonyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	cyclohexanemethyl	R,R
351	indole-3-acetyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	cyclohexanemethyl	R,R
352	4-biphenylcarbonyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	cyclohexanemethyl	R,S
353	indole-3-carbonyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	cyclohexanemethyl	R,S
354	2-naphthoyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	cyclohexanemethyl	R,S
355	2-naphthylacetyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	cyclohexanemethyl	R,S
356	quinoline-3-carbonyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	cyclohexanemethyl	R,S
357	4-chloro-phenylacetyl	H	H	CH ₂	(CH ₂) ₃ NHC(=NH)NH ₂	(S)-CH(CO ₂ Me)-CH ₂ (2-naphthyl)	S,R
358	4-chloro-phenylacetyl	H	H	CH ₂	CH ₂ CH ₂ CH ₂ NH ₂	(S)-CH(CONHMe)-CH ₂ (2-naphthyl)	S,R
359	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ N[-(CH ₂) ₆ -]	(S)-2-phenylbutyl	S,S
360	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ NHCONHiPr	(S)-2-phenylbutyl	S,S
361	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CO ₂ Bn	(S)-2-phenylbutyl	S,S
362	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ CO ₂ Bn	(S)-2-phenylbutyl	S,S
363	4-chloro-biphenyl-2-carbonyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidiny)	(S)-2-phenylbutyl	S,S
364	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ N(Ac)iPr	(S)-2-phenylbutyl	S,S

Cpd	R ¹ X	R ²	R ³	Y	R	W	3,5-conf
365	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ NHiPr	(S)-2-phenylbutyl	S,S
366	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ NC(=NH)NH ₂	(S)-2-phenylbutyl	S,S
367	3,4-dichlorobenzoyl	H	H	CH ₂	CH ₂ CH ₂ NH ₂	2,4-dichlorobenzyl	S,S
368	3,4-dichlorobenzoyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidinyl)	2,4-dichlorobenzyl	S,S
369	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidinyl)	2,4-dichlorobenzyl	S,S
370	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidinyl)	(R)-2-(3-thienyl)butyl	S,S
371	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidinyl)	(S)-2-(3-thienyl)butyl	S,S
372	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ NH ₂	2-ethyl-2-methylbutyl	S,S
373	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidinyl)	2-ethyl-2-methylbutyl	S,S
374	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ (4-morpholinyl)	2,2-diphenylethyl	S,S
375	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ (4-morpholinyl)	(S)-2-phenylbutyl	S,S
376	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ (4-morpholinyl)	3,5-dichlorobenzyl	S,S
377	3,4-dichlorobenzoyl	H	H	CH ₂	CH ₂ CH ₂ (4-morpholinyl)	3,5-dichlorobenzyl	S,S
378	(4-chlorobenzyl)NHCO	H	H	CH ₂	CH ₂ CH ₂ (1-piperidinyl)	(S)-2-phenylbutyl	S,S
379	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidinyl)	2,3,5-trichlorobenzyl	S,S
380	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ NHSO ₂ iPr	(S)-2-phenylbutyl	S,S
381	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ NHCO ₂ nBu	(S)-2-phenylbutyl	S,S
382	6-chloro-2-naphthoyl	H	H	CH ₂	1-iPr-4-piperidinyl	(S)-2-phenylbutyl	S,S / R,R
383	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidinyl)	(R)-2-phenylbutyl	S,S
384	5-(4-chlorophenyl)-isoxazole-3-carbonyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidinyl)	3,5-dichlorobenzyl	S,S
385	6-methoxy-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidinyl)	3,5-dichlorobenzyl	S,S
386	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidinyl)	(R)-2-phenylbutyl	R,R
387	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidinyl)	(S)-2-phenylbutyl	S,R
388	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidinyl)	(S)-2-phenylbutyl	R,S
389	6-chloro-2-naphthoyl	H	H	CH ₂	CH ₂ CH ₂ (1-piperidinyl)	(S)-2-phenylbutyl	R,R

Table 3: Synthesis of Compounds

Cpd.	Route to A	Scheme 1: VN(R ²)-Y-CO ₂ H	P ² NH-CH(U)-CO ₂ H	Conversion of A to Product	U modification
100	Scheme 1	2-naphthoic-Gly-OH	Fmoc-L-Arg(Pbf)-OH	Scheme 3	P3 deprotection
101	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection
102	Scheme 1	Alloc-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection
103	Scheme 1	Cbz-Sar-OH	Fmoc-L-Orn(Boc)-OH	Scheme 4	P3 deprotection
104	Scheme 1	Cbz-Gly-OH	Fmoc-L-Orn(Boc)-OH	Scheme 3	P1 deprotect, R1 acylate, ring methylate, P3 deprotect

Cpd.	Route to A	Scheme 1: VN(R ²)-Y- CO ₂ H	P ² NH-CH(U)-CO ₂ H	Conversion of A to Product	U modification
105	Scheme 1	2-naphthoic-Gly-OH	Fmoc-L-Orn(Boc)-OH	Scheme 3	P3 deprotection, guanylation
106	Scheme 1 with N-methylation	Boc-Gly-OH	Fmoc-L-Orn(Boc)-OH	Scheme 4	P3 deprotection
107	Scheme 1	Alloc-β-(2-naphthyl)-L-Ala	Boc-L-Arg-(Cbz) ₂ -OH	Scheme 4	P3 deprotection
108	Scheme 2	Boc-Gly-OH	H-L-Orn(Cbz)-Oallyl	Scheme 5	P3 deprotection, guanylation, then deprotection after R1 derivatization
109	Scheme 2	Boc-Gly-OH	H-L-Arg(Cbz) ₂ -Oallyl	Scheme 4	P3 deprotection
110	Scheme 2	Boc-Gly-OH	H-D-Orn(Cbz)-Oallyl	Scheme 5	P3 deprotection, guanylation, then deprotection after R1 derivatization
111	Scheme 2	Boc-Gly-OH	H-D-Orn(Cbz)-Oallyl	Scheme 5	P3 deprotection, guanylation, then deprotection after R1 derivatization
112	Scheme 2	Boc-Gly-OH	H-L-Orn(Cbz)-Oallyl	Scheme 5	P3 deprotection, guanylation, then deprotection after R1 derivatization
113	Scheme 2	Boc-Gly-OH	H-L-Arg(Cbz) ₂ -Oallyl	Scheme 4	P3 deprotection
114	Scheme 2	Boc-Gly-OH	H-L-Arg(Cbz) ₂ -Oallyl	Scheme 4	P3 deprotection
115	Scheme 2	Boc-Gly-OH	H-L-Arg(Cbz) ₂ -Oallyl	Scheme 4	P3 deprotection
116	Scheme 2	Boc-Gly-OH	H-L-Arg(Cbz) ₂ -Oallyl	Scheme 4	P3 deprotection
117	Scheme 2	Boc-Gly-OH	H-D-Lys(Cbz)-Oallyl	Scheme 4 with urea formation after R1 derivatization	P3 deprotection
118	Scheme 2	Boc-Gly-OH	H-L-Lys(Cbz)-Oallyl	Scheme 4	P3 deprotection
119	Scheme 2	Boc-Gly-OH	H-L-Lys(Cbz)-Oallyl	Scheme 4	P3 deprotection
120	Scheme 2	Boc-Gly-OH	H-L-Lys(Cbz)-Oallyl	Scheme 4 with urea formation after R1 derivatization	P3 deprotection
121	Scheme 2	Boc-Gly-OH	H-L-Lys(Cbz)-Oallyl	Scheme 4	P3 deprotection
122	Scheme 2	Boc-Gly-OH	H-L-Lys(Cbz)-Oallyl	Scheme 4	P3 deprotection
123	Scheme 2	Boc-Gly-OH	H-L-Lys(Cbz)-Oallyl	Scheme 4 with urea formation after R1 derivatization	P3 deprotection
124	Scheme 2	Boc-Gly-OH	H-L-Arg(Cbz) ₂ -Oallyl	Scheme 4	P3 deprotection
125	Scheme 2	Boc-Gly-OH	H-L-Arg(Cbz) ₂ -Oallyl	Scheme 4 with urea formation after R1 derivatization	P3 deprotection
126	Scheme 2	Boc-Gly-OH	H-L-Arg(Cbz) ₂ -Oallyl	Scheme 4	P3 deprotection
127	Scheme 2	Boc-Gly-OH	H-L-Arg(Cbz) ₂ -Oallyl	Scheme 4	P3 deprotection
128	Scheme 2	Boc-Gly-OH	H-L-Arg(Cbz) ₂ -Oallyl	Scheme 4	P3 deprotection
129	Scheme 2	Boc-Gly-OH	H-L-Arg(Cbz) ₂ -Oallyl	Scheme 4	P3 deprotection

Cpd.	Route to A	Scheme 1: VN(R ²)-Y- CO ₂ H	P ² NH-CH(U)-CO ₂ H	Conversion of A to Product	U modification
130	Scheme 2	Boc-Gly-OH	H-L-Arg(Cbz) ₂ -Oallyl	Scheme 4 with urea formation after R1 derivatization	P3 deprotection
131	Scheme 2	Boc-Gly-OH	H-L-Arg(Cbz) ₂ -Oallyl	Scheme 4	P3 deprotection
132	Scheme 2	Boc-Gly-OH	H-L-Arg(Cbz) ₂ -Oallyl	Scheme 4 with urea formation after R1 derivatization	P3 deprotection
133	Scheme 2	Boc-Gly-OH	H-D-Arg(Cbz) ₂ -Oallyl	Scheme 4	P3 deprotection
134	Scheme 2	Boc-Gly-OH	H-D-Arg(Cbz) ₂ -Oallyl	Scheme 4	P3 deprotection
135	Scheme 2	Boc-Gly-OH	H-D-Arg(Cbz) ₂ -Oallyl	Scheme 4	P3 deprotection
136	Scheme 2	Boc-Gly-OH	H-D-Arg(Cbz) ₂ -Oallyl	Scheme 4 with urea formation after R1 derivatization	P3 deprotection
137	Scheme 2	Boc-Gly-OH	H-L-Lys(Cbz)-Oallyl	Scheme 4	P3 deprotection
138	Scheme 2	Boc-Gly-OH	H-L-Lys(Cbz)-Oallyl	Scheme 4	P3 deprotection
139	Scheme 2	Boc-Gly-OH	H-L-Lys(Cbz)-Oallyl	Scheme 4 with urea formation after R1 derivatization	P3 deprotection
140	Scheme 2	Boc-Gly-OH	H-L-Lys(Cbz)-Oallyl	Scheme 4	P3 deprotection
141	Scheme 2	Boc-Gly-OH	H-L-Lys(Cbz)-Oallyl	Scheme 4 with urea formation after R1 derivatization	P3 deprotection
142	Scheme 2	Boc-Gly-OH	H-L-Lys(Cbz)-Oallyl	Scheme 4	P3 deprotection
143	Scheme 2	Boc-Gly-OH	H-L-Lys(Cbz)-Oallyl	Scheme 4	P3 deprotection
144	Scheme 2	Boc-Gly-OH	H-D-Lys(Cbz)-Oallyl	Scheme 4	P3 deprotection
145	Scheme 2	Boc-Gly-OH	H-D-Lys(Cbz)-Oallyl	Scheme 4	P3 deprotection
146	Scheme 2	Boc-Gly-OH	H-D-Lys(Cbz)-Oallyl	Scheme 4 with urea formation after R1 derivatization	P3 deprotection
147	Scheme 2	Boc-Gly-OH	H-D-Lys(Cbz)-Oallyl	Scheme 4	P3 deprotection
148	Scheme 2	Boc-Gly-OH	H-D-Lys(Cbz)-Oallyl	Scheme 4	P3 deprotection
149	Scheme 2	Boc-Gly-OH	H-D-Lys(Cbz)-Oallyl	Scheme 4 with urea formation after R1 derivatization	P3 deprotection
150	Scheme 2	Boc-Gly-OH	H-D-Lys(Cbz)-Oallyl	Scheme 4	P3 deprotection
151	Scheme 2	Boc-Gly-OH	H-D-Lys(Cbz)-Oallyl	Scheme 4	P3 deprotection
152	Scheme 2	Boc-Gly-OH	H-D-Lys(Cbz)-Oallyl	Scheme 4	P3 deprotection
153	Scheme 2	Boc-Gly-OH	H-D-Lys(Cbz)-Oallyl	Scheme 4	P3 deprotection
154	Scheme 2	Boc-Gly-OH	H-L-Lys(Cbz)-Oallyl	Scheme 4	P3 deprotection
155	Scheme 2	Boc-Gly-OH	H-L-Lys(Cbz)-Oallyl	Scheme 4	P3 deprotection

Cpd.	Route to A	Scheme 1: VN(R ²)-Y- CO ₂ H	P ² NH-CH(U)-CO ₂ H	Conversion of A to Product	U modification
156	Scheme 2	Boc-Gly-OH	H-L-Lys(Cbz)-Oallyl	Scheme 4 with urea formation after R1 derivatization	P3 deprotection
157	Scheme 2	Boc-Gly-OH	H-L-Lys(Cbz)-Oallyl	Scheme 4	P3 deprotection
158	Scheme 2	Boc-Gly-OH	H-L-Lys(Cbz)-Oallyl	Scheme 4	P3 deprotection
159	Scheme 2	Boc-Gly-OH	H-L-Lys(Cbz)-Oallyl	Scheme 4	P3 deprotection
160	Scheme 2	Boc-Gly-OH	H-L-Lys(Cbz)-Oallyl	Scheme 4	P3 deprotection
161	Scheme 2	Boc-Gly-OH	H-L-Lys(Cbz)-Oallyl	Scheme 4 with urea formation after R1 derivatization	P3 deprotection
162	Scheme 2	Boc-Gly-OH	H-L-Lys(Cbz)-Oallyl	Scheme 4	P3 deprotection
163	Scheme 2	Boc-Gly-OH	H-L-Lys(Cbz)-Oallyl	Scheme 4	P3 deprotection
164	Scheme 2	Boc-Gly-OH	H-L-Lys(Cbz)-Oallyl	Scheme 4	P3 deprotection
165	Scheme 2	Boc-Gly-OH	H-D-Lys(Cbz)-Oallyl	Scheme 4	P3 deprotection
166	Scheme 2	Boc-Gly-OH	H-D-Lys(Cbz)-Oallyl	Scheme 4	P3 deprotection
167	Scheme 2	Boc-Gly-OH	H-D-Lys(Cbz)-Oallyl	Scheme 4 with urea formation after R1 derivatization	P3 deprotection
168	Scheme 2	Boc-Gly-OH	H-D-Lys(Cbz)-Oallyl	Scheme 4	P3 deprotection
169	Scheme 2	Boc-Gly-OH	H-D-Lys(Cbz)-Oallyl	Scheme 4	P3 deprotection
170	Scheme 2	Boc-Gly-OH	H-D-Lys(Cbz)-Oallyl	Scheme 4	P3 deprotection
171	Scheme 2	Boc-Gly-OH	H-D-Lys(Cbz)-Oallyl	Scheme 4 with urea formation after R1 derivatization	P3 deprotection
172	Scheme 2	Boc-Gly-OH	H-L-Arg(Cbz) ₂ -Oallyl	Scheme 4	P3 deprotection
173	Scheme 2	Boc-Gly-OH	H-L-Arg(Cbz) ₂ -Oallyl	Scheme 4	P3 deprotection
174	Scheme 2	Boc-Gly-OH	H-L-Arg(Cbz) ₂ -Oallyl	Scheme 4	P3 deprotection
175	Scheme 2	Boc-Gly-OH	H-L-Arg(Cbz) ₂ -Oallyl	Scheme 4	P3 deprotection
176	Scheme 2	Boc-Gly-OH	H-L-Arg(Cbz) ₂ -Oallyl	Scheme 4	P3 deprotection
177	Scheme 2	Boc-Gly-OH	H-L-Arg(Cbz) ₂ -Oallyl	Scheme 4	P3 deprotection
178	Scheme 2	Boc-Gly-OH	H-L-Arg(Cbz) ₂ -Oallyl	Scheme 4	P3 deprotection
179	Scheme 2	Boc-Gly-OH	H-L-Arg(Cbz) ₂ -Oallyl	Scheme 4	P3 deprotection
180	Scheme 2	Boc-Gly-OH	H-L-Arg(Cbz) ₂ -Oallyl	Scheme 4	P3 deprotection
181	Scheme 2	Boc-Gly-OH	H-L-Arg(Cbz) ₂ -Oallyl	Scheme 4	P3 deprotection
182	Scheme 1	Alloc-Gly-OH	Boc-L- Canavanine(Fmoc)-OH	Scheme 4	P3 deprotection
183	Scheme 1	Alloc-Gly-OH	Boc-L-Arg(Fmoc) ₂ -OH	Scheme 4	P3 deprotection
184	allylboration as in WO_199904 8913	Boc-D-Phe-OH	H-L-Orn(Cbz)-OMe	Scheme 5	P3 deprotection, guanylation, with another deprotection after P1 deprotection/ derivatization

Cpd.	Route to A	Scheme 1: VN(R ²)-Y- CO ₂ H	P ² NH-CH(U)-CO ₂ H	Conversion of A to Product	U modification
185	allylboration as in WO_199904 8913	Boc-D-Phe-OH	H-L-Orn(Cbz)-OMe	Scheme 5	P3 deprotection, guanylation, with another deprotection after P1 deprotection/ derivatization
186	Scheme 1	2-naphthoic- Gly-OH	Fmoc-L-Arg(Pbf)-OH	Scheme 3	P3 deprotection
187	Scheme 1	Cbz-Gly-OH	Fmoc-L-Orn(Boc)-OH	Scheme 4	P3 deprotection
188	Scheme 1	Cbz-Gly-OH	Fmoc-L-Orn(Boc)-OH	Scheme 4	P3 deprotection
189	Scheme 1	2-naphthoic- Gly-OH	Fmoc-L-Arg(NMe ₂)Pbf- OH	Scheme 3	P3 deprotection
190	Scheme 1	Cbz-Gly-OH	Fmoc-L-Orn(Boc)-OH	Scheme 4	P3 deprotection
191	Scheme 1	Cbz-Gly-OH	Fmoc-L-Orn(Boc)-OH	Scheme 4	P3 deprotection
192	Scheme 1	Cbz-Gly-OH	Fmoc-L-Orn(Boc)-OH	Scheme 4	P3 deprotection
193	Scheme 1	Cbz-Gly-OH	Fmoc-L-Orn(Boc)-OH	Scheme 4	P3 deprotection
194	Scheme 1	2-naphthoic- Gly-OH	Fmoc-L-Orn(Boc)-OH	Scheme 3	P3 deprotection, reductive alkylation
195	Scheme 1	2-naphthoic- Gly-OH	Fmoc-L-Arg(Pbf)-OH	Scheme 3	P3 deprotection
196	Scheme 1	2-naphthoic- Gly-OH	Fmoc-L-Arg(Pbf)-OH	Scheme 3	P3 deprotection
197	Scheme 1	Cbz-Gly-OH	Fmoc-L-Orn(Boc)-OH	Scheme 4	P3 deprotection, reductive alkylation
198	Scheme 1	Cbz-Gly-OH	Fmoc-L-Orn(Boc)-OH	Scheme 4	P3 deprotection
199	Scheme 1	Cbz-Gly-OH	Fmoc-L-Orn(Boc)-OH	Scheme 4	P3 deprotection
200	Scheme 1	Cbz-Gly-OH	Fmoc-L-Orn(Boc)-OH	Scheme 4	P3 deprotection
201	Scheme 1	2-naphthoic- Gly-OH	Fmoc-L-Arg(Pbf)-OH	Scheme 3	P3 deprotection
202	Scheme 1	2-naphthoic- Gly-OH	Fmoc-L-Arg(Pbf)-OH	Scheme 3	P3 deprotection
203	Scheme 1	2-naphthoic- Gly-OH	Fmoc-L-Arg(Pbf)-OH	Scheme 3	P3 deprotection
204	allylboration as in WO_199904 8913	Boc-D-Phe-OH	H-L-Orn(Cbz)-OMe	Scheme 5	P3 deprotection, guanylation, with another deprotection after P1 deprotection/ derivatization
205	Scheme 1	Cbz-Gly-OH	Fmoc-L-Orn(Boc)-OH	Scheme 4	P3 deprotection
206	Scheme 1	Cbz-Gly-OH	Fmoc-L-Orn(Boc)-OH	Scheme 4	XXXX, P1 deprotect, R1 acylate, ring methylate, P3 deprotect
207	Scheme 1	Cbz-Gly-OH	Fmoc-L-Orn(Boc)-OH	Scheme 4	P3 deprotection then dialkylation with alkyl dibromide
208	Scheme 1	Cbz-Gly-OH	Fmoc-L-Orn(Boc)-OH	Scheme 4	P3 deprotection then dialkylation with alkyl dibromide
209	Scheme 1	2-naphthoic- Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 3	P3 deprotection
210	Scheme 1	2-naphthoic- Gly-OH	Fmoc-L-Arg(Pbf)-OH	Scheme 3	P3 deprotection
211	Scheme 1	2-naphthoic- Gly-OH	Fmoc-L-Arg(Pbf)-OH	Scheme 3	P3 deprotection
212	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dap(Boc)-OH	Scheme 4	P3 deprotection

