SUBSTITUTED-QUINOXALINE-TYPE PIPERIDINE COMPOUNDS AND THE USES THEREOF

1. FIELD OF THE INVENTION

The invention relates to Substituted-Quinoxaline-Type Piperidine Compounds, compositions comprising an effective amount of a Substituted-Quinoxaline-Type Piperidine Compound and methods to treat or prevent a condition, such as pain, comprising administering to an animal in need thereof an effective amount of a Substituted-Quinoxaline-Type Piperidine Compound.

2. BACKGROUND OF THE INVENTION

Chronic pain is a major contributor to disability and is the cause of much suffering. The successful treatment of severe and chronic pain is a primary goal of the physician, with opioid analgesics being preferred drugs for doing so.

Until recently, there was evidence of three major classes of opioid receptors in the central nervous system (CNS), with each class having subtype receptors. These receptor classes are known as μ, κ and δ. As opiates have a high affinity for these receptors while not being endogenous to the body, research followed in order to identify and isolate the endogenous ligands to these receptors. These ligands were identified as endorphins, dynorphins and enkephalins,respectively.

Recent experimentation has led to the identification of a cDNA encoding an opioid receptor-like (ORL-1) receptor with a high degree of homology to the known receptor classes. The ORL-1 receptor was classified as an opioid receptor based only on structural grounds, as the receptor did not exhibit pharmacological homology. It was initially demonstrated that non-selective ligands having a high affinity for μ, κ and δ receptors had low affinity for the ORL-1 receptor. This characteristic, along with the fact that an endogenous ligand had not yet been discovered, led to the term "orphan receptor".

Subsequent research led to the isolation and structure of the endogenous ligand of the ORL-1 receptor (*i.e.*, nociceptin; also known as orphanin FQ (OFQ)). This ligand is a seventeen amino acid peptide structurally similar to members of the opioid peptide family.

The discovery of the ORL-1 receptor presents an opportunity in drug discovery for novel compounds that can be administered for pain management or other syndromes modulated by this receptor.

International PCT Publication No. WO 99/46260 A1 describes quinoxalinone derivatives as inhibitors of protein kinase C.

International PCT Publication No. WO 99/50254 A1 describes quinoxalinone derivatives as serine protease inhibitors.

International PCT Publication No. WO 01/90102 A2 describes 6-heterocyclyl-3-oxo-3,4-dihydro-quinoxalines for use as herbicides.

International PCT Publication No. WO 2005/028451 A1 describes tetrahydroquinoxaline derivatives for use as M2 acetylcholine receptor agonists.

International PCT Publication No. WO 2003/062234 A1 describes quinoxaline derivatives for use in remedying diseases in which poly(ADP-ribose) polymerase (PARP) participates.

U.S. published patent application No. US 2005/0256000 by Schaper *et al.* describes quinoxaline-2-one derivatives for use as safeners for plants.

Citation of any reference in Section 2 of this application is not to be construed as an admission that such reference is prior art to the present application.

3. SUMMARY OF THE INVENTION

It is an object of the invention to provide new compounds that exhibit affinity for the ORL-1 receptor.

In certain embodiments of the invention, such new compounds exhibit agonist activity at the ORL-1 receptor.

In certain embodiments of the invention, such new compounds exhibit partial agonist activity at the ORL-1 receptor.

In certain other embodiments of the invention, such new compounds exhibit antagonist activity at the ORL-1 receptor.

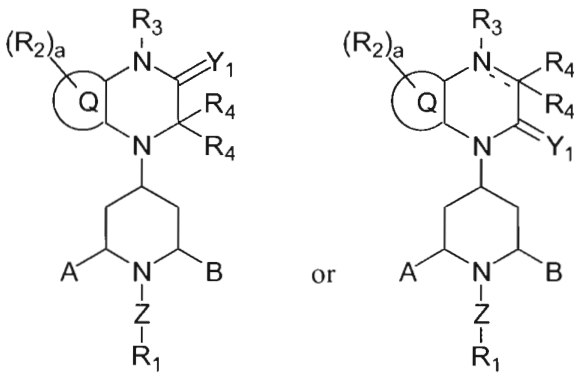
In