Cpd.	Route to A	Scheme 1: VN(R ²)-Y- CO ₂ H	P ² NH-CH(U)-CO ₂ H	Conversion of A to Product	U modification
213	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dap(Boc)-OH	Scheme 4	P3 deprotection then dialkylation with alkyl dibromide
214	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dap(Boc)-OH	Scheme 4	P3 deprotection then dialkylation with alkyl dibromide
215	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection
216	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection
217	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection then dialkylation with alkyl dibromide
218	Scheme 1	2-naphthoic-Gly-OH	Fmoc-L-Arg(Pbf)-OH	Scheme 3	P3 deprotection
219	Scheme 1	2-naphthoic-Gly-OH	Fmoc-L-Arg(Pbf)-OH	Scheme 3	P3 deprotection
220	Scheme 1	2-naphthoic-Gly-OH	Fmoc-L-Arg(Pbf)-OH	Scheme 3	P3 deprotection
221	allylboration as in WO_199904 8913	Boc-D-Phe-OH	H-L-Orn(Cbz)-OMe	Scheme 5	P3 deprotection, guanylation, with another deprotection after P1 deprotection/derivatization
222	allylboration as in WO_199904 8913	Boc-D-Phe-OH	H-L-Orn(Cbz)-OMe	Scheme 5	P3 deprotection, guanylation, with another deprotection after P1 deprotection/derivatization
223	Scheme 1	Cbz-Gly-OH	Boc-L-Nle-OH	Scheme 4	none
224	Scheme 1	Cbz-Gly-OH	Boc-L-Gln-OH	Scheme 4	none
225	Scheme 1	Cbz-Gly-OH	Fmoc-L-Orn(Boc)-OH	Scheme 4	P3 deprotection then acylation
226	Scheme 1	2-naphthoic-Gly-OH	Fmoc-L-Arg(Pbf)-OH	Scheme 3	P3 deprotection
227	Scheme 1	2-naphthoic-Gly-OH	Fmoc-L-Arg(Pbf)-OH	Scheme 3	P3 deprotection
228	Scheme 1	2-naphthoic-Gly-OH	Fmoc-L-Arg(Pbf)-OH	Scheme 3	P3 deprotection
229	Scheme 1	Cbz-b-Ala	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection then dialkylation with alkyl dibromide
230	Scheme 1	Alloc-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection
231	Scheme 1	Alloc-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection
232	Scheme 2	Cbz-Gly-OH	H-L-Arg(Pbf)-Oallyl	Scheme 4 with urea formation	P3 deprotection
233	Scheme 2	Cbz-Gly-OH	H-L-Arg(Pbf)-Oallyl	Scheme 4	P3 deprotection
234	Scheme 2	Cbz-Gly-OH	H-L-Arg(Pbf)-Oallyl	Scheme 4	P3 deprotection
235	Scheme 2	Cbz-Gly-OH	H-L-Arg(Pbf)-Oallyl	Scheme 4	P3 deprotection
236	Scheme 2	Cbz-Gly-OH	H-L-Arg(Pbf)-Oallyl	Scheme 4	P3 deprotection
237	Scheme 1	2-naphthoic-Gly-OH	Fmoc-L-Arg(Pbf)-OH	Scheme 3	P3 deprotection
238	Scheme 1	2-naphthoic-Gly-OH	Fmoc-L-Orn(Boc)-OH	Scheme 3	P3 deprotection
239	Scheme 1	Alloc-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection then dialkylation with alkyl dibromide

Cpd.	Route to A	Scheme 1: VN(R ²)-Y- CO ₂ H	P ² NH-CH(U)-CO ₂ H	Conversion of A to Product	U modification
240	Scheme 1	Alloc-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection then dialkylation with alkyl dibromide
241	Scheme 1	Alloc-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection then dialkylation with alkyl dibromide
242	Scheme 2	Boc-Gly-OH	H-D-Orn(Boc)-Oallyl	Scheme 4	P3 deprotection, guanylation, deprotection
243	Scheme 2	Boc-Gly-OH	H-D-Orn(Boc)-Oallyl	Scheme 4	P3 deprotection, guanylation, deprotection
244	Scheme 2	Boc-Gly-OH	H-D-Orn(Boc)-Oallyl	Scheme 4	P3 deprotection, guanylation, deprotection
245	Scheme 2	Boc-Gly-OH	H-D-Orn(Boc)-Oallyl	Scheme 4	P3 deprotection
246	Scheme 2	Boc-Gly-OH	H-D-Orn(Boc)-Oallyl	Scheme 4	P3 deprotection
247	Scheme 2	Boc-Gly-OH	H-D-Orn(Boc)-Oallyl	Scheme 4	P3 deprotection, guanylation, deprotection
248	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 5	P3 deprotection then dialkylation with alkyl dibromide
249	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 5	P3 deprotection then dialkylation with alkyl dibromide
250	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dap(Boc)-OH	Scheme 5	P3 deprotection then dialkylation with alkyl dibromide
251	Scheme 1	2-naphthoic-Gly-OH	Fmoc-L-Arg(Pbf)-OH	Scheme 3	R5 deprotection and amidation then P3 deprotection
252	Scheme 1	2-naphthoic-Gly-OH	Fmoc-L-Arg(Pbf)-OH	Scheme 3	R5 deprotection and amidation then P3 deprotection
253	Scheme 1	Alloc-Gly-OH	Fmoc-L-Dap(Boc)-OH	Scheme 4	P3 deprotection
254	Scheme 1	Alloc-Gly-OH	Fmoc-L-Dap(Boc)-OH	Scheme 4	P3 deprotection
255	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection
256	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dap(Boc)-OH	Scheme 5	P3 deprotection then dialkylation with alkyl dibromide
257	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dap(Boc)-OH	Scheme 5	P3 deprotection then dialkylation with alkyl dibromide
258	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection
259	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection
260	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 5	P3 deprotection then dialkylation with alkyl dibromide
261	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection then dialkylation with alkyl dibromide
262	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection then dialkylation with alkyl dibromide
263	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection

Cpd.	Route to A	Scheme 1: VN(R ²)-Y- CO ₂ H	P ² NH-CH(U)-CO ₂ H	Conversion of A to Product	U modification
264	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection then dialkylation with alkyl dibromide
265	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection
266	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection then dialkylation with alkyl dibromide
267	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection
268	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection then dialkylation with alkyl dibromide
269	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection, condensation, reduction
270	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection then dialkylation with alkyl dibromide
271	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection then dialkylation with alkyl dibromide
272	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection then dialkylation with alkyl dibromide
273	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 5	P3 deprotection then dialkylation with alkyl dibromide
274	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 5	P3 deprotection then dialkylation with alkyl dibromide
275	Scheme 1	Cbz-Gly-OH	Boc-L-Gln(piperidyl)-OH	Scheme 4	none
276	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dap(Boc)-OH	Scheme 5	P3 deprotection then dialkylation with alkyl dibromide
277	Scheme 1	Cbz-Gly-OH	Fmoc-L-Orn(Boc)-OH	Scheme 5	P3 deprotection then dialkylation with alkyl dibromide
278	Scheme 1	Boc-Aib-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection
279	Scheme 1	Boc-Aib-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection then dialkylation with alkyl dibromide
280	Scheme 1	Alloc-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection, reductive alkylation
281	Scheme 1	Alloc-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection, reductive alkylation
282	Scheme 1	Alloc-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection, reductive alkylation
283	Scheme 1	Alloc-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 3	P3 deprotection
284	Scheme 2	Boc-Gly-OH	H-L-3-(imidazol-1-yl)Ala-Oallyl	Scheme 4	none
285	Scheme 1	Cbz-Gly-OH	Fmoc-L-Asp[N(Me)OMe]-OH	Scheme 4	P3 conversion to aldehyde then reductive amination
286	Scheme 1	Cbz-Gly-OH	Fmoc-L-Asp[N(Me)OMe]-OH	Scheme 4	P3 conversion to aldehyde then reductive amination
287	Scheme 1	Cbz-Gly-OH	N-Fmoc-1(1-Boc-piperidin-4yl)-D,L-Gly-OH	Scheme 4	P3 deprotection

Cpd.	Route to A	Scheme 1: VN(R ²)-Y- CO ₂ H	P ² NH-CH(U)-CO ₂ H	Conversion of A to Product	U modification
288	Scheme 1	Cbz-Gly-OH	N-Fmoc-1-(1-Boc-piperidin-4-yl)-D,L-Gly-OH	Scheme 4	P3 deprotection, reductive alkylation
289	Scheme 1	Cbz-Gly-OH	Fmoc-L-HoLeu-OH	Scheme 4	none
290	Scheme 1	Cbz-Gly-OH	Fmoc-L-Asp[N(Me)OMe]-OH	Scheme 4	P3 conversion to aldehyde then reductive amination
291	Scheme 1	Cbz-Gly-OH	Fmoc-L-Asp[N(Me)OMe]-OH	Scheme 4	P3 conversion to aldehyde then reductive amination
292	Scheme 1	Cbz-Gly-OH	Fmoc-L-Asp[N(Me)OMe]-OH	Scheme 4	P3 conversion to aldehyde then reductive amination
293	Scheme 1	Cbz-Gly-OH	Fmoc-L-Asp[N(Me)OMe]-OH	Scheme 4	P3 conversion to aldehyde then reductive amination
294	Scheme 1	Cbz-Gly-OH	Fmoc-L-Asp[N(Me)OMe]-OH	Scheme 4	P3 conversion to aldehyde then reductive amination
295	Scheme 1	2-naphthoic-Gly-OH	Boc-L-Gln(Me,nBu)	Scheme 4	none
296	Scheme 1	2-naphthoic-Gly-OH	Boc-L-Gln(chex)	Scheme 4	none
297	Scheme 1	Cbz-Gly-OH	N-Fmoc-1-(1-Boc-piperidin-4-yl)-D,L-Gly	Scheme 4	P3 deprotection, reductive alkylation
298	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)	Scheme 5	P3 deprotection, alkylation
299	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)	Scheme 5	P3 deprotection, alkylation
300	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)	Scheme 5	P3 deprotection, alkylation
301	Scheme 2	Cbz-Gly-OH	H-L-Arg(Pbf)-Oallyl	Scheme 4	P3 deprotection
302	Scheme 2	Cbz-Gly-OH	H-L-Arg(Pbf)-Oallyl	Scheme 4	P3 deprotection
303	Scheme 2	Cbz-Gly-OH	H-L-Arg(Pbf)-Oallyl	Scheme 4	P3 deprotection
304	Scheme 2	Cbz-Gly-OH	H-L-Arg(Pbf)-Oallyl	Scheme 4	P3 deprotection
305	Scheme 1	Boc-Gly-OH	Cbz-DL-γ-nitro-Leu	Scheme 4	P3 reduction to amine
306	Scheme 1	Boc-Gly-OH	Cbz-DL-γ-nitro-Leu	Scheme 4	P3 reduction to amine
307	Scheme 2	Cbz-Gly-OH	H-L-Arg(Pbf)-Oallyl	Scheme 4	P3 deprotection
308	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)	Scheme 4	P3 deprotection
309	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)	Scheme 4	P3 deprotection
310	Scheme 2	Cbz-Gly-OH	H-L-Arg(Pbf)-Oallyl	Scheme 4	P3 deprotection
311	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)	Scheme 4	P3 deprotection, dialkylation with alkyl dibromide
312	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)	Scheme 4	P3 deprotection, dialkylation with alkyl dibromide
313	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)	Scheme 4	P3 deprotection
314	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)	Scheme 4	P3 deprotection then reductive alkylation
315	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)	Scheme 4	P3 deprotection
316	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)	Scheme 4	P3 deprotection then dialkylation

Cpd.	Route to A	Scheme 1: VN(R ²)-Y- CO ₂ H	P ² NH-CH(U)-CO ₂ H	Conversion of A to Product	U modification
317	Scheme 1	Boc-Gly-OH	Cbz-DL-γ-nitro-Leu	Scheme 4	P3 reduction to amine then dialkylation with alkyl dibromide
318	Scheme 2	Cbz-Gly-OH	H-L-Arg(Pbf)-Oallyl	Scheme 4	P3 deprotection
319	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)	Scheme 4	P3 deprotection
320	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)	Scheme 4	P3 deprotection
321	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)	Scheme 4	P3 deprotection, dialkylation with alkyl dibromide
322	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)	Scheme 4	P3 deprotection, dialkylation with alkyl dibromide
323	Scheme 2	Cbz-Gly-OH	H-L-Arg(Pbf)-Oallyl	Scheme 4	P3 deprotection
324	Scheme 2	Cbz-Gly-OH	H-L-Arg(Pbf)-Oallyl	Scheme 4	P3 deprotection
325	Scheme 2	Cbz-Gly-OH	H-L-Arg(Pbf)-Oallyl	Scheme 4	P3 deprotection
326	Scheme 2	Cbz-Gly-OH	H-L-Arg(Pbf)-Oallyl	Scheme 4	P3 deprotection
327	Scheme 2	Cbz-Gly-OH	H-L-Arg(Pbf)-Oallyl	Scheme 4	P3 deprotection
328	Scheme 2	Cbz-Gly-OH	H-L-Arg(Pbf)-Oallyl	Scheme 4	P3 deprotection
329	Scheme 1	Cbz-Gly-OH	Fmoc-L-2- aminooctanoic	Scheme 4	none
330	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)	Scheme 5	P3 deprotection, alkylation
331	Scheme 1	Cbz-Gly-OH	Boc-L-5-HO-Nle	Scheme 4	none
332	Scheme 1	Cbz-Gly-OH	Fmoc-L-HoSer(Me)	Scheme 4	none
333	Scheme 1	Alloc-Gly-OH	Boc-L-HoSer(Bzl)	Scheme 4	none
334	Scheme 1	Cbz-Gly-OH	Boc-L-Leu	Scheme 4	none
335	Scheme 2	Cbz-Gly-OH	H-L-Arg(Pbf)-Oallyl	Scheme 4	P3 deprotection
336	Scheme 2	Cbz-Gly-OH	H-L-Arg(Pbf)-Oallyl	Scheme 4	P3 deprotection
337	Scheme 2	Cbz-Gly-OH	H-L-Arg(Pbf)-Oallyl	Scheme 4	P3 deprotection
338	Scheme 2	Cbz-Gly-OH	H-L-Arg(Pbf)-Oallyl	Scheme 4	P3 deprotection
339	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)	Scheme 4	P3 deprotection
340	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)	Scheme 4	P3 deprotection, dialkylation with alkyl dibromide
341	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)	Scheme 4	P3 deprotection, dialkylation with alkyl dibromide
342	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)	Scheme 4	P3 deprotection
343	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)	Scheme 4	P3 deprotection, dialkylation with alkyl dibromide
344	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)	Scheme 4	P3 deprotection, dialkylation with alkyl dibromide
345	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)	Scheme 4	P3 deprotection, dialkylation with alkyl dibromide
346	Scheme 2	Boc-Gly-OH	H-L-Arg(Cbz) ₂ -Oallyl	Scheme 4	P3 deprotection

Cpd.	Route to A	Scheme 1: VN(R ²)-Y- CO ₂ H	P ² NH-CH(U)-CO ₂ H	Conversion of A to Product	U modification
347	Scheme 2	Boc-Gly-OH	H-L-Arg(Cbz) ₂ -Oallyl	Scheme 4	P3 deprotection
348	Scheme 2	Boc-Gly-OH	H-L-Arg(Cbz) ₂ -Oallyl	Scheme 4	P3 deprotection
349	Scheme 2	Boc-Gly-OH	H-L-Arg(Cbz) ₂ -Oallyl	Scheme 4	P3 deprotection
350	Scheme 2	Boc-Gly-OH	H-D-Arg(Cbz) ₂ -Oallyl	Scheme 4	P3 deprotection
351	Scheme 2	Boc-Gly-OH	H-D-Arg(Cbz) ₂ -Oallyl	Scheme 4	P3 deprotection
352	Scheme 2	Boc-Gly-OH	H-D-Arg(Cbz) ₂ -Oallyl	Scheme 4	P3 deprotection
353	Scheme 2	Boc-Gly-OH	H-D-Arg(Cbz) ₂ -Oallyl	Scheme 4	P3 deprotection
354	Scheme 2	Boc-Gly-OH	H-D-Arg(Cbz) ₂ -Oallyl	Scheme 4	P3 deprotection
355	Scheme 2	Boc-Gly-OH	H-D-Arg(Cbz) ₂ -Oallyl	Scheme 4	P3 deprotection
356	Scheme 2	Boc-Gly-OH	H-D-Arg(Cbz) ₂ -Oallyl	Scheme 4	P3 deprotection
357	Scheme 2	Cbz-Gly-OH	H-L-Orn(Boc)-Oallyl	Scheme 4	P3 deprotection, guanylation, deprotection
358	Scheme 2	Cbz-Gly-OH	H-L-Orn(Boc)-Oallyl	Scheme 4	P3 deprotection
359	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)	Scheme 4	P3 deprotection then dalkylation with alkyl dibromide
360	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)	Scheme 4	P3 deprotection, then acylation with isocyanate
361	Scheme 1	Alloc-Gly-OH	Fmoc-L-Asp(OBn)-OH	Scheme 4	none
362	Scheme 1	Alloc-Gly-OH	Fmoc-L-Glu(OBn)-OH	Scheme 4	none
363	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 5	P3 deprotection then dalkylation with alkyl dibromide
364	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection then reductive alkylation then acetylation
365	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dap(Boc)-OH	Scheme 4	P3 deprotection then reductive alkylation
366	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dap(Boc)-OH	Scheme 4	P3 deprotection then guanylation
367	Scheme 1	Alloc-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection
368	Scheme 1	Alloc-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection then dalkylation with alkyl dibromide
369	Scheme 1	Alloc-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection then dalkylation with alkyl dibromide
370	Scheme 1	N-(6-Cl-2-naphthoic)-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 3	P3 deprotection then dalkylation with alkyl dibromide
371	Scheme 1	N-(6-Cl-2-naphthoic)-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 3	P3 deprotection then dalkylation with alkyl dibromide
372	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection
373	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection then dalkylation with alkyl dibromide
374	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection then dalkylation with alkyl dibromide

Cpd.	Route to A	Scheme 1: VN(R ²)-Y- CO ₂ H	P ² NH-CH(U)-CO ₂ H	Conversion of A to Product	U modification
375	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection then dialkylation with alkyl dibromide
376	Scheme 1	Alloc-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection then dialkylation with alkyl dibromide
377	Scheme 1	Alloc-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection then dialkylation with alkyl dibromide
378	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 5, use isocyanate for R1X	P3 deprotection then dialkylation with alkyl dibromide
379	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection then dialkylation with alkyl dibromide
380	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection then sulfonylation
381	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection then acylation with chloroformate
382	Scheme 1	Cbz-Gly-OH	Fmoc-DL-2-(1-Boc-4-piperidyl)-Gly-OH	Scheme 4	P3 deprotection then reductive alkylation with ketone
383	Scheme 1	Cbz-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 4	P3 deprotection then dialkylation with alkyl dibromide
384	Scheme 1	Alloc-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 5	P3 deprotection then dialkylation with alkyl dibromide
385	Scheme 1	Alloc-Gly-OH	Fmoc-L-Dab(Boc)-OH	Scheme 5	P3 deprotection then dialkylation with alkyl dibromide
386	Scheme 1	Cbz-Gly-OH	Fmoc-D-Dab(Boc)-OH	Scheme 4	P3 deprotection then dialkylation with alkyl dibromide
387	Scheme 2	Cbz-Gly-OH	H-L-Dab(Boc)-Oallyl	Scheme 4	P3 deprotection then dialkylation with alkyl dibromide
388	Scheme 2	Cbz-Gly-OH	H-D-Dab(Boc)-Oallyl	Scheme 4	P3 deprotection then dialkylation with alkyl dibromide
389	Scheme 1	Cbz-Gly-OH	Fmoc-D-Dab(Boc)-OH	Scheme 4	P3 deprotection then dialkylation with alkyl dibromide

Example 74 – Human MC3R and MC4R Radioligand Binding Assay

Assessments of compound binding to human MC3R (hMC3R) and human MC4R (hMC4R) by displacement of an ¹²⁵I-labeled NDP-MSH receptor ligand peptide were performed essentially as described in the data sheets produced by Perkin Elmer to accompany their frozen hMC3R membranes (Perkin Elmer catalog number RBXMC3M400UA) and their frozen hMC4R membranes (Perkin Elmer catalog number RBHMC4M400UA).

Alternatively, the frozen hMC3R and hMC4R plasma membranes were prepared as described below from transfected mammalian cells (prepared as in Example 76, using plasmid DNA

containing the human MC3R or MC4R gene in a plasmid vector with a mammalian origin of replication.

Preparation of Frozen hMC3R and hMC4R Plasma Membranes:

5 Adherent cells were washed with warm Hanks buffered saline solution (HBSS). 1 mL of cold HBSS was added to each flask and the cells were scraped off with a rubber policeman. The scraped cells were added to a 50 mL tube on ice. The plates were then rinsed twice with 5 mL cold HBSS and this was also added to the tube. The cells were centrifuged at 1000 x *g* for 5 mins in a bench top centrifuge and the supernatant was
10 decanted. The remaining cell pellet was resuspended in 0.25 M sucrose. The cell suspension was centrifuged again as previously and the pellet resuspended in 5 mL of 0.25 M sucrose containing protease inhibitors. The cells were homogenised by a 10 second pulse with an Ika disperser followed by 30 seconds on ice. The homogenisation and ice incubation was repeated three times. The mixture was then centrifuged at 1260 x *g* for 5 mins. The
15 supernatant was decanted into another centrifuge tube, to which a buffer containing 50 mM Tris, pH 7.4, 12.5 mM MgCl₂, 5 mM EGTA and protease inhibitors was added to make the volume up to 30 mL. This was centrifuged at 30,000 x *g* for 90 mins at 4°C. The resulting pellet was resuspended in 1 mL of the buffer above also containing 10% glycerol. Membranes were aliquoted into cryovials which were snap-frozen in a dry-ice/ethanol bath before being
20 stored at -80°C until required for use.

[¹²⁵I] NDP-MSH: radiolabeled in house and purified by HPLC:

Na¹²⁵I (0.5 mCi, 17.4 Ci/mg) was added to 50 µL sodium phosphate (50 mM, pH 7.4) in an eppendorf tube precoated with IODOGEN. After incubation for 10 mins the phosphate buffer
25 containing the iodine was added to NDP-MSH (10 µL at 1 mg/mL) in a separate eppendorf tube. This was incubated for a further 10 mins. The iodinated NDP-MSH was purified by HPLC on a Zorbax SB 300 column using solvent A: 0.05% TFA and solvent B: 90% acetonitrile 0.045% TFA with a linear gradient, 0-67% B over 60 mins. The ¹²⁵I NDP-MSH eluted at 52 mins after the unlabeled starting material (48 min) and was counted and stored in
30 the freezer. It was used within 48 hrs, as radioactive decay and ligand decomposition resulted in greatly reduced specific binding observed after 72 hrs.

Reagents:

Incubation buffer: 25 mM HEPES-KOH (pH 7.0), 1.5 mM CaCl₂, 1 mM MgSO₄, 0.1 M NaCl, 1
35 mM 1,10-phenanthroline, and 1 CompleteTM protease inhibitor tablet/100 mL (Roche, catalog number 1873580)

Perkin Elmer frozen hMC3 or hMC4 membranes: catalog number RBXMC3M400UA / RBHMC4M400UA, 0.4 mL/vial; 400 microassays/vial, 0.78 mg/mL protein concentration

Vials of frozen membranes were thawed rapidly immediately before use, diluted with binding buffer and vortexed. Resuspended membranes were kept on ice until they were added to the wells of the plate.

Binding Protocol for 400 microassays per vial:

Assays were performed in 96 well polypropylene plates. Membranes (0.78 μ g 40 μ L of a 1:40 dilution in incubation buffer) were added to [125 I] NDP-MSH (0.84 nM; 2200 Ci/mmol) and test compounds in a total volume of 140 μ L. This was incubated for 1 hr at 37 $^{\circ}$ C. Non-specific binding was determined with 3 mM NDP-MSH. Plates were filtered using a Tomtec cell harvester with GF/A filters (Wallac) (presoaked in 0.6% polyethylenimine) and washed three times with 1.0 mL ice-cold wash buffer (the above incubation buffer without 1,10-phenanthroline and CompleteTM protease inhibitor tablet). The filters were dried in a 37 $^{\circ}$ C oven, placed in a sample bag and 5 mL Betaplatescint (Wallac) was added. Prepared filters were counted in cassettes in a Microbeta Trilux (Wallac) for 1 min. Non-specific binding just under 5%. Data analysis was performed using GraphPad Prism 4, employing competition binding with a single site model and a fixed Hill coefficient. The following equation was used: $Y = \text{Bottom} + (\text{Top}-\text{Bottom})/1/10^{(X-\log EC_{50})}$, where $X = \log(\text{concentration})$ and $Y = \text{binding}$ to fit the data.

Example 75 – Activity of Selected Compounds: hMC3R and hMC4R binding

Representative compounds of the present invention were tested for binding in the hMC3R and hMC4R assays as in Example 74, as listed in Table 4. The compounds were tested as their trifluoroacetate or hydrochloride salts, or as their free base.

Table 4: Experimental Properties and MC3R/MC4R Radioligand Binding of Compounds

x = <10 μ M; xx = < 1 μ M; xxx = < 100 nM

Cpd.	MS (M+1)	t_R (min)	MC3R radioligand IC ₅₀	MC4R radioligand IC ₅₀
100	556.2	5.74	x	x
101	473.4	5.59	x	x
102	499.3	5.77	x	x
103	629.4	6.27	x	x
104	629.3	6.22	xx	xx
105	591.1	5.94	x	x
106	549.3	5.93	x	
107	606.4	6.033	x	x
108	603.3	6.11	x	x

Cpd.	MS (M+1)	t _R (min)	MC3R radioligand IC ₅₀	MC4R radioligand IC ₅₀
109	612.3	5.43	x	xx
110	603.3	6.45	x	x
111	603.4	6.23	x	x
112	603.2	6.21	x	xx
113	578.3	5.26	x	x
114	579.3	5.52	x	x
115	578.3	5.72		x
116	578.3	5.78		x
117	561.3	7.2	x	xx
118	561.3	6.14	xx	x
119	575.4	6.22	xx	x
120	573.2	7.31	xx	xx
121	535.5	5.85	x	x
122	549.3	5.83	x	x
123	547.3	7.26	xx	x
124	603.4	6.26	x	x
125	601.2	7.15	x	x
126	563.3	5.84	x	x
127	577.4	5.98	x	xx
128	589.2	6.37	xx	xx
129	603.3	6.29	xx	xx
130	601.2	7.38	xx	x
131	577.6	6.21	x	xx
132	575.5	6.98	xx	x
133	589.2	6.12	x	x
134	603.2	6.16	x	x
135	577.3	5.84	x	x
136	575.3	7.02	x	x
137	535.2	5.83	x	
138	549.4	5.88	x	x
139	547.3	6.89	xx	x
140	509.2	5.51	x	
141	547.3	6.99	x	x
142	509.2	5.51	x	x
143	523.3	5.56	x	x
144	535.4	5.82	x	
145	549.3	5.87	x	x
146	547.3	6.88	x	x
147	535.2	5.84	x	xx
148	548.3	5.91	xx	xx
149	547.4	6.92	xx	xx
150	509.2	5.51	x	x
151	523.3	5.66	x	x
152	509.2	5.39	x	x
153	523.3	5.51		x
154	535.3	5.92	x	x
155	549.4	5.96	xx	xx

Cpd.	MS (M+1)	t _R (min)	MC3R radioligand IC ₅₀	MC4R radioligand IC ₅₀
156	547.3	6.92	x	xx
157	509.2	5.56	x	x
158	523.4	5.63		x
159	535.4	5.85	x	x
160	549.4	5.95	xx	xx
161	547.4	6.96	xx	xx
162	509.5	5.54	x	x
163	523.1	5.60	xx	xx
164	523.3	5.56	x	xx
165	535.4	5.88	x	x
166	549.3	5.95	x	x
167	547.2	6.90	xx	xx
168	509.4	5.55	x	
169	535.3	5.86	x	x
170	549.3	5.88	x	x
171	547.4	6.92	xx	x
172	527.2	5.33		x
173	533.3	5.54		x
174	620.2	6.16	x	x
175	620.2	6.21	x	x
176	566.3	5.70	x	x
177	555.2	5.55		x
178	555.2	5.74		x
179	583.4	6.21	x	x
180	587.2	4.90		x
181	547.4	5.78		x
182	579.3	5.83	x	
183	557.3	6.06	x	x
184	562.3	5.21	x	x
185	635.4	-	x	x
186	493.3	5.41	x	x
187	615.3	6.20	x	x
188	545.4	5.92	x	x
189	605.3	5.94	x	x
190	525.2	5.79	x	
191	529.5	5.59	x	
192	553.5	5.87	x	
193	553.3	5.89	x	
194	617.1	6.21	x	x
195	523.2	5.49	x	x
196	575.4	5.72	x	x
197	611.2	6.2	x	x
198	585.5	6.23	x	x
199	550.5	5.81		x
200	586.5	6.18	x	x
201	506.3	5.73	x	x
202	613.2	6.06	x	x

Cpd.	MS (M+1)	t _R (min)	MC3R radioligand IC ₅₀	MC4R radioligand IC ₅₀
203	537.2	5.66	x	x
204	592.3	6.75	x	x
205	543.5	5.77	x	x
206	543.5	5.66	x	x
207	599.4	5.99	x	x
208	613.5	6.08	x	x
209	521.2	5.85	x	x
210	537.4	5.61	x	x
211	551.3	5.70	x	x
212	517.4	6.51	x	x
213	575.3	6.71	x	x
214	585.4	6.83	x	x
215	539.3	5.87	x	x
216	531.4	5.89	x	x
217	607.3	6.29	x	x
218	620.5	5.44	x	x
219	557.4	5.61	x	x
220	557.3	5.71	x	x
221	634.4	5.53	x	xx
222	634.3	-	x	xx
223	544.5	7.42	x	
224	559.4	6.59	x	
225	635.5	7.34	x	
226	593.5	6.02	xx	x
227	481.3	5.47	x	
228	521.5	6.10	x	x
229	621.2	6.06	x	x
230	519.2	5.93	x	x
231	511.2	5.94	x	x
232	588.4	6.08	x	x
233	590.4	-		x
234	590.4	5.21		x
235	562.5	4.86	x	xx
236	604.3	5.27		xx
237	540	5.61	x	
238	527	5.96	x	x
239	587.2	6.33	x	x
240	567.3	6.12	x	x
241	577.2	6.31	x	x
242	576.3	4.84		x
243	576.4	4.92		x
244	590.5	4.99		x
245	684.3	6.32		x
246	684.5	6.50		x
247	590.3	6.28		x
248	511.4	5.73	x	
249	493.7	5.71	x	

Cpd.	MS (M+1)	t _R (min)	MC3R radioligand IC ₅₀	MC4R radioligand IC ₅₀
250	489.4	6.42		x
251	612.6	5.49	x	
252	620.4	5.71	x	x
253	505.1	6.46	x	x
254	485.2	6.26	x	x
255	491.2	5.69	x	x
256	573.1	6.07	x	x
257	565.2	6.88	x	x
258	491.2	5.69	x	x
259	483.4	5.77	x	x
260	527.3	5.95	x	
261	623.2	6.41	x	x
262	607.5	6.6	x	
263	539.4	6.32	x	x
264	593.5	6.26	x	
265	525.3	6.03	x	
266	601.3	6.09	x	
267	533.2	5.81	x	
268	601.3	6.10	x	
269	613.4	6.31	x	
270	575.3	6.26	xx	x
271	561.4	6.26	xx	
272	559.1	6.11	x	
273	645.3	6.28	x	x
274	640.2	6.7	x	x
275	603.2	7.23	x	
276	561.4	6.88	x	
277	589.4	6.24	x	x
278	559.1	5.90	x	x
279	627.4	6.56	x	x
280	577.1	6.37	xx	x
281	561.1	6.17	x	x
282	549.2	6.28	x	x
283	507.2	6	x	
284	568.2	-	x	
285	595.2	6.5	x	
286	575.2	6.62	xx	
287	547.2	5.96	x	x
288	617.2	6.52	x	x
289	534.3	7.66	x	
290	587.4	6.55	xx	x
291	575.2	5.82	x	
292	603.4	5.98	x	
293	573.1	6.32	x	
294	573.1	6.18	x	
295	571.1	7.11	x	
296	583.3	6.98	x	

Cpd.	MS (M+1)	t _R (min)	MC3R radioligand IC ₅₀	MC4R radioligand IC ₅₀
297	575.2	6.06	x	x
298	593.4	6.01	x	x
299	549.2	5.87	x	x
300	563.3	6.05	x	x
301	619.2	4.41		xx
302	606.2	5.16	xx	xxx
303	619.4	4.45	x	xx
304	622.4	5.31	x	xx
305	535.2	6.33	x	
306	535.2	6.5	x	
307	602.3	5.17	x	x
308	457.2	5.64	x	
309	457.2	5.78	x	
310	608.4	5.39	xx	x
311	525.2	6.05	xx	
312	525.3	6.13	x	
313	491	5.63	x	
314	533.2	5.94	x	
315	533.1	6.44	xx	x
316	603	6.44	xx	x
317	603.2	6.96	xxx	x
318	619.9	5.45	xx	x
319	473.1	5.99	x	x
320	473.2	6.09	x	
321	541.2	6.34	xx	
322	541.1	6.43	xx	x
323	635.3	4.75	x	xxx
324	635.3	4.75	x	xxx
325	602.3	4.90		x
326	586.4	5.50	x	x
327	620.3	5.42		xxx
328	618.3	5.54		x
329	548.3	7.86	x	
330	591.1	6.36	x	x
331	536.2	6.57	x	
332	522.4	6.72	xx	
333	598.2	7.49	x	
334	520.1	7.36	x	
335	640.2	5.44	xx	x
336	827.7	7.30	xx	x
337	606.1	5.19	x	x
338	757.9	6.89	xx	x
339	455	5.16	x	
340	525.2	6.10	xx	
341	523.3	6.09	x	
342	471.1	5.53	x	
343	539.3	6.11	x	

Cpd.	MS (M+1)	t _R (min)	MC3R radioligand IC ₅₀	MC4R radioligand IC ₅₀
344	539.2	6.19	xx	x
345	541.3	6.32		
346	519.3	5.72	x	
347	494.4	4.65	x	
348	519.3	5.71	x	
349	494.0	4.59	x	
350	519.3	5.74	x	
351	496.3	4.93	x	
352	519.3	5.71	xx	
353	482.4	4.80	x	
354	493.1	5.35	x	
355	507.2	5.42	x	
356	494.0	4.63	x	
357	607.1	5.58		x
358	564.2	5.24		x
359	589.3	6.588	xx	x
360	592.3	7.079	x	
361	612.2	7.610	x	x
362	626.4	7.694	x	
363	601.3	6.692	x	x
364	591.3	7.237	x	
365	535.3	6.940	x	
366	535.3	6.375	x	
367	519.2	5.979	x	
368	587.1	6.342	x	x
369	603.1	6.572	x	x
370	581.2	6.217	xx	
371	581.0	6.331	xx	
372	473.3	6.030	x	
373	541.1	6.363	x	
374	625.4	6.570	x	
375	577.2	6.297	x	
376	603.1	6.451	x	
377	589.1	6.227	x	
378	554.3	6.017	xx	xx
379	637.0	6.755	x	x
380	613.3	7.028	x	
381	607.2	-	x	
382	589.5	6.186	x	
383	574.8	6.265	x	
384	618.9	6.745	x	
385	596.9	6.196	x	
386	575.4	6.404	x	
387	575.2	6.262	x	
388	575.2	6.110	x	
389	575.4	6.274	xx	x

Example 76 – Inhibition or stimulation of cAMP signal in cells expressing human MC4R
Transient transfection of mammalian cell lines:

The mammalian cell line, human embryonic kidney cells (HEK 293), were maintained in Dulbeccos Modified Eagle's medium (DMEM) with 5% fetal bovine serum, L- glutamine, high glucose and antibiotics/antimycotics. On the day prior to transfection, cells were passaged using trypsin/EDTA and seeded into 75 cm² flasks so that they would be approximately 90% confluent the next day. The next day, the cell media was replaced with fresh antibiotic/antimycotic-containing DMEM. Approximately 100 µl of the transfection lipid Turbofectin 8.0 (Origene Technologies, MD, USA), was diluted in 1.0 mL of serum and antibiotic/antimycotic-free OptiMEM in a sterile 15 mL tube and incubated for 5 mins at room temperature. Following incubation, approximately 10-20 µg of plasmid DNA expressing the gene of interest (for example: Homo sapiens melanocortin 4 receptor) was diluted into the transfection mix and incubated for a further 30 mins at room temperature. The DNA/lipid solution was then added drop-wise to the media covering the cells while rocking the flask gently. 24 hrs post-transfection, the cells were passaged and seeded directly into two, 75cm² flasks and left to recover. 48 hrs post transfection, cells were harvested for use in assays with cell dissociation solution.

Cyclic-Adenosine Monophosphate [cAMP] stimulation assay:

HEK 293 cells transiently expressing the melanocortin MC4 receptor were suspended in stimulation buffer (Hanks buffered saline solution (HBSS), 0.1 % bovine serum albumin, protease inhibitors and 0.5 mM 3-Isobutyl-1-methylxanthine) at 4 x 10⁶ cells/mL. 5 µl of cells, plus the compounds/peptides as described below, were added to wells of a 384-well plate as soon as possible after resuspension.

To detect antagonist activity, test compounds at varying concentrations were diluted in stimulation buffer at four times concentrate and 2.5 µl was added to wells containing cells. 2.5 µl of a four times required concentration of NDP-MSH or alpha-MSH was added to all wells containing compounds. Negative control wells contained two times concentrated NDP-MSH or alpha-MSH alone without compound. The concentration of NDP-MSH or alpha-MSH employed was calculated to give a response equivalent to approximately 60% of the maximal stimulation.

To detect agonist activity, test compounds at varying concentrations were diluted in stimulation buffer at two times concentrate and 5 µl was added to wells containing cells. Positive control wells contained NDP-MSH or alpha-MSH alone (no compound) at two times concentrate.

Basal level (of cAMP) control wells contained stimulation buffer only (no agonist or compounds). Known concentrations of cAMP (standards) in stimulation buffer were included on the plate, but no cells were added to these wells. The plate was then incubated for 30 mins at 37 °C with gentle shaking. After incubation, 10 µl of lysis buffer (10 % Tween 20, 1 M HEPES, 0.1% BSA, protease inhibitors, ddH₂O) was added to all wells to be measured. Detection of cAMP was then achieved using the Alphascreen cAMP kit (Perkin Elmer, USA), briefly described as follows. A dilution of 10 µl acceptor beads/mL of lysis buffer was prepared in low light conditions. 5 µl of diluted acceptor beads were added to each well to be measured, then the plate was incubated for 30 mins at room temperature, in the dark, with gentle shaking. In low light conditions, donor beads were diluted at 10 µl/mL of lysis buffer, to which 0.75 µl biotinylated cAMP/mL of lysis buffer was added. This mixture was allowed to incubate for 30 mins at room temperature (in the dark) before proceeding with the assay. Following incubation, 5 µl/mL of biotinylated cAMP/Donor bead mix were added per well in low light conditions and the plate was incubated in the dark, at room temperature, for a further hr. Plates were read on an Envision plate reader (Perkin Elmer) after 1 hr and ~16hrs incubation. cAMP concentration in the cells was determined by the use of a 'standard curve' generated from the output of known cAMP concentrations as described below.

Each assay plate contained a "standard curve" of known concentrations of cAMP, in 10 fold dilutions. This is an essential part of the assay as there is high inter-plate variability. The plates were read on an Envision multilabel plate reader fitted with Alphascreen technology and the raw data was imported into GraphPad Prism 4 software (GraphPad, USA) for analysis. A curve was fitted to the known concentrations using non-linear regression, specifically using a sigmoidal dose-response equation ($Y = \text{Bottom} + (\text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + 10^{\log \text{EC}_{50} - X}))$), where the equation shows the response as a function of the logarithm of concentration. X is the logarithm of peptide/compound concentration and Y is the response. Also considered in this equation are bottom plateau, top plateau of the curve and EC₅₀ (effective concentration, 50%)

Example 77 – Activity of Selected Compounds: hMC4R agonism

Representative compounds of the present invention were tested for agonism of the hMC4R, as in Example 76, results are listed in Table 5.

Table 5: Agonism of hMC4 by Selected Compounds

Cpd.	human MC4R agonism (cAMP EC ₅₀ , HEK293 cell) (μ M)
302	29
303	0.75
323	0.18
324	0.69
327	0.54

References

- Adan, R.A.H.; Tiesjema, B.; Hillebrand, J.J.G.; la Fleur, S.E.; Kas, M.J.H.; de Krom, M. *Brit. J. Pharmacol.* **2006**, *149*, 815-827 "The MC4 Receptor and control of appetite"
- Böhm, M.; Luger, T.A.; Tobin, D.J.; Garcia-Borron, J.C. *J. Invest. Dermatol.* **2006**, *126*, 1966-1975 "Melanocortin Receptor Ligands: New Horizons for Skin Biology and Clinical Dermatology"
- Bertile, F.; Raclot, T. *Peptides* **2006**, *27*, 291-300 "The melanocortin system during fasting"
- Butler, A.A.; Kesterson, R.A.; Khong, K.; Cullen, M.J.; Pelleymounter, M.A.; Dekoning, J.; Baetscher, M.; Cone, R.D. *Endocrinology* **2000**, *141*, 3518-3521 "A unique metabolic syndrome causes obesity in the melanocortin-3 receptor-deficient mouse"
- Butler, A.A. *Peptides* **2006**, *27*, 281-290 "The melanocortin system and energy balance"
- Catania, A.; Gatti, S.; Colombo, G.; Lipton, J.M. *Pharmacol. Rev.* **2004**, *56*, 1-29 "Targeting Melanocortin Receptors as a Novel Strategy to Control Inflammation".
- Chaki, S.; Okuyama, S. *Peptides* **2005**, *26*, 1952-1964 "Involvement of melanocortin-4 receptor in anxiety and depression"
- Chaki, S.; Okubo, T. *Curr. Top. Med. Chem.* **2007**, *7*, 1145-1151 "Melanocortin-4 Receptor Antagonists for the Treatment of Depression and Anxiety Disorders"
- Chen, A.S.; Marsh, D.J.; Trumbauer, M.E.; Frazier, E.G.; Guan, X.-M.; Yu, H.; Rosenblum, C.I.; Vongs, A.; Feng, Y.; Cao, L.; Metzger, J.M.; Strack, A.M.; Camacho, R.E.; Mellin, T.N.; Nunes, C.N.; Min, W.; Fisher, J.; Gopal-Truter, S.; MacIntyre, D.E.; Chen, H.Y.; Van der Ploeg, L.H.T. *Nature Genetics* **2000**, *26*, 97-102 "Inactivation of the mouse melanocortin-3 receptor results in increased fat mass and reduced lean body mass"
- Diamond, L.E.; Earle, D.C.; Rosen, R.C.; Willett, M.S.; Molinoff, P.B. *Int. J. Impotence Res.* **2004**, *16*, 51-59 "Double-blind, placebo-controlled evaluation of the safety, pharmacokinetics properties and pharmacodynamic effects of intranasal PT-141, a

melanocortin receptor agonist, in healthy males and patients with mild to moderate erectile dysfunction”

Emmerson, P.J.; Fisher, M.J.; Yan, L.Z.; Mayer, J.P. *Curr. Top. Med. Chem.* **2007**, *7*, 1121-1130 “Melanocortin-4 Receptor Agonists for the Treatment of Obesity”

5 Foster, A.C.; Chen, C. *Curr. Top. Med. Chem.* **2007**, *7*, 1131-1136 “Melanocortin-4 Receptor Antagonists as Potential Therapeutics in the Treatment of Cachexia”

Gantz, I.; Konda, Y.; Tashiro, T.; Shimoto, Y.; Miwa, H.; Munzert, G.; Watson, S.J.; DelValle, J.; Yamada, T. *J. Biol. Chem.* **1993a**, *268*, 8246-8250 “Molecular cloning of a novel melanocortin receptor”

10 Gantz, I.; Miwa, H.; Konda, Y.; Shimoto, Y.; Tashiro, T.; Watson, S.J.; DelValle, J.; Yamada, T. *J. Biol. Chem.* **1993b**, *268*, 15174-15179 “Molecular cloning, expression, and gene localization of a fourth melanocortin receptor”

Getting, S.J.; Christian, H.C.; Lam, C.W.; Gavins, F.N.E.; Flower, R.J.; Schiöth, H.B.; Perretti, M. *J. Immunol.* **2003**, *170*, 3323-3330 “Redundancy of a Functional Melanocortin 1
15 Receptor in the Anti-inflammatory Actions of Melanocortin Peptides: Studies on the Recessive Yellow (e/e) Mouse Suggest an Important Role for Melanocortin 3 Receptor”

Giuliani, D.; Mioni, C.; Bazzani, C.; Zaffe, D.; Botticelli, A.R.; Capolongo, S.; Sabba, A.; Galantucci, M.; Iannone, A.; Grieco, P.; Novellino, E.; Colombo, G.; Tomasi, A.; Catania, A.; Guarini, S. *Br. J. Pharmacol.* **2007**, *150*, 595-603 “Selective melanocortin MC₄
20 receptor agonists reverse haemorrhagic shock and prevent multiple organ damage”

Hall, J.E.; Brands, M.W.; Hildebrandt, D.A.; Kuo, J.; Fitzgerald, S. *Brazilian J. Med. Biol. Res.* **2000**, *33*, 605-618 “Role of sympathetic nervous system and neuropeptides in obesity hypertension”

Holder, J.R.; Bauzo, R.M.; Xiang, Z.; Haskell-Luevano, C. *J. Med. Chem.* **2002**, *45*, 3073-
25 3081 “Structure-Activity Relationships of the Melanocortin Tetrapeptide Ac-His-DPhe-Arg-Trp-NH₂ at the Mouse Melanocortin Receptors: Part 2 Modifications at the Phe Position”

Holder, J.R.; Marques, F.F.; Xiang, Z.; Bauzo, R.M.; Haskell-Luevano, C. *Eur. J. Pharmacol.* **2003**, *462*, 41-52 “Characterization of aliphatic, cyclic and aromatic N-terminally
30 “capped” His-DPhe-Arg-Trp-NH₂ tetrapeptides at the melanocortin receptors”

Hruby, V.J.; Cai, M.; Cain, J.P.; Mayorov, A.V.; Dedek, M.M.; Trivedi, D. *Curr. Top. Med. Chem.* **2007**, *7*, 1085-1097 “Design, Synthesis and Biological Evaluation of Ligands Selective for the Melanocortin-3 Receptor”

Huszar, D.; Lynch, C.A.; Fairchild-Huntress, V.; Dunmore, J.H.; Fang, Q.; Berkemeier, L.R.;
35 Gu, W.; Kesterson, R.A.; Boston, B.A.; Cone, R.D.; Smith, F.J.; Campfield, L.A.; Burn, P.; Lee, F. *Cell* **1997**, *88*, 131-141 “Targeted Disruption of the Melanocortin-4 Receptor Results in Obesity in Mice”

- Irani, B.G.; Haskell-Luevano, C. *Peptides* **2005**, *26*, 1788-1799 "Feeding effects of melanocortin ligands - A historical perspective"
- King, S.H.; Mayorov, A.V.; Balse-Srinivasan, P.; Hruby, V.J.; Vanderah, T.W.; Wessells, H. *Curr. Top. Med. Chem.* **2007**, *7*, 1111-1119 "Melanocortin Receptors, Melanotropic Peptides and Penile Erection"
- 5 Lam, D.D.; Farooqi, I.S.; Heisler, L.K. *Curr. Top. Med. Chem.* **2007**, *7*, 1098-1110 "Melanocortin Receptors as Targets in the Treatment of Obesity"
- Lasaga, M.; Debeljuk, L.; Durand, D.; Scimonelli, T.N.; Caruso, C. *Peptides* **2008**, *29*, 1825-1835 "Role of α -melanocyte stimulating hormone and melanocortin 4 receptor in brain inflammation"
- 10 MacNeil, D.J.; Howard, A.D.; Guan, X, Fong, T.M.; Nargund, R.P.; Bednarek, M.A.; Goulet, M.T.; Weinberg, D.H.; Strack, A.M.; Marsh, D.J.; Chen, H.Y.; Shen, C.-P.; Chen, A.S.; Rosenblum, C.I.; MacNeil, T.; Tota, M.; MacIntyre, E.D.; Van der Ploeg, L.H.T. *Eur. J. Pharmacol.* **2002**, *440*, 141-157 "The role of melanocortins in body weight regulation: opportunities for the treatment of obesity"
- 15 Marks, D.L.; Hruby, V.; Brookhart, G.; Cone, R.D. *Peptides* **2006**, *27*, 259-264 "The regulation of food intake by selective stimulation of the type 3 melanocortin receptor (MC3R)"
- Mazur, A.W.; Kulesza, A.; Mishra, R.K.; Cross-Doersen, D.; Russell, A.F.; Ebetino, F.H. *Bioorg. Med. Chem.* **2003**, *11*, 3053-3063 "Novel tetrahydropyran-based peptidomimetics from a bioisosteric transformation of a tripeptide. Evidence of their activity at melanocortin receptors"
- 20 Mutulis, F.; Mutule, I.; Liepinsh, E.; Yahorau, A.; Lapinsh, M.; Kopantshuk, S.; Veiksina, S.; Rinken, A.; Wikberg, J.E.S. *Peptides* **2005**, *26*, 1997-2016 "*N*-Alkylated dipeptide amides and related structures as imitations of the melanocortins' active core"
- 25 Nargund, R.P.; Strack, A.M.; Fong, T.M. *J. Med. Chem.* **2006**, *49*, 4035-4053 "Melanocotin-4 Receptor (MC4R) Agonists for the Treatment of Obesity"
- Ploj, K.; Roman, E.; Kask, A.; Hyytiä, P.; Schiöth, H.B.; Wikberg, J.E.S.; Nylander, I. *Brain Res. Bull.* **2002**, *59*, 97-104 "Effects of melanocortin receptor ligands on ethanol intake and opioid peptide levels in alcohol-preferring AA rats"
- 30 Schuler, S.; Ebling, F.J.P. *Peptides* **2006**, *27*, 301-309 "Role of melanocortin in the long-term regulation of energy balance: Lessons from a seasonal model"
- Shadiack, A.M.; Sharma, S.D.; Earle, D.C.; Spana, C.; Hallam, T.J. *Drug Disc. Today: Ther. Strat.* **2006**, *3*, 605-611 "A role for melanocortin agonists in treating male and female sexual dysfunction"
- 35 Shadiack, A.M.; Sharma, S.D.; Earle, D.C.; Spana, C.; Hallam, T.J. *Curr. Top. Med. Chem.* **2007**, *7*, 1137-1144 "Melanocortins in the Treatment of Male and Female Sexual Dysfunction"

Thorleifsson et al, *Nature Genetics* **2009**, *41*, 18-24 "Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity"

Tian, X.; Switzer, A.G.; Derose, S.A.; Mishra, R.K.; Solinsky, M.G.; Mumin, R.N.; Ebetino, F.H.; Jayasinghe, L.R. Webster, M.E.; Colson, A.-O.; Crossdoersen, D.; Pinney, B.B.;
5 Farmer, J.A.; Dowty, M.E.; Obringer, C.M.; Cruze, C.A.; Burklow, M.L.; Suchanek, P.M.; Dong, L; Dirr, M.K.; Sheldon, R.J.; Wos, J.A. *J. Med. Chem.* **2008**, *51*, 6055-6066
"Discovery of Orally Bioavailable 1,3,4-Trisubstituted 2-Oxopiperazine-Based Melanocortin-4 Receptor Agonists as Potential Antiobesity Agents"

Todorovic, A.; Haskell-Luevano, C. *Peptides* **2005**, *26*, 2026-2036 "A review of melanocortin
10 receptor small molecule ligands"

Ujjainwalla, F.; Sebhat, I.K. *Curr. Top. Med. Chem.* **2007**, *7*, 1068-1084 "Small Molecule Ligands of the Human Melanocortin-4 Receptor"

Voisey, J.; Carroll, L.; van Daal, A. *Curr. Drug Targets* **2003**, *4*, 586-597 "Melanocortins and their Receptors and Antagonists"

15 Wessells, H.; Blevins, J.E.; Vanderah, T.W. *Peptides* **2005**, *26*, 1972-1977 "Melanocortinergic control of penile erection"

Wikberg, J.E.S.; Muceniece, R.; Mandrika, I.; Prusis, P.; Lindblom, J.; Post, C.; Skottner, A. *Pharmacol. Res.* **2000**, *42*, 393-420 "New Aspects on the Melanocortins and their Receptors"

20 Wikberg, J.E.S. *Exp. Opin. Ther. Patents* **2001**, *11*, 61-76 "Melanocortin receptors: new opportunities in drug discovery"

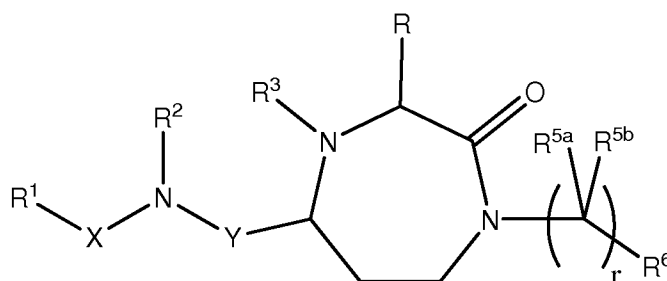
Wikberg, J.E.S.; Mululis, F. *Nature Rev. Drug Disc.* **2008**, *7*, 307-323 "Targeting melanocortin receptors: an approach to treat weight disorders and sexual dysfunction"

Willer et al, *Nature Genetics* **2009**, *41*, 24-34 "Six new loci associated with body mass index
25 highlight a neuronal influence on body weight regulation"

The details of specific embodiments described in this invention are not to be construed as limitations. Various equivalents and modifications may be made without departing from the essence and scope of this invention, and it is understood that such
30 equivalent embodiments are part of this invention.

The Claims defining the Invention are as follows

1 A method of modulating the activity of a receptor selected from the group consisting of
 5 MC3R and MC4R or a fragment, analogue or functional equivalent thereof comprising
 exposing the receptor or a fragment or analogue or functional equivalent thereof to a
 compound of the formula (I):



Formula (I)

wherein

Y is a group of formula $-(CR^9R^{10})_n-$;

15 X is selected from the group consisting $-C(=O)-$, $-OC(=O)-$, $-NHC(=O)-$,
 $-(CR^{11}R^{12})_s$, and $-S(=O)_2-$;

R is an amino acid side chain group;

20 R^1 is selected from the group consisting of H, optionally substituted C_1 - C_{12} alkyl,
 optionally substituted $CH_2(C_6$ - C_{18} aryl) optionally substituted C_2 - C_{12} alkenyl, optionally
 substituted C_2 - C_{12} alkynyl, optionally substituted C_1 - C_{12} heteroalkyl, optionally substituted C_3 -
 C_{12} cycloalkyl, optionally substituted C_2 - C_{12} heterocycloalkyl, optionally substituted C_6 - C_{18} aryl,
 and optionally substituted C_1 - C_{18} heteroaryl;

25 R^2 and R^3 are each independently selected from the group consisting of H, optionally
 substituted C_1 - C_{12} alkyl, optionally substituted C_2 - C_{12} alkenyl, optionally substituted C_2 -
 C_{12} alkynyl, optionally substituted C_1 - C_{12} heteroalkyl, optionally substituted C_3 - C_{12} cycloalkyl,
 optionally substituted C_2 - C_{12} heterocycloalkyl, optionally substituted C_6 - C_{18} aryl, and optionally
 30 substituted C_1 - C_{18} heteroaryl, or

R^2 and R^3 may be joined to form a linker between the two nitrogen atoms to which they are attached, wherein the linker is selected from the group consisting of $-C(=O)-$, $-CH_2-$, $-C(=O)CH_2-$ and $-CH_2C(=O)-$;

5 R^{5a} , R^{5b} and R^6 are each independently selected from the group consisting of H, halogen, hydroxy, optionally substituted C_1 - C_{12} alkyl, optionally substituted C_2 - C_{12} alkenyl, optionally substituted C_2 - C_{12} alkynyl, optionally substituted C_1 - C_{12} heteroalkyl, optionally substituted C_1 - C_{10} heteroalkenyl, optionally substituted C_3 - C_{12} cycloalkyl, optionally substituted C_2 - C_{12} heterocycloalkyl, optionally substituted C_6 - C_{18} aryl, optionally substituted C_1 -
10 C_{18} heteroaryl, optionally substituted amino, optionally substituted carboxy, optionally substituted carboxamide, optionally substituted C_1 - C_{12} alkyloxy, and optionally substituted thio;

each R^9 and R^{10} is independently selected from the group consisting of H, optionally substituted C_1 - C_{12} alkyl, optionally substituted C_6 - C_{18} aryl, and optionally substituted C_1 -
15 C_{18} heteroaryl;

each R^{11} and R^{12} is independently selected from the group consisting of H, and optionally substituted C_1 - C_{12} alkyl;

20 n is an integer selected from the group consisting of 1, 2, 3 and 4;

r is an integer selected from the group consisting of 0, 1, 2, 3, and 4;

s is an integer selected from the group consisting of 0, 1, 2, 3, and 4;

25

or a pharmaceutically acceptable salt or prodrug thereof.

2. A method according to claim 1 wherein the activity of the receptor or a fragment, analogue or functional equivalent thereof is modulated in a mammal, the method comprising
30 administering a receptor modulating amount of a compound of formula (I) to the mammal.

3. A method of preventing or treating a condition associated with the activity of a receptor selected from the group consisting of MC3R and MC4R or a fragment, analogue or functional equivalent thereof in a mammal the method comprising administering a
35 therapeutically effective amount of a compound of formula (I) as described in claim 1 to the mammal.

4. A method according to any one of claims 2 to 3 wherein the mammal is a human.

5. A method according to any one of claims 1 to 3 wherein in the method the activity of the receptor is up-regulated.

5

6. A method according to any one of claims 1 to 3 wherein in the method the activity of the receptor is down-regulated.

7. A method according to claim 3 wherein the condition is selected from the group consisting of obesity, eating disorders, metabolic syndrome, diabetes, sexual dysfunction, anxiety, depression, inflammation, addiction and alcohol intake.

8. A method according to claim 3 wherein the condition is selected from the group consisting of cachexia, anorexia, weight gain, weight loss, Type II diabetes, erectile dysfunction and female sexual dysfunction.

15

9. A method according to any one of claims 2 to 4, 7 and 8 wherein the compound is administered topically.

10. A method according to any one of claims 2 to 4, 7 and 8 wherein the compound is administered orally.

20

11. A method according to any one of claims 2 to 4, 7 and 8 wherein the compound is administered parenterally.

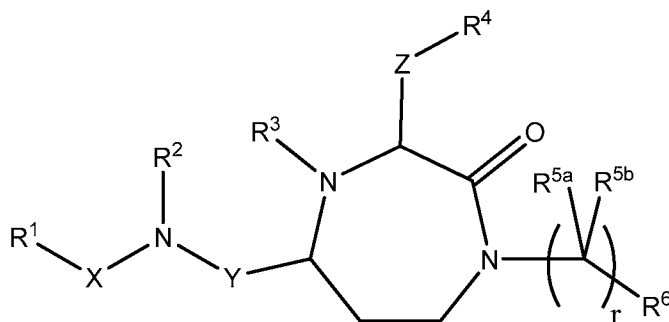
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12. A method according to any one of claims 2 to 4 and 7 to 11 wherein the compound of formula (I) is administered in combination with a second active agent.

13. A method according to any one of claims 1 to 12 wherein the compound of formula (I) is a compound of the formula (Ia):

30

160



Formula (Ia)

R^1 , R^2 , R^3 , R^{5a} , R^{5b} , R^6 , X , Y and r are as defined in claim 1;

5

Z is a group of formula $-(CR^{13}R^{14})_q-$;

R^4 is selected from the group consisting of H, optionally substituted C_1 - C_{12} alkyl, optionally substituted C_2 - C_{12} alkenyl, optionally substituted C_2 - C_{12} alkynyl, optionally substituted C_3 - C_{12} cycloalkyl, optionally substituted C_6 - C_{18} aryl, optionally substituted C_1 - C_{18} heteroaryl, $NR^{4a}R^{4b}$, $C(=O)R^{15}$, $C(=O)NR^{16}R^{17}$, $-C(=NR^{16})NR^{17}R^{18}$, SR^{20} , $SC(=O)R^{20}$, SO_2R^{20} , OR^{20} , $ONR^{16}R^{17}$, $OCR^{17}R^{18}R^{20}$, $OC(=O)R^{20}$, $OC(=O)OR^{20}$, $OC(=O)NR^{16}R^{17}$, and $ONR^{16}C(=NR^{17})NR^{18}R^{19}$;

15

R^{4a} is selected from the group consisting of H, optionally substituted C_1 - C_{12} alkyl, optionally substituted C_2 - C_{12} alkenyl, optionally substituted C_2 - C_{12} alkynyl, optionally substituted C_1 - C_{12} heteroalkyl, optionally substituted C_3 - C_{12} cycloalkyl, optionally substituted C_2 - C_{12} heterocycloalkyl, optionally substituted C_6 - C_{18} aryl, optionally substituted C_1 - C_{18} heteroaryl, $C(=O)R^{15a}$, $C(=O)NR^{15a}R^{16a}$, $C(=O)OR^{15a}$, SO_2R^{15a} , $C(=O)H$, $-C(=NR^{15a})-$, $NR^{16a}R^{17a}$, and OR^{15a} ,

20

R^{4b} is selected from the group consisting of H, optionally substituted C_1 - C_{12} alkyl, optionally substituted C_2 - C_{12} alkenyl, optionally substituted C_2 - C_{12} alkynyl, optionally substituted C_1 - C_{12} heteroalkyl, optionally substituted C_3 - C_{12} cycloalkyl, optionally substituted C_2 - C_{12} heterocycloalkyl, optionally substituted C_6 - C_{18} aryl, optionally substituted C_1 - C_{18} heteroaryl, $C(=O)R^{15a}$, $C(=O)NR^{15a}R^{16a}$, $C(=O)OR^{15a}$, or

25

R^{4a} and R^{4b} when taken together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic moiety, or

30

one of R^{4a} and R^{4b} when taken together with any R^{13} or R^{14} and the atoms to which they are attached forms an optionally substituted heterocyclic moiety;

R^{13} and R^{14} are each independently selected from the group consisting of H, halogen, OH, C_1 - C_{12} alkyl, C_6 - C_{18} aryl, C_1 - C_{12} hydroxyalkyl, C_1 - C_{12} haloalkyl, C_1 - C_{12} alkyloxy and C_1 - C_{12} haloalkyloxy, or

when taken together with the carbon to which they are attached R^{13} and R^{14} form an optionally substituted C_3 - C_{12} cycloalkyl, or an optionally substituted C_1 - C_{12} heterocycloalkyl group, or

one of R^{13} and R^{14} when taken together with one of R^{4a} , and R^{4b} and the atoms to which they are attached form an optionally substituted heterocyclic moiety, or

one of R^{13} and R^{14} when taken together with one of R^{15} , R^{16} , R^{17} , R^{18} , R^{19} or R^{20} and the atoms to which they are attached form an optionally substituted cyclic moiety;

each R^{15} , R^{15a} , R^{16} , R^{16a} , R^{17} , R^{17a} , R^{18} , R^{19} and R^{20} is independently selected from the group consisting of H, optionally substituted C_1 - C_{12} alkyl, optionally substituted C_1 - C_{12} heteroalkyl, optionally substituted C_3 - C_{12} cycloalkyl, optionally substituted C_2 - C_{12} heterocycloalkyl, optionally substituted C_6 - C_{18} aryl, and optionally substituted C_1 - C_{18} heteroaryl, or

any two of R^{15} , R^{15a} , R^{16} , R^{16a} , R^{17} , R^{17a} , R^{18} , R^{19} and R^{20} when taken together with the atoms to which they are attached form an optionally substituted cyclic group, or

one of R^{15} , R^{16} , R^{17} , R^{18} , R^{19} and R^{20} when taken together with one of R^{13} and R^{14} and the atoms to which they are attached form an optionally substituted cyclic moiety;

q is an integer selected from the group consisting of 0, 1, 2, 3, 4, and 5;

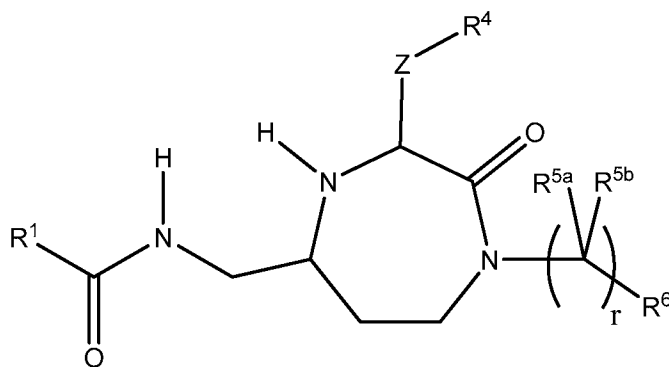
or a pharmaceutically acceptable salt or prodrug thereof.

14. A method according to any one of claims 1 to 13 wherein Y is CH_2 .

15. A method according to any one of claims 1 to 14 wherein R^2 is H.

16. A method according to any one of claims 1 to 15 wherein R^3 is H.

17. A method according to any one of claims 1 to 16 wherein Y is CH_2 , X is $C(=O)$, R^2 is H, R^3 is H and R is a group of formula $-Z-R^4$, resulting in a compound of the formula (Ib):

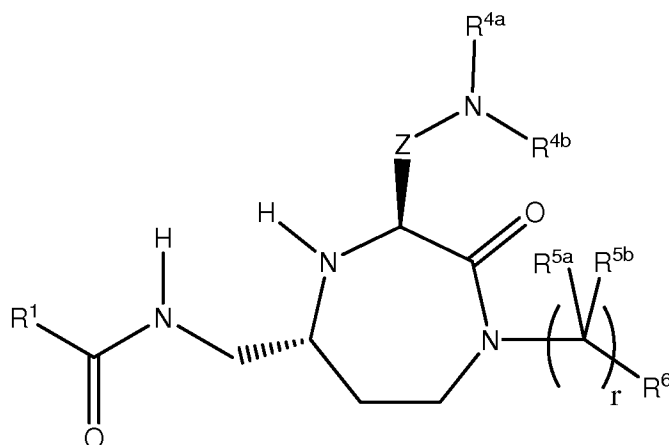


Formula (Ib)

wherein R^1 , R^{5a} , R^{5b} , R^6 , and r are as defined in claim 1 and Z and R^4 are as defined in claim 13.

18. A method according to claim 13 or 17 wherein $R^4 = NR^{4a}R^{4b}$.

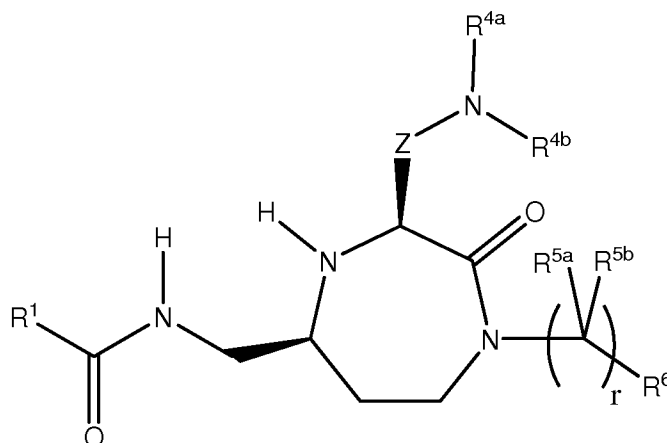
19. A method according to any one of claims 1 to 18 wherein the compound is a compound of the formula



Formula (Id)

wherein R^1 , R^{5a} , R^{5b} , R^6 , Z, and r are as defined in claim 1 and R^{4a} and R^{4b} are as defined in claim 13 and the stereochemistry is as shown, or a pharmaceutically acceptable salt or prodrug thereof.

20 A method according to any one of claims 1 to 18 wherein the compound is a compound of the formula (Ie)



Formula (Ie)

wherein R^1 , R^{5a} , R^{5b} , R^6 , Z , and r are as defined in claim 1 and R^{4a} and R^{4b} are as defined in claim 13 and the stereochemistry is as shown, or a pharmaceutically acceptable salt or prodrug thereof.

21. A method according to any one of claims 18 to 20 wherein R^{4a} is selected from the group consisting of H, $-C(=NH)NH_2$, $-C(=NH)N(CH_3)_2$, $-C(=NH)NHCH(CH_3)_2$, $-C(=O)CH_3$, $-C(=O)cyclohexyl$, CH_3 , CH_2CH_3 , $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $-CH(CH_3)CH_2CH_3$, $CH_2CH(CH_3)_2$, $C(CH_3)_3$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, benzyl, and phenyl, or a halogenated derivative thereof.

22. A method according to any one of claims 18 to 21 R^{4b} is selected from the group consisting of H, CH_3 , CH_2CH_3 , $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH(CH_3)CH_2CH_3$, $CH_2CH(CH_3)_2$, $C(CH_3)_3$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, benzyl, and phenyl, or a halogenated derivative thereof.

23. A method according to any one of claims 18 to 20 wherein R^{4a} and R^{4b} when taken together with the nitrogen atom to which they are attached form an optionally substituted C_2 - C_{12} heterocycloalkyl group, an optionally substituted C_2 - C_{12} heterocycloalkenyl group or an optionally substituted C_1 - C_{18} heteroaryl group.

24. A method according to claim 23 wherein R^{4a} and R^{4b} when taken together with the nitrogen atom to which they are attached form an optionally substituted C_2 -

C₁₂heterocycloalkyl group selected from the group consisting of piperidin-1-yl, pyrrolidin-1-yl, azepan-1-yl, azetidin-1-yl, piperazin-1-yl, and morpholin-4-yl.

25. A method according to any one of claims 18 to 20 wherein one of R^{4a} and R^{4b} when taken together with the nitrogen atom to which it is attached and one of R¹³ and R¹⁴ and the carbon atom to which it is attached form an optionally substituted C₂-C₁₂heterocycloalkyl group.

26. A method according to claim 25 wherein one of R^{4a} and R^{4b} when taken together with the nitrogen atom to which it is attached and one of R¹³ and R¹⁴ and the carbon atom to which it is attached form an optionally substituted C₂-C₁₂heterocycloalkyl group selected from the group consisting of piperidinyl, pyrrolidinyl, azepanyl, azetidiny, morpholinyl, and piperazinyl.

27. A method according to any one of claims 13 to 26 wherein Z is selected from the group consisting of -CH₂-, -(CH₂)₂-, -(CH₂)₃-, -(CH₂)₄-, and -(CH₂)₅-.

28. A method according to any one of claims 1 to 27 wherein R¹ is selected from the group consisting of optionally substituted C₂-C₁₂alkenyl, optionally substituted C₆-C₁₈aryl, optionally substituted CH₂(C₆-C₁₈aryl), optionally substituted CH₂(C₆-C₁₈aryl), and optionally substituted C₁-C₁₈heteroaryl.

29. A method according to any one of claims 1 to 28 wherein R^{5a} and R^{5b} are each independently selected from the group consisting of H, optionally substituted C₁-C₁₂alkyl, optionally substituted C₆-C₁₈aryl, optionally substituted C₁-C₁₈heteroaryl, optionally substituted carboxy and optionally substituted carboxamide.

30. A method according to any one of claims 1 to 29 wherein R⁶ is selected from the group consisting of optionally substituted C₁-C₁₂alkyl, optionally substituted C₆-C₁₈aryl and optionally substituted C₁-C₁₈heteroaryl.

31. A method according to any one of claims 1 to 30 wherein r is 0.

32. A method according to any one of claims 1 to 30 wherein r is 1.

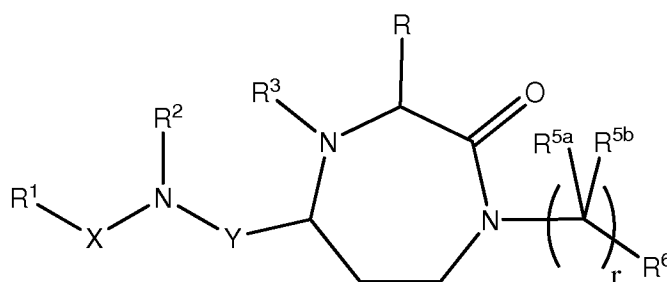
33. A method according to any one of claims 1 to 30 wherein r is 2.

34. A method according to any one of claims 1 to 33 wherein in the compound of formula (I) each optional substituent is independently selected from the group consisting of: halogen, =O, =S, -CN, -NO₂, -CF₃, -OCF₃, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, heteroalkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, heteroarylalkyl, arylalkyl, cycloalkylalkenyl, heterocycloalkylalkenyl, arylalkenyl, heteroarylalkenyl, cycloalkylheteroalkyl, heterocycloalkylheteroalkyl, arylheteroalkyl, heteroarylheteroalkyl, hydroxy, hydroxyalkyl, alkyloxy, alkyloxyalkyl, alkyloxycycloalkyl, alkyloxyheterocycloalkyl, alkyloxyaryl, alkyloxyheteroaryl, alkyloxycarbonyl, alkylaminocarbonyl, alkenyloxy, alkynyloxy, cycloalkyloxy, cycloalkenyloxy, heterocycloalkyloxy, heterocycloalkenyloxy, aryloxy, phenoxy, benzyloxy, heteroaryloxy, arylalkyloxy, amino, alkylamino, acylamino, aminoalkyl, arylamino, sulfonylamino, sulfinylamino, sulfonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, sulfinyl, alkylsulfinyl, arylsulfinyl, aminosulfinylaminoalkyl, -C(=O)OH, -C(=O)R^a, -C(=O)OR^a, C(=O)NR^aR^b, C(=NOH)R^a, C(=NR^a)NR^bR^c, NR^aR^b, NR^aC(=O)R^b, NR^aC(=O)OR^b, NR^aC(=O)NR^bR^c, NR^aC(=NR^b)NR^cR^d, NR^aSO₂R^b, -SR^a, SO₂NR^aR^b, -OR^a, OC(=O)NR^aR^b, OC(=O)R^a and acyl,

wherein R^a, R^b, R^c and R^d are each independently selected from the group consisting of H, C₁-C₁₂ alkyl, C₁-C₁₂ haloalkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, C₁-C₁₀ heteroalkyl, C₃-C₁₂ cycloalkyl, C₃-C₁₂ cycloalkenyl, C₁-C₁₂ heterocycloalkyl, C₁-C₁₂ heterocycloalkenyl, C₆-C₁₈aryl, C₁-C₁₈heteroaryl, and acyl, or any two or more of R^a, R^b, R^c and R^d, when taken together with the atoms to which they are attached form a heterocyclic ring system with 3 to 12 ring atoms.

35. A method according to any one of claims 1 to 34 wherein in the compound of formula (I) each optional substituent is independently selected from the group consisting of F, Cl, Br, I, CH₃, CH₂CH₃, OH, OCH₃, CF₃, OCF₃, NO₂, NH₂, and CN.

36 Use of a compound of the formula (I):



Formula (I)

wherein

Y is a group of formula $-(CR^9R^{10})_n-$;

5 X is selected from the group consisting $-C(=O)-$, $-OC(=O)-$, $-NHC(=O)-$, $-(CR^{11}R^{12})_s$, and $-S(=O)_2-$;

R is an amino acid side chain group;

10 R^1 is selected from the group consisting of H, optionally substituted C_1-C_{12} alkyl, optionally substituted $CH_2(C_6-C_{18}aryl)$, optionally substituted C_2-C_{12} alkenyl, optionally substituted C_2-C_{12} alkynyl, optionally substituted C_1-C_{12} heteroalkyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_2-C_{12} heterocycloalkyl, optionally substituted $C_6-C_{18}aryl$, and optionally substituted C_1-C_{18} heteroaryl;

15 R^2 and R^3 are each independently selected from the group consisting of H, optionally substituted C_1-C_{12} alkyl, optionally substituted C_2-C_{12} alkenyl, optionally substituted C_2-C_{12} alkynyl, optionally substituted C_1-C_{12} heteroalkyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_2-C_{12} heterocycloalkyl, optionally substituted $C_6-C_{18}aryl$, and optionally substituted C_1-C_{18} heteroaryl, or

20

R^2 and R^3 may be joined to form a linker between the two nitrogen atoms to which they are attached, wherein the linker is selected from the group consisting of $-C(=O)-$, $-CH_2-$, $-C(=O)CH_2-$ and $-CH_2C(=O)-$;

25 R^{5a} , R^{5b} and R^6 are each independently selected from the group consisting of H, halogen, hydroxy, optionally substituted C_1-C_{12} alkyl, optionally substituted C_2-C_{12} alkenyl, optionally substituted C_2-C_{12} alkynyl, optionally substituted C_1-C_{12} heteroalkyl, optionally substituted C_1-C_{10} heteroalkenyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_2-C_{12} heterocycloalkyl, optionally substituted $C_6-C_{18}aryl$, optionally substituted C_1-C_{18} heteroaryl, optionally substituted amino, optionally substituted carboxy, optionally substituted carboxamide, optionally substituted C_1-C_{12} alkyloxy, and optionally substituted thio;

30

each R^9 and R^{10} is independently selected from the group consisting of H, optionally substituted C_1-C_{12} alkyl, optionally substituted $C_6-C_{18}aryl$, and optionally substituted C_1-C_{18} heteroaryl;

35

each R^{11} and R^{12} is independently selected from the group consisting of H, and optionally substituted C_1 - C_{12} alkyl;

n is an integer selected from the group consisting of 1, 2, 3 and 4;

r is an integer selected from the group consisting of 0, 1, 2, 3, and 4;

s is an integer selected from the group consisting of 0, 1, 2, 3, and 4;

or a pharmaceutically acceptable salt or prodrug thereof in modulating the activity of a receptor selected from the group consisting of MC3R and MC4R or a fragment, analogue or functional equivalent thereof.

37. Use of a compound of formula (I) as described in claim 36 in the preparation of a medicament for treating, preventing, or controlling a condition associated with the activity of a receptor selected from the group consisting of MC3R and MC4R or a fragment, analogue or functional equivalent thereof in a mammal.

38. A use according to claim 37 wherein the mammal is a human.

39. A use according to claim 37 wherein the condition is selected from the group consisting of obesity, eating disorders, metabolic syndrome, diabetes, sexual dysfunction, anxiety, depression, inflammation, addiction and alcohol intake.

40. A use according to claim 37 wherein the condition is selected from the group consisting of cachexia, anorexia, weight gain, weight loss, Type II diabetes, erectile dysfunction and female sexual dysfunction

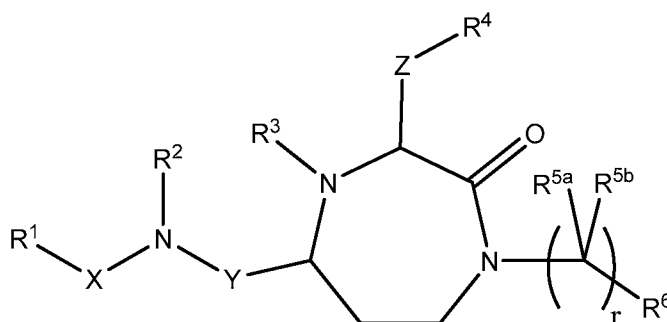
41. A use according to any one of claims 37 to 40 wherein the medicament is adapted to be administered topically.

42. A use according to any one of claims 37 to 40 wherein the medicament is adapted to be administered orally.

43. A use according to any one of claims 37 to 40 wherein the medicament is adapted to be administered parenterally.

44. A use according to any one of claims 37 to 43 wherein the medicament contains a second active agent.

45. A use according to any one of claims 36 to 44 wherein the compound of formula (I) is a compound of the formula (Ia):



Formula (Ia)

wherein R^1 , R^2 , R^3 , R^{5a} , R^{5b} , R^6 , X , Y and r are as defined in claim 36;

Z is a group of formula $-(CR^{13}R^{14})_q-$;

R^4 is selected from the group consisting of H, optionally substituted C_1 - C_{12} alkyl, optionally substituted C_2 - C_{12} alkenyl, optionally substituted C_2 - C_{12} alkynyl, optionally substituted C_3 - C_{12} cycloalkyl, optionally substituted C_6 - C_{18} aryl, optionally substituted C_1 - C_{18} heteroaryl, $NR^{4a}R^{4b}$, $C(=O)R^{15}$, $C(=O)NR^{16}R^{17}$, $-C(=NR^{16})NR^{17}R^{18}$, SR^{20} , $SC(=O)R^{20}$, SO_2R^{20} , OR^{20} , $ONR^{16}R^{17}$, $OCR^{17}R^{18}R^{20}$, $OC(=O)R^{20}$, $OC(=O)OR^{20}$, $OC(=O)NR^{16}R^{17}$, and $ONR^{16}C(=NR^{17})NR^{18}R^{19}$;

R^{4a} is selected from the group consisting of H, optionally substituted C_1 - C_{12} alkyl, optionally substituted C_2 - C_{12} alkenyl, optionally substituted C_2 - C_{12} alkynyl, optionally substituted C_1 - C_{12} heteroalkyl, optionally substituted C_3 - C_{12} cycloalkyl, optionally substituted C_2 - C_{12} heterocycloalkyl, optionally substituted C_6 - C_{18} aryl, optionally substituted C_1 - C_{18} heteroaryl, $C(=O)R^{15a}$, $C(=O)NR^{15a}R^{16a}$, $C(=O)OR^{15a}$, SO_2R^{15a} , $C(=O)H$, $-C(=NR^{15a})-NR^{16a}R^{17a}$, and OR^{15a} ,

R^{4b} is selected from the group consisting of H, optionally substituted C_1 - C_{12} alkyl, optionally substituted C_2 - C_{12} alkenyl, optionally substituted C_2 - C_{12} alkynyl, optionally substituted C_1 - C_{12} heteroalkyl, optionally substituted C_3 - C_{12} cycloalkyl, optionally substituted

C₂-C₁₂heterocycloalkyl, optionally substituted C₆-C₁₈aryl, optionally substituted C₁-C₁₈heteroaryl, C(=O)R^{15a}, C(=O)NR^{15a}R^{16a}, C(=O)OR^{15a}, or

R^{4a} and R^{4b} when taken together with the nitrogen atom to which they are attached
5 form an optionally substituted heterocyclic moiety, or

one of R^{4a} and R^{4b} when taken together with any R¹³ or R¹⁴ and the atoms to which they are attached forms an optionally substituted heterocyclic moiety;

10 R¹³ and R¹⁴ are each independently selected from the group consisting of H, halogen, OH, C₁-C₁₂alkyl, C₆-C₁₈aryl, C₁-C₁₂hydroxyalkyl, C₁-C₁₂haloalkyl, C₁-C₁₂alkyloxy and C₁-C₁₂haloalkyloxy, or

when taken together with the carbon to which they are attached R¹³ and R¹⁴ form an
15 optionally substituted C₃-C₁₂cycloalkyl, or an optionally substituted C₁-C₁₂heterocycloalkyl group, or

one of R¹³ and R¹⁴ when taken together with one of R^{4a}, and R^{4b} and the atoms to which they are attached form an optionally substituted heterocyclic moiety, or

20

one of R¹³ and R¹⁴ when taken together with one of R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹ or R²⁰ and the atoms to which they are attached form an optionally substituted cyclic moiety;

each R¹⁵, R^{15a}, R¹⁶, R^{16a}, R¹⁷, R^{17a}, R¹⁸, R¹⁹ and R²⁰ is independently selected from the
25 group consisting of H, optionally substituted C₁-C₁₂alkyl, optionally substituted C₁-C₁₂heteroalkyl, optionally substituted C₃-C₁₂cycloalkyl, optionally substituted C₂-C₁₂heterocycloalkyl, optionally substituted C₆-C₁₈aryl, and optionally substituted C₁-C₁₈heteroaryl, or

30 any two of R¹⁵, R^{15a}, R¹⁶, R^{16a}, R¹⁷, R^{17a}, R¹⁸, R¹⁹ and R²⁰ when taken together with the atoms to which they are attached form an optionally substituted cyclic group, or

one of R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹ and R²⁰ when taken together with one of R¹³ and R¹⁴ and the atoms to which they are attached form an optionally substituted cyclic moiety;

35

q is an integer selected from the group consisting of 0, 1, 2, 3, 4, and 5;

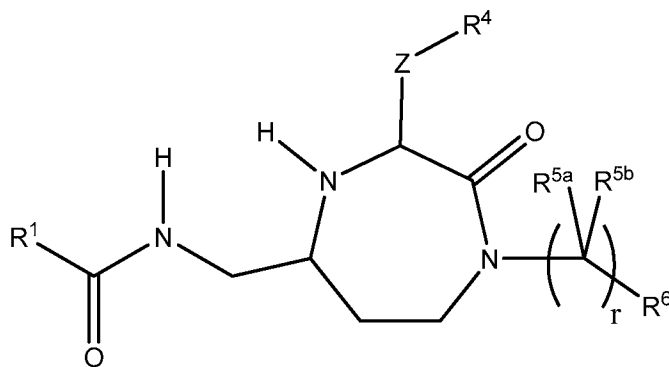
or a pharmaceutically acceptable salt or prodrug thereof.

46. A use according to any one of claims 36 to 45 wherein Y is CH₂.

5 47. A use according to any one of claims 36 to 46 wherein R² is H.

48. A use according to any one of claims 36 to 47 wherein R³ is H.

10 49. A use according to any one of claims 36 to 48 wherein in the compound of formula (I) Y is CH₂, X is C(=O), R² is H, R³ is H and R is a group of formula -Z-R⁴, resulting in a compound of the formula (Ib):



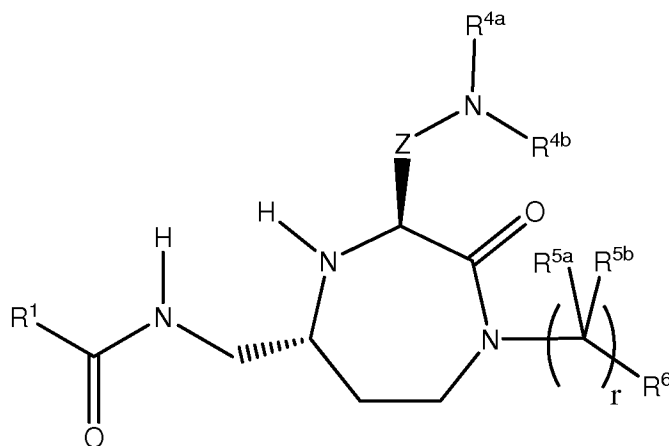
Formula (Ib)

15 wherein R¹, R^{5a}, R^{5b}, R⁶, and r are as defined in claim 36 and Z and R⁴ are as defined in claim 45.

50. A use according to claim 45 or 49 wherein R⁴ = NR^{4a}R^{4b}.

20 51. A use according to any one of claims 36 to 50 wherein the compound of formula (I) is a compound of the formula (Id)

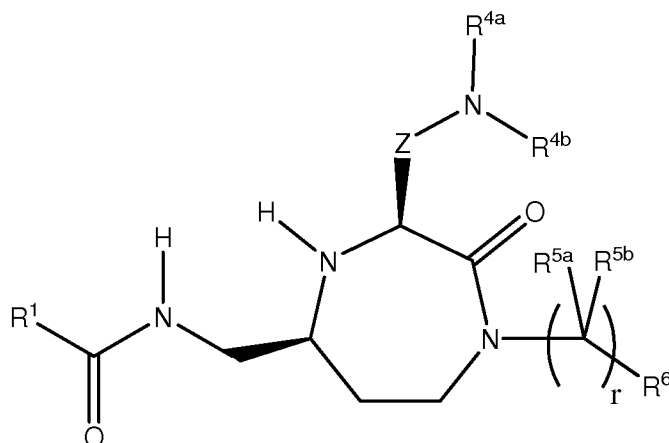
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Formula (Id)

wherein R¹, R^{5a}, R^{5b}, R⁶, Z, Y and r are as defined in claim 36 and R^{4a} and R^{4b} are as
 5 defined in claim 45 and the stereochemistry is as shown, or a pharmaceutically acceptable salt or prodrug thereof.

52. A use according to any one of claims 36 to 50 wherein the compound of formula (I) is a compound of the formula (Ie)



Formula (Ie)

10

wherein R¹, R^{5a}, R^{5b}, R⁶, Z, Y and r are as defined in claim 36 and R^{4a} and R^{4b} are as
 15 defined in claim 45 and the stereochemistry is as shown, or a pharmaceutically acceptable salt or prodrug thereof.

53. A use according to any one of claims 50 to 52 wherein R^{4a} is selected from the group consisting of H, -C(=NH)NH₂, -C(=NH)N(CH₃)₂, -C(=NH)NHCH(CH₃)₂, -C(=O)CH₃, -C(=O)cyclohexyl, CH₃, CH₂CH₃, CH₂CH₂CH₃, CH(CH₃)₂, CH₂CH₂CH₂CH₃, -CH(CH₃)CH₂CH₃,

CH₂CH(CH₃)₂, C(CH₃)₃, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, benzyl, and phenyl, or a halogenated derivative thereof.

54. A use according to any one of claims 50 to 53 wherein R^{4b} is selected from the group
5 consisting of H, CH₃, CH₂CH₃, CH₂CH₂CH₃, CH(CH₃)₂, CH₂CH₂CH₂CH₃, CH(CH₃)CH₂CH₃,
CH₂CH(CH₃)₂, C(CH₃)₃, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, benzyl, and phenyl, or
a halogenated derivative thereof.

55. A use according to any one of claims 50 to 52 wherein R^{4a} and R^{4b} when taken
10 together with the nitrogen atom to which they are attached form an optionally substituted C₂-
C₁₂heterocycloalkyl group, an optionally substituted C₂-C₁₂ heterocycloalkenyl group or an
optionally substituted C₁-C₁₈ heteroaryl group.

56. A use according to claim 55 wherein in the compound of formula (I) R^{4a} and R^{4b} when
15 taken together with the nitrogen atom to which they are attached form an optionally
substituted C₂-C₁₂heterocycloalkyl group selected from the group consisting of piperidin-1-yl,
pyrrolidin-1-yl, azepan-1-yl, azetidin-1-yl, piperazin-1-yl, and morpholin-4-yl.

57. A use according to any one of claims 50 to 52 wherein one of R^{4a} and R^{4b} when taken
20 together with the nitrogen atom to which it is attached and one of R¹³ and R¹⁴ and the carbon
atom to which it is attached form an optionally substituted C₂-C₁₂heterocycloalkyl group.

58. A use according to claim 57 wherein one of R^{4a} and R^{4b} when taken together with the
nitrogen atom to which it is attached and one of R¹³ and R¹⁴ and the carbon atom to which it is
25 attached form an optionally substituted C₂-C₁₂heterocycloalkyl group selected from the group
consisting of piperidinyl, pyrrolidinyl, azepanyl, azetidiny, morpholinyl, and piperazinyl.

59. A use according to any one of claims 45 to 58 wherein Z is selected from the group
consisting of -CH₂-, -(CH₂)₂-, -(CH₂)₃-, -(CH₂)₄-, and -(CH₂)₅-.

30

60. A use according to any one of claims 36 to 59 wherein R¹ is selected from the group
consisting of optionally substituted C₂-C₁₂alkenyl, optionally substituted C₆-C₁₈aryl, optionally
substituted CH₂(C₆-C₁₈aryl), optionally substituted CH₂(C₆-C₁₈aryl), and optionally substituted
C₁-C₁₈heteroaryl.

35

61. A use according to any one of claims 36 to 60 wherein R^{5a} and R^{5b} are each
independently selected from the group consisting of H, optionally substituted C₁-C₁₂alkyl,

optionally substituted C₆-C₁₈aryl, optionally substituted C₁-C₁₈heteroaryl, optionally substituted carboxy and optionally substituted carboxamide.

62. A use according to any one of claims 36 to 61 wherein in the compound of formula (I)
 5 R⁶ is selected from the group consisting of optionally substituted C₁-C₁₂alkyl, optionally substituted C₆-C₁₈aryl and optionally substituted C₁-C₁₈heteroaryl.

63. A use according to any one of claims 36 to 62 wherein r is 0.

10 64. A use according to any one of claims 36 to 62 wherein r is 1.

65. A use according to any one of claims 36 to 62 wherein r is 2.

66. A use according to any one of claims 36 to 65 wherein in the compound of formula (I)
 15 each optional substituent is independently selected from the group consisting of: halogen, =O, =S, -CN, -NO₂, -CF₃, -OCF₃, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, heteroalkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, heteroarylalkyl, arylalkyl, cycloalkylalkenyl, heterocycloalkylalkenyl, arylalkenyl, heteroarylalkenyl, cycloalkylheteroalkyl,
 20 heterocycloalkylheteroalkyl, arylheteroalkyl, heteroarylheteroalkyl, hydroxy, hydroxyalkyl, alkyloxy, alkyloxyalkyl, alkyloxycycloalkyl, alkyloxyheterocycloalkyl, alkyloxyaryl, alkyloxyheteroaryl, alkyloxycarbonyl, alkylaminocarbonyl, alkenyloxy, alkynyloxy, cycloalkyloxy, cycloalkenyloxy, heterocycloalkyloxy, heterocycloalkenyloxy, aryloxy, phenoxy, benzyloxy, heteroaryloxy, arylalkyloxy, amino, alkylamino, acylamino, aminoalkyl, arylamino,
 25 sulfonylamino, sulfinylamino, sulfonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, sulfinyl, alkylsulfinyl, arylsulfinyl, aminosulfinylaminoalkyl, -C(=O)OH, -C(=O)R^a, -C(=O)OR^a, C(=O)NR^aR^b, C(=NOH)R^a, C(=NR^a)NR^bR^c, NR^aR^b, NR^aC(=O)R^b, NR^aC(=O)OR^b, NR^aC(=O)NR^bR^c, NR^aC(=NR^b)NR^cR^d, NR^aSO₂R^b, -SR^a, SO₂NR^aR^b, -OR^a, OC(=O)NR^aR^b, OC(=O)R^a and acyl,

30

wherein R^a, R^b, R^c and R^d are each independently selected from the group consisting of H, C₁-C₁₂ alkyl, C₁-C₁₂ haloalkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, C₁-C₁₀ heteroalkyl, C₃-C₁₂ cycloalkyl, C₃-C₁₂ cycloalkenyl, C₁-C₁₂ heterocycloalkyl, C₁-C₁₂ heterocycloalkenyl, C₆-C₁₈aryl, C₁-C₁₈heteroaryl, and acyl, or any two or more of R^a, R^b, R^c
 35 and R^d, when taken together with the atoms to which they are attached form a heterocyclic ring system with 3 to 12 ring atoms.

67. A use according to any one of claims 36 to 66 wherein in the compound of formula (I) each optional substituent is independently selected from the group consisting of F, Cl, Br, I, CH₃, CH₂CH₃, OH, OCH₃, CF₃, OCF₃, NO₂, NH₂, and CN.

68. A method according to any one of claims 1 to 35 or a use according to any one of claims 36 to 67 wherein the compound is selected from the group consisting of:

- N-(((3S,5S)-1-(3,5-dichlorobenzyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- N-(((3S,5S)-3-(2-aminoethyl)-2-oxo-1-(2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- N-(((3S,5S)-3-(2-aminoethyl)-1-(3,5-dichlorobenzyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- N-(((3S,5S)-3-(3-aminopropyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-6-bromo-N-methyl-2-naphthamide
- N-(((3S,5S)-3-(3-aminopropyl)-1-(2,2-diphenylethyl)-4-methyl-2-oxo-1,4-diazepan-5-yl)methyl)-6-bromo-2-naphthamide
- N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(3-(3-methylguanidino)propyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (E)-N-(((3S,5S)-3-butyl-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3-(4-chlorophenyl)acrylamide
- N-((S)-1-(((3S,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)-2-(naphthalen-2-yl)ethyl)acetamide
- N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)biphenyl-4-carboxamide
- (S)-methyl 2-(((3S,5R)-3-(3-guanidinopropyl)-5-((2-(naphthalen-1-yl)acetamido)methyl)-2-oxo-1,4-diazepan-1-yl)-3-(1H-indol-3-yl)propanoate
- N-(((3R,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)biphenyl-4-carboxamide
- N-(((3R,5R)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)biphenyl-4-carboxamide
- N-(((3S,5R)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)biphenyl-4-carboxamide
- N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)quinoline-3-carboxamide
- N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)quinoxaline-2-carboxamide

- N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)isoquinoline-3-carboxamide
- N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)quinoline-2-carboxamide
- 5 • (5R,9aS)-5-(4-aminobutyl)-2-(biphenyl-4-ylmethyl)-7-(2-(naphthalen-1-yl)ethyl)tetrahydro-1H-imidazo[1,5-d][1,4]diazepine-3,6(2H,5H)-dione
- N-(((3S,5S)-3-(4-aminobutyl)-1-benzhydryl-2-oxo-1,4-diazepan-5-yl)methyl)biphenyl-4-carboxamide
- N-(((3S,5S)-3-(4-aminobutyl)-1-benzhydryl-2-oxo-1,4-diazepan-5-yl)methyl)-2-(biphenyl-4-yl)acetamide
- 10 • (5S,9aS)-5-(4-aminobutyl)-7-benzhydryl-2-(biphenyl-4-ylmethyl)tetrahydro-1H-imidazo[1,5-d][1,4]diazepine-3,6(2H,5H)-dione
- N-(((3S,5S)-3-(4-aminobutyl)-1-benzhydryl-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 15 • N-(((3S,5S)-3-(4-aminobutyl)-1-benzhydryl-2-oxo-1,4-diazepan-5-yl)methyl)-2-(naphthalen-2-yl)acetamide
- (5S,9aS)-5-(4-aminobutyl)-7-benzhydryl-2-(naphthalen-2-ylmethyl)tetrahydro-1H-imidazo[1,5-d][1,4]diazepine-3,6(2H,5H)-dione
- N-(((3S,5S)-1-benzhydryl-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-
- 20 (biphenyl-4-yl)acetamide
- 1-(3-((5S,9aS)-7-benzhydryl-2-(biphenyl-4-ylmethyl)-3,6-dioxooctahydro-1H-imidazo[1,5-d][1,4]diazepin-5-yl)propyl)guanidine
- N-(((3S,5S)-1-benzhydryl-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 25 • N-(((3S,5S)-1-benzhydryl-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-(naphthalen-2-yl)acetamide
- N-(((3S,5R)-1-benzhydryl-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)biphenyl-4-carboxamide
- N-(((3S,5R)-1-benzhydryl-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-
- 30 (biphenyl-4-yl)acetamide
- 1-(3-((5S,9aR)-7-benzhydryl-2-(biphenyl-4-ylmethyl)-3,6-dioxooctahydro-1H-imidazo[1,5-d][1,4]diazepin-5-yl)propyl)guanidine
- N-(((3S,5R)-1-benzhydryl-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-
- (naphthalen-2-yl)acetamide
- 35 • 1-(3-((5S,9aR)-7-benzhydryl-2-(naphthalen-2-ylmethyl)-3,6-dioxooctahydro-1H-imidazo[1,5-d][1,4]diazepin-5-yl)propyl)guanidine

- N-(((3R,5R)-1-benzhydryl-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)biphenyl-4-carboxamide
- N-(((3R,5R)-1-benzhydryl-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-(biphenyl-4-yl)acetamide
- 5 • N-(((3R,5R)-1-benzhydryl-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-(naphthalen-2-yl)acetamide
- 1-(3-((5R,9aR)-7-benzhydryl-2-(naphthalen-2-ylmethyl)-3,6-dioxooctahydro-1H-imidazo[1,5-d][1,4]diazepin-5-yl)propyl)guanidine
- N-(((3S,5R)-3-(4-aminobutyl)-1-(naphthalen-1-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)biphenyl-4-carboxamide
- 10 • N-(((3S,5R)-3-(4-aminobutyl)-1-(naphthalen-1-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-(biphenyl-4-yl)acetamide
- (5S,9aR)-5-(4-aminobutyl)-2-(biphenyl-4-ylmethyl)-7-(naphthalen-1-ylmethyl)tetrahydro-1H-imidazo[1,5-d][1,4]diazepine-3,6(2H,5H)-dione
- 15 • N-(((3S,5R)-3-(4-aminobutyl)-1-(naphthalen-1-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (5S,9aS)-5-(4-aminobutyl)-2-(biphenyl-4-ylmethyl)-7-(naphthalen-1-ylmethyl)tetrahydro-1H-imidazo[1,5-d][1,4]diazepine-3,6(2H,5H)-dione
- N-(((3S,5S)-3-(4-aminobutyl)-1-(naphthalen-1-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 20 • N-(((3S,5S)-3-(4-aminobutyl)-1-(naphthalen-1-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-(naphthalen-2-yl)acetamide
- N-(((3R,5R)-3-(4-aminobutyl)-1-(naphthalen-1-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)biphenyl-4-carboxamide
- 25 • N-(((3R,5R)-3-(4-aminobutyl)-1-(naphthalen-1-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-(biphenyl-4-yl)acetamide
- (5R,9aR)-5-(4-aminobutyl)-2-(biphenyl-4-ylmethyl)-7-(naphthalen-1-ylmethyl)tetrahydro-1H-imidazo[1,5-d][1,4]diazepine-3,6(2H,5H)-dione
- N-(((3R,5S)-3-(4-aminobutyl)-1-(naphthalen-1-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)biphenyl-4-carboxamide
- 30 • N-(((3R,5S)-3-(4-aminobutyl)-1-(naphthalen-1-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-(biphenyl-4-yl)acetamide
- (5R,9aS)-5-(4-aminobutyl)-2-(biphenyl-4-ylmethyl)-7-(naphthalen-1-ylmethyl)tetrahydro-1H-imidazo[1,5-d][1,4]diazepine-3,6(2H,5H)-dione
- 35 • N-(((3R,5S)-3-(4-aminobutyl)-1-(naphthalen-1-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide

- N-(((3R,5S)-3-(4-aminobutyl)-1-(naphthalen-1-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-(naphthalen-2-yl)acetamide
- N-(((3R,5S)-3-(4-aminobutyl)-1-(naphthalen-1-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-1-naphthamide
- 5 • N-(((3R,5S)-3-(4-aminobutyl)-1-(naphthalen-1-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-(naphthalen-1-yl)acetamide
- N-(((3S,5S)-3-(4-aminobutyl)-1-(naphthalen-2-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)biphenyl-4-carboxamide
- N-(((3S,5S)-3-(4-aminobutyl)-1-(naphthalen-2-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-(biphenyl-4-yl)acetamide
- 10 • (5S,9aS)-5-(4-aminobutyl)-2-(biphenyl-4-ylmethyl)-7-(naphthalen-2-ylmethyl)tetrahydro-1H-imidazo[1,5-d][1,4]diazepine-3,6(2H,5H)-dione
- N-(((3S,5S)-3-(4-aminobutyl)-1-(naphthalen-2-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 15 • N-(((3S,5S)-3-(4-aminobutyl)-1-(naphthalen-2-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-(naphthalen-2-yl)acetamide
- N-(((3S,5R)-3-(4-aminobutyl)-1-(naphthalen-2-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)biphenyl-4-carboxamide
- N-(((3S,5R)-3-(4-aminobutyl)-1-(naphthalen-2-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-(biphenyl-4-yl)acetamide
- 20 • (5S,9aR)-5-(4-aminobutyl)-2-(biphenyl-4-ylmethyl)-7-(naphthalen-2-ylmethyl)tetrahydro-1H-imidazo[1,5-d][1,4]diazepine-3,6(2H,5H)-dione
- N-(((3S,5R)-3-(4-aminobutyl)-1-(naphthalen-1-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 25 • N-(((3S,5R)-3-(4-aminobutyl)-1-(naphthalen-2-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-(naphthalen-2-yl)acetamide
- N-(((3S,5R)-3-(4-aminobutyl)-1-(naphthalen-2-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-(naphthalen-1-yl)acetamide
- N-(((3R,5R)-3-(4-aminobutyl)-1-(naphthalen-2-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)biphenyl-4-carboxamide
- 30 • N-(((3R,5R)-3-(4-aminobutyl)-1-(naphthalen-2-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-(biphenyl-4-yl)acetamide
- (5R,9aR)-5-(4-aminobutyl)-2-(biphenyl-4-ylmethyl)-7-(naphthalen-2-ylmethyl)tetrahydro-1H-imidazo[1,5-d][1,4]diazepine-3,6(2H,5H)-dione
- 35 • N-(((3R,5R)-3-(4-aminobutyl)-1-(naphthalen-2-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide

- N-(((3R,5S)-3-(4-aminobutyl)-1-(naphthalen-2-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)biphenyl-4-carboxamide
- N-(((3R,5S)-3-(4-aminobutyl)-1-(naphthalen-2-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-(biphenyl-4-yl)acetamide
- 5 • (5R,9aS)-5-(4-aminobutyl)-2-(biphenyl-4-ylmethyl)-7-(naphthalen-2-ylmethyl)tetrahydro-1H-imidazo[1,5-d][1,4]diazepine-3,6(2H,5H)-dione
- N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)benzamide
- N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)cyclohexanecarboxamide
- 10 • N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3-phenoxybenzamide
- N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-4-phenoxybenzamide
- 15 • N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-1H-indole-2-carboxamide
- N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3-phenylpropanamide
- N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3,4-dimethylbenzamide
- 20 • 4-tert-butyl-N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)benzamide
- N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2,4-dimethoxybenzamide
- 25 • 2-cyclohexyl-N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)acetamide
- N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(2-(guanidinoxy)ethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (E)-3-(4-chlorophenyl)-N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)acrylamide
- 30 • propyl (R)-1-((3R,5R)-1-(2-(1H-indol-3-yl)ethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)-2-phenylethylcarbamate
- (R)-N-((S)-1-((3S,5S)-1-(2-(1H-indol-3-yl)ethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)-2-phenylethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide
- 35 • N-(((3S,5S)-1-(cyclohexylmethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide

- N-(((3S,5S)-3-(3-aminopropyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-6-bromo-2-naphthamide
- (E)-N-(((3S,5S)-3-(3-aminopropyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3-(4-chlorophenyl)acrylamide
- 5 • N-(((3S,5S)-3-(3-(3,3-dimethylguanidino)propyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (E)-N-(((3S,5S)-3-(3-aminopropyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3-p-tolylacrylamide
- (E)-N-(((3S,5S)-3-(3-aminopropyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3-(4-fluorophenyl)acrylamide
- 10 • N-(((3S,5S)-3-(3-aminopropyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-6-fluoro-2-naphthamide
- N-(((3S,5S)-3-(3-aminopropyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3,4-dichlorobenzamide
- 15 • N-(((3S,5S)-3-(3-(cyclohexylamino)propyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- N-(((3S,5S)-3-(3-guanidinopropyl)-1-(naphthalen-2-yl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 20 • N-(((3S,5S)-1-((9H-fluoren-9-yl)methyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (E)-N-(((3S,5S)-3-(3-(cyclohexylamino)propyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3-(4-fluorophenyl)acrylamide
- N-(((3S,5S)-3-(3-aminopropyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-5-(4-chlorophenyl)furan-2-carboxamide
- 25 • N-(((3S,5S)-3-(3-aminopropyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-4-(1H-pyrrol-1-yl)benzamide
- N-(((3S,5S)-3-(3-aminopropyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-5-(4-chlorophenyl)isoxazole-3-carboxamide
- N-(((3S,5S)-1-(2-cyclohexylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 30 • N-(((3S,5S)-1-(2,2-bis(4-fluorophenyl)ethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (N-(((3S,5S)-3-(3-guanidinopropyl)-1-(naphthalen-2-yl)methyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 35 • 1-(3-((1R,5S,9aS)-7-(2-(1H-indol-3-yl)ethyl)-1,2-dibenzyl-3,6-dioxooctahydro-1H-imidazo[1,5-d][1,4]diazepin-5-yl)propyl)guanidine

- (E)-N-(((3S,5S)-3-(3-aminopropyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3-(4-fluorophenyl)-N-methylacrylamide
- (E)-N-(((3S,5S)-3-(3-aminopropyl)-1-(2,2-diphenylethyl)-4-methyl-2-oxo-1,4-diazepan-5-yl)methyl)-3-(4-fluorophenyl)acrylamide
- 5 • (E)-3-(4-chlorophenyl)-N-(((3S,5S)-1-(2,2-diphenylethyl)-2-oxo-3-(3-(pyrrolidin-1-yl)propyl)-1,4-diazepan-5-yl)methyl)acrylamide
- (E)-3-(4-chlorophenyl)-N-(((3S,5S)-1-(2,2-diphenylethyl)-2-oxo-3-(3-(piperidin-1-yl)propyl)-1,4-diazepan-5-yl)methyl)acrylamide
- N-(((3S,5S)-3-(2-aminoethyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 10 • N-(((3S,5S)-3-(3-guanidinopropyl)-1-(naphthalen-1-ylmethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- N-(((3S,5S)-3-(3-guanidinopropyl)-1-(2-(naphthalen-2-yl)ethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 15 • (E)-N-(((3S,5S)-3-(aminomethyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3-(4-chlorophenyl)acrylamide
- N-(((3S,5S)-1-(2,2-diphenylethyl)-2-oxo-3-(piperidin-1-ylmethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (E)-3-(4-chlorophenyl)-N-(((3S,5S)-1-(2,2-diphenylethyl)-2-oxo-3-(piperidin-1-ylmethyl)-1,4-diazepan-5-yl)methyl)acrylamide
- 20 • N-(((3S,5S)-3-(2-aminoethyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3,4-dichlorobenzamide
- (E)-N-(((3S,5S)-3-(2-aminoethyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3-(4-chlorophenyl)acrylamide
- 25 • 3,4-dichloro-N-(((3S,5S)-1-(2,2-diphenylethyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)benzamide
- N-(((3S,5S)-1-((S)-2-benzamido-2-phenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- N-(((3S,5S)-1-(2-(allyloxy)-2-phenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 30 • N-(((3S,5S)-1-((R)-2-(allyloxy)-2-phenylethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (S)-2-amino-N-((R)-1-(((3S,5R)-3-(3-guanidinopropyl)-1-(2-(naphthalen-2-yl)ethyl)-2-oxo-1,4-diazepan-5-yl)-2-phenylethyl)-3-phenylpropanamide
- 35 • (S)-2-amino-N-((R)-1-(((3S,5S)-3-(3-guanidinopropyl)-1-(2-(naphthalen-2-yl)ethyl)-2-oxo-1,4-diazepan-5-yl)-2-phenylethyl)-3-phenylpropanamide

- (E)-N-(((3S,5S)-3-butyl-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3-(4-chlorophenyl)acrylamide
- (E)-N-(((3S,5S)-3-(3-amino-3-oxopropyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3-(4-chlorophenyl)acrylamide
- 5 • N-(3-((2S,7S)-4-(2,2-diphenylethyl)-3-oxo-7-(((E)-3-p-tolylacrylamido)methyl)-1,4-diazepan-2-yl)propyl)cyclohexanecarboxamide
- N-(((3S,5S)-3-(3-guanidinopropyl)-2-oxo-1-(2-phenoxy-2-phenylethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 10 • N-(((3S,5S)-1-(2-ethylbutyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- N-(((3S,5S)-1-((3,5-dimethylcyclohexyl)methyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 3,4-dichloro-N-(2-((3S,5R)-1-(2,2-diphenylethyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)ethyl)benzamide
- 15 • N-(((3S,5S)-3-(2-aminoethyl)-1-(3,5-dichlorobenzyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3,4-dichlorobenzamide
- (E)-N-(((3S,5S)-3-(2-aminoethyl)-1-(3,5-dichlorobenzyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3-(4-chlorophenyl)acrylamide
- (S)-2-((5S,9aS)-2-(4-fluorobenzyl)-5-(3-guanidinopropyl)-3,6-dioxotetrahydro-1H-imidazo[1,5-d][1,4]diazepin-7(8H,9H,9aH)-yl)-N-methyl-3-(naphthalen-2-yl)propanamide
- 20 • (S)-2-((3S,5R)-5-((2-(4-fluorophenyl)acetamido)methyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide
- (S)-2-((3S,5S)-5-((2-(4-fluorophenyl)acetamido)methyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide
- 25 • (S)-2-((3S,5R)-5-((4-fluorobenzylamino)methyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide
- (S)-2-((3S,5R)-5-((N-(4-fluorobenzyl)acetamido)methyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide
- N-(((3S,5S)-1-(3-chloro-5-fluorobenzyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 30 • N-(((3S,5S)-3-(3-aminopropyl)-2-oxo-1-((1-phenylcyclohexyl)methyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 3,4-dichloro-N-(((3S,5S)-1-(3,5-dichlorobenzyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)benzamide
- 35 • N-(((3S,5S)-1-(3,5-dichlorobenzyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide

- (E)-3-(4-chlorophenyl)-N-(((3S,5S)-1-(3,5-dichlorobenzyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)acrylamide
- 4-fluoro-N-(((3R,5R)-3-(3-guanidinopropyl)-1-((S)-1-(methylamino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)-2-oxo-1,4-diazepan-5-yl)methyl)benzamide
- 5 • 4-fluoro-N-(((3R,5S)-3-(3-guanidinopropyl)-1-((S)-1-(methylamino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)-2-oxo-1,4-diazepan-5-yl)methyl)benzamide
- (S)-2-((3R,5R)-5-((2-(4-fluorophenyl)acetamido)methyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide
- (S)-2-((3R,5R)-5-((2-(4-fluorophenyl)acetamido)methyl)-3-(3-(2-(4-
10 fluorophenyl)acetamido)propyl)-2-oxo-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide
- (S)-2-((3R,5S)-5-((2-(4-fluorophenyl)acetamido)methyl)-3-(3-(2-(4-
fluorophenyl)acetamido)propyl)-2-oxo-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide
- 15 • (S)-2-((3R,5S)-5-((2-(4-fluorophenyl)acetamido)methyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide
- 3,4-dichloro-N-(((3S,5S)-1-(2-ethylbutyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)benzamide
- N-(((3S,5S)-1-(2-ethylbutyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-
20 2-naphthamide
- (E)-3-(4-chlorophenyl)-N-(((3S,5S)-1-(2-ethylbutyl)-2-oxo-3-(piperidin-1-yl)methyl)-1,4-diazepan-5-yl)methyl)acrylamide
- N-(((3S,5S)-3-(3-guanidinopropyl)-2-oxo-1-(3-oxo-2-phenyl-3-(piperidin-1-yl)propyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 25 • N-(((3S,5S)-3-(3-guanidinopropyl)-2-oxo-1-(3-oxo-2-phenyl-3-(phenylamino)propyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- N-(((3S,5S)-3-(aminomethyl)-1-(3,5-dichlorobenzyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3,4-dichlorobenzamide
- N-(((3S,5S)-3-(aminomethyl)-1-(3,5-dichlorobenzyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-
30 naphthamide
- (E)-N-(((3S,5S)-3-(aminomethyl)-1-(3,5-dichlorobenzyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3-(4-chlorophenyl)acrylamide
- 3,4-dichloro-N-(((3S,5S)-1-(3,5-dichlorobenzyl)-2-oxo-3-(piperidin-1-yl)methyl)-1,4-diazepan-5-yl)methyl)benzamide
- 35 • (E)-3-(4-chlorophenyl)-N-(((3S,5S)-1-(3,5-dichlorobenzyl)-2-oxo-3-(piperidin-1-yl)methyl)-1,4-diazepan-5-yl)methyl)acrylamide

- N-(((3S,5S)-3-(2-aminoethyl)-2-oxo-1-(2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-3,4-dichlorobenzamide
- (E)-N-(((3S,5S)-3-(2-aminoethyl)-2-oxo-1-(2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-3-(4-chlorophenyl)acrylamide
- 5 • 6-chloro-N-(((3S,5S)-1-(2-ethylbutyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 6-chloro-N-(((3S,5S)-1-(2,2-diphenylethyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 10 • (E)-N-(((3S,5S)-1-(2,2-diphenylethyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-3-(4-isopropylphenyl)acrylamide
- (E)-N-(((3S,5S)-3-(2-aminoethyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3-(4-isopropylphenyl)acrylamide
- (E)-3-(2,4-dimethylphenyl)-N-(((3S,5S)-1-(2,2-diphenylethyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)acrylamide
- 15 • (E)-N-(((3S,5S)-3-(2-aminoethyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3-(2,4-dimethylphenyl)acrylamide
- (E)-3-(2,4-difluorophenyl)-N-(((3S,5S)-1-(2,2-diphenylethyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)acrylamide
- (E)-N-(((3S,5S)-3-(2-aminoethyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-20 3-(2,4-difluorophenyl)acrylamide
- (E)-3-(4-chlorophenyl)-N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(2-morpholinoethyl)-2-oxo-1,4-diazepan-5-yl)methyl)acrylamide
- E-3-(4-chlorophenyl)-N-(((3S,5S)-3-(2-(2,5-dimethylpyrrolidin-1-yl)ethyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)acrylamide
- 25 • 6-chloro-N-(((3S,5S)-2-oxo-1-((S)-2-phenylbutyl)-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 6-chloro-N-(((3S,5S)-2-oxo-1-((S)-2-phenylbutyl)-3-(2-(pyrrolidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 3,4-dichloro-N-(((3S,5S)-2-oxo-1-((S)-2-phenylbutyl)-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)benzamide
- 30 • (E)-3-(4-bromophenyl)-N-(((3S,5S)-1-(2,2-diphenylethyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)acrylamide
- 5-(4-chlorophenyl)-N-(((3S,5S)-1-(2,2-diphenylethyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)isoxazole-3-carboxamide
- 35 • 6-chloro-N-(((3S,5S)-2-oxo-3-(3-oxo-3-(piperidin-1-yl)propyl)-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide

- 6-chloro-N-(((3S,5S)-2-oxo-1-((S)-2-phenylbutyl)-3-(piperidin-1-ylmethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 6-chloro-N-(((3S,5S)-2-oxo-1-((S)-2-phenylbutyl)-3-(3-(piperidin-1-yl)propyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 5 • (E)-N-(2-(((3S,5S)-3-(2-aminoethyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)propan-2-yl)-3-(4-chlorophenyl)acrylamide
- (E)-3-(4-chlorophenyl)-N-(2-(((3S,5S)-1-(2,2-diphenylethyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)propan-2-yl)acrylamide
- 6-chloro-N-(((3S,5S)-1-(3,5-dichlorobenzyl)-3-(2-(isopropylamino)ethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 10 • 3,4-dichloro-N-(((3S,5S)-1-(3,5-dichlorobenzyl)-3-(2-(isopropylamino)ethyl)-2-oxo-1,4-diazepan-5-yl)methyl)benzamide
- 6-chloro-N-(((3S,5S)-3-(2-(isopropylamino)ethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 15 • N-(((3S,5S)-3-(2-aminoethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-6-chloro-2-naphthamide
- (E)-N-(((3S,5S)-3-((1H-imidazol-1-yl)methyl)-1-(2,2-diphenylethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3-(4-chlorophenyl)acrylamide
- N-(((3S,5S)-3-(2-(benzyl(methyl)amino)ethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-3,4-dichlorobenzamide
- 20 • 3,4-dichloro-N-(((3S,5S)-3-(2-(methyl(pentyl)amino)ethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)benzamide
- (S)-6-chloro-N-((2-oxo-1-(2-phenylbutyl)-3-(piperidin-4-yl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 25 • (S)-6-chloro-N-(3-(1-isopentylpiperidin-4-yl)-2-oxo-1-(2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 6-chloro-N-(((3S,5S)-3-isopentyl-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 3,4-dichloro-N-(((3S,5S)-3-(2-(3,5-dimethylpiperidin-1-yl)ethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)benzamide
- 30 • 3,4-dichloro-N-(((3S,5S)-3-(2-(4-hydroxypiperidin-1-yl)ethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)benzamide
- 1-(2-((2S,7S)-7-((3,4-dichlorobenzamido)methyl)-3-oxo-4-((S)-2-phenylbutyl)-1,4-diazepan-2-yl)ethyl)piperidine-4-carboxylic acid
- 35 • N-(((3S,5S)-3-(2-(azepan-1-yl)ethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-3,4-dichlorobenzamide

- 3,4-dichloro-N-(((3S,5S)-3-(2-((S)-2-methylpiperidin-1-yl)ethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)benzamide
- N-(((3S,5S)-3-(3-(butyl(methyl)amino)-3-oxopropyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 5 • N-(((3S,5S)-3-(3-(cyclohexylamino)-3-oxopropyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 6-chloro-N-((3-(1-ethylpiperidin-4-yl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- (3S,5S)-5-((3,4-dichlorobenzylamino)methyl)-1-(2,2-diphenylethyl)-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-2-one
- 10 • 6-chloro-N-(((3S,5S)-3-(2-guanidinoethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 6-chloro-N-(((3S,5S)-3-(2-(3-methylguanidino)ethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 15 • (S)-2-amino-3-(4-fluorophenyl)-N-(((3S,5R)-3-(3-guanidinopropyl)-1-((S)-1-(methylamino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)-2-oxo-1,4-diazepan-5-yl)methyl)propanamide
- (S)-2-((3S,5R)-5-((2-(4-chlorophenyl)acetamido)methyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide
- 20 • (R)-2-amino-3-(4-fluorophenyl)-N-(((3S,5R)-3-(3-guanidinopropyl)-1-((S)-1-(methylamino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)-2-oxo-1,4-diazepan-5-yl)methyl)propanamide
- (S)-2-((3S,5R)-3-(3-guanidinopropyl)-5-((2-(naphthalen-1-yl)acetamido)methyl)-2-oxo-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide
- 25 • N-(((3S,5S)-3-(2-aminoethyl)-1-((R)-2-ethyl-3-methylbutyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3,4-dichlorobenzamide
- N-(((3S,5S)-3-(2-aminoethyl)-1-((S)-2-ethyl-3-methylbutyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3,4-dichlorobenzamide
- (E)-3-(4-fluorophenyl)-N-(((3S,5R)-3-(3-guanidinopropyl)-1-((S)-1-(methylamino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)-2-oxo-1,4-diazepan-5-yl)methyl)acrylamide
- 30 • 3,4-dichloro-N-(((3S,5S)-1-((R)-2-ethyl-3-methylbutyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)benzamide
- 3,4-dichloro-N-(((3S,5S)-1-((S)-2-ethyl-3-methylbutyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)benzamide
- 35 • (S)-2-((3S,5R)-5-((3-(4-fluorophenyl)propanamido)methyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide

- N-(((3S,5S)-3-(2-amino-2-methylpropyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-6-chloro-2-naphthamide
- N-(((3R,5R)-3-(2-amino-2-methylpropyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-6-chloro-2-naphthamide
- 5 • N-(((3S,5S)-3-(2-aminoethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-3,4-dichlorobenzamide
- 3,4-dichloro-N-(((3S,5S)-3-(2-(isopropylamino)ethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)benzamide
- N-(((3S,5S)-3-(2-aminoethyl)-1-(3,5-dichlorobenzyl)-2-oxo-1,4-diazepan-5-yl)methyl)-6-chloro-2-naphthamide
- 10 • 6-chloro-N-(((3S,5S)-1-(3,5-dichlorobenzyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 6-chloro-N-(((3S,5S)-3-(2-methyl-2-(piperidin-1-yl)propyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 15 • (E)-3-(4-chlorophenyl)-N-(((3S,5R)-3-(3-guanidinopropyl)-1-((S)-1-(methylamino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)-2-oxo-1,4-diazepan-5-yl)methyl)acrylamide
- N-(((3S,5S)-3-(2-aminoethyl)-1-((R)-2-ethyl-3-methylbutyl)-2-oxo-1,4-diazepan-5-yl)methyl)-6-chloro-2-naphthamide
- N-(((3S,5S)-3-(2-aminoethyl)-1-((S)-2-ethyl-3-methylbutyl)-2-oxo-1,4-diazepan-5-yl)methyl)-6-chloro-2-naphthamide
- 20 • 6-chloro-N-(((3S,5S)-1-((R)-2-ethyl-3-methylbutyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 6-chloro-N-(((3S,5S)-1-((S)-2-ethyl-3-methylbutyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 25 • (S)-2-amino-3-(4-chlorophenyl)-N-(((3S,5R)-3-(3-guanidinopropyl)-1-((S)-1-(methylamino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)-2-oxo-1,4-diazepan-5-yl)methyl)propanamide
- (R)-2-amino-3-(4-chlorophenyl)-N-(((3S,5R)-3-(3-guanidinopropyl)-1-((S)-1-(methylamino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)-2-oxo-1,4-diazepan-5-yl)methyl)propanamide
- 30 • (S)-2-(((3S,5R)-3-(3-guanidinopropyl)-5-((2-(4-methoxyphenyl)acetamido)methyl)-2-oxo-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide
- (S)-2-(((3S,5R)-3-(3-guanidinopropyl)-2-oxo-5-((3-phenylpropanamido)methyl)-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide
- 35 • (S)-2-(((3S,5R)-5-((3-(4-chlorophenyl)propanamido)methyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide

- (E)-3-(4-chlorophenyl)-N-(((3S,5R)-3-(3-guanidinopropyl)-1-((S)-1-(methylamino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)-2-oxo-1,4-diazepan-5-yl)methyl)acrylamide
- 6-chloro-N-(((3S,5S)-3-hexyl-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 5 • 6-chloro-N-(((3S,5S)-3-(2-(3-isopropylguanidino)ethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 6-chloro-N-(((3S,5S)-3-(4-hydroxybutyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 10 • 6-chloro-N-(((3S,5S)-3-(2-methoxyethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- N-(((3S,5S)-3-(2-(benzyloxy)ethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-6-chloro-2-naphthamide
- 6-chloro-N-(((3S,5S)-3-isobutyl-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 15 • (S)-2-((3S,5R)-5-((2-(2,4-dichlorophenyl)acetamido)methyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide
- (S)-2-((3S,5R)-5-((2-(2,4-dichlorophenyl)acetamido)methyl)-3-(3-(3-(2-(2,4-dichlorophenyl)acetyl)guanidino)propyl)-2-oxo-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide
- 20 • (S)-2-((3S,5R)-5-((2-(3-chlorophenyl)acetamido)methyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide
- (S)-2-((3S,5R)-5-((2-(3-chlorophenyl)acetamido)methyl)-3-(3-(3-(2-(3-chlorophenyl)acetyl)guanidino)propyl)-2-oxo-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide
- 25 • N-(((3S,5S)-3-(2-aminoethyl)-1-(2-ethyl-3-methylbut-3-enyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3,4-dichlorobenzamide
- 3,4-dichloro-N-(((3S,5S)-1-(2-ethyl-3-methylbutyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)benzamide
- 3,4-dichloro-N-(((3S,5S)-1-(2-ethyl-3-methylbut-3-enyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)benzamide
- 30 • N-(((3S,5S)-3-(2-aminoethyl)-1-(2-ethyl-3-methylbut-3-enyl)-2-oxo-1,4-diazepan-5-yl)methyl)-6-chloro-2-naphthamide
- 6-chloro-N-(((3S,5S)-1-((R)-2-ethyl-3-methylbut-3-enyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 35 • 6-chloro-N-(((3S,5S)-1-((S)-2-ethyl-3-methylbut-3-enyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide

- 6-chloro-N-(((3S,5S)-1-(2-ethyl-3-methylbutyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- N-(((3S,5S)-1-(cyclohexylmethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)biphenyl-4-carboxamide
- 5 • N-(((3S,5S)-1-(cyclohexylmethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)quinoline-3-carboxamide
- N-(((3S,5R)-1-(cyclohexylmethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)biphenyl-4-carboxamide
- N-(((3S,5R)-1-(cyclohexylmethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)quinoline-3-carboxamide
- 10 • N-(((3R,5R)-1-(cyclohexylmethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)biphenyl-4-carboxamide
- N-(((3R,5R)-1-(cyclohexylmethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-(1H-indol-3-yl)acetamide
- 15 • N-(((3R,5S)-1-(cyclohexylmethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)biphenyl-4-carboxamide
- N-(((3R,5S)-1-(cyclohexylmethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-1H-indole-3-carboxamide
- N-(((3R,5S)-1-(cyclohexylmethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 20 • N-(((3R,5S)-1-(cyclohexylmethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-(naphthalen-2-yl)acetamide
- N-(((3R,5S)-1-(cyclohexylmethyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-5-yl)methyl)quinoline-3-carboxamide
- 25 • (S)-methyl 2-(((3S,5R)-5-((2-(4-chlorophenyl)acetamido)methyl)-3-(3-guanidinopropyl)-2-oxo-1,4-diazepan-1-yl)-3-(naphthalen-2-yl)propanoate
- (S)-2-(((3S,5R)-3-(3-aminopropyl)-5-((2-(4-chlorophenyl)acetamido)methyl)-2-oxo-1,4-diazepan-1-yl)-N-methyl-3-(naphthalen-2-yl)propanamide
- N-(((3S,5S)-3-(2-(azepan-1-yl)ethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-6-chloro-2-naphthamide
- 30 • 6-chloro-N-(((3S,5S)-3-(2-(3-isopropylureido)ethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- benzyl 2-((2S,7S)-7-((6-chloro-2-naphthamido)methyl)-3-oxo-4-((S)-2-phenylbutyl)-1,4-diazepan-2-yl)acetate
- 35 • benzyl 3-((2S,7S)-7-((6-chloro-2-naphthamido)methyl)-3-oxo-4-((S)-2-phenylbutyl)-1,4-diazepan-2-yl)propanoate

- 4'-chloro-N-(((3S,5S)-2-oxo-1-((S)-2-phenylbutyl)-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)biphenyl-2-carboxamide
- 6-chloro-N-(((3S,5S)-3-(2-(N-isopropylacetamido)ethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 5 • 6-chloro-N-(((3S,5S)-3-((isopropylamino)methyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 6-chloro-N-(((3S,5S)-3-(guanidinomethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 10 • N-(((3S,5S)-3-(2-aminoethyl)-1-(2,4-dichlorobenzyl)-2-oxo-1,4-diazepan-5-yl)methyl)-3,4-dichlorobenzamide
- 3,4-dichloro-N-(((3S,5S)-1-(2,4-dichlorobenzyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)benzamide
- 6-chloro-N-(((3S,5S)-1-(2,4-dichlorobenzyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 15 • 6-chloro-N-(((3S,5S)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1-((R)-2-(thiophen-3-yl)butyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 6-chloro-N-(((3S,5S)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1-((S)-2-(thiophen-3-yl)butyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- N-(((3S,5S)-3-(2-aminoethyl)-1-(2-ethyl-2-methylbutyl)-2-oxo-1,4-diazepan-5-yl)methyl)-20 6-chloro-2-naphthamide
- 6-chloro-N-(((3S,5S)-1-(2-ethyl-2-methylbutyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 6-chloro-N-(((3S,5S)-1-(2,2-diphenylethyl)-3-(2-morpholinoethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 25 • 6-chloro-N-(((3S,5S)-3-(2-morpholinoethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 6-chloro-N-(((3S,5S)-1-(3,5-dichlorobenzyl)-3-(2-morpholinoethyl)-2-oxo-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 3,4-dichloro-N-(((3S,5S)-1-(3,5-dichlorobenzyl)-3-(2-morpholinoethyl)-2-oxo-1,4-diazepan-5-yl)methyl)benzamide
- 30 • N-(3,4-dichlorobenzyl)-N-(((3S,5S)-2-oxo-1-((S)-2-phenylbutyl)-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)acetamide
- 6-chloro-N-(((3S,5S)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1-(2,3,5-trichlorobenzyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 35 • 6-chloro-N-(((3S,5S)-3-(2-(1-methylethylsulfonamido)ethyl)-2-oxo-1-((S)-2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide

- butyl 2-((2S,7S)-7-((6-chloro-2-naphthamido)methyl)-3-oxo-4-((S)-2-phenylbutyl)-1,4-diazepan-2-yl)ethylcarbamate
- (S)-6-chloro-N-((3-(1-isopropylpiperidin-4-yl)-2-oxo-1-(2-phenylbutyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 5 • 6-chloro-N-(((3S,5S)-2-oxo-1-((R)-2-phenylbutyl)-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 5-(4-chlorophenyl)-N-(((3S,5S)-1-(3,5-dichlorobenzyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)isoxazole-3-carboxamide
- 10 • N-(((3S,5S)-1-(3,5-dichlorobenzyl)-2-oxo-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-6-methoxy-2-naphthamide
- 6-chloro-N-(((3R,5R)-2-oxo-1-((R)-2-phenylbutyl)-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 6-chloro-N-(((3S,5R)-2-oxo-1-((S)-2-phenylbutyl)-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 15 • 6-chloro-N-(((3R,5S)-2-oxo-1-((S)-2-phenylbutyl)-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 6-chloro-N-(((3R,5R)-2-oxo-1-((S)-2-phenylbutyl)-3-(2-(piperidin-1-yl)ethyl)-1,4-diazepan-5-yl)methyl)-2-naphthamide
- 20 or a pharmaceutically acceptable salt or prodrug thereof.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2009/000229

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/551 (2006.01) **C07D 243/06** (2006.01) **C07D 409/06** (2006.01)
A61P 3/00 (2006.01) **C07D 401/04** (2006.01) **C07D 413/12** (2006.01)
A61P 3/04 (2006.01) **C07D 401/12** (2006.01) **C07D 487/04** (2006.01)
A61P 15/10 (2006.01) **C07D 403/06** (2006.01)
A61P 29/00 (2006.01) **C07D 403/12** (2006.01)

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)

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 practicable, search terms used)

CA: Substructure search based on formula (I).

WIPO PatentScope: Keywordsearch (melanocortin receptor, acne, pharmaceutical and like terms)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 1999/048913 A1 (THE UNIVERSITY OF QUEENSLAND) 30 September 1999 Compounds 63-66, 74, 75, 80-84, 96, 97 and A9 on pages 29, 37, 44, 58 and 69.	
A	NOUVET, A et al, "Convenient introduction of 2-(trimethylsilyl)ethylsulfonyl (SES) amino protection on different amino acids and its use in peptidomimetic chemistry", 1999, Letters in Peptide Science Vol. 6, No. 4, pages 239-242. Compound 8 page 241.	
A	NOUVET, A et al, "Synthesis of perhydrodiazepinones as new putative peptidomimetics", 1999, Tetrahedron, Vol. 55, No. 15, pages 4685-4698. Compound 16 page 4687.	
A	WO 2008/017852 A1 (PALATIN TECHNOLOGIES, INC.) 14 February 2008 Whole document	



Further documents are listed in the continuation of Box C



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	"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
"E" earlier application or patent but published on or after the international filing date	"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
"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)	"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
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search
19 March 2009 20 March 2009

Date of mailing of the international search report 24 MAR 2009

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/AU2009/000229

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	1999/408913	AU	30193/99	CA	2325937	EP	1064300
WO	2008/017852	AR	062219	AU	2004235792	BR	PI0410694
		CA	2462200	CN	1816337	CN	101272788
		CN	101272789	EP	1425029	EP	1622618
		EP	1919479	EP	1922072	KR	20060009285
		MX	PA05011729	US	7189755	US	7326707
		US	7354923	US	7456184	US	2004152134
		US	2004157264	US	2004167201	US	2004171520
		US	2004224957	US	2005124636	US	2005130988
		US	2005176728	US	2006287330	US	2006287331
		US	2006287332	US	2007155670	US	2008070921
		US	2008234289	WO	2003/013571	WO	2004/098602
		WO	2005/102340	WO	2007/021990	WO	2007/021991
		WO	2008/090357				

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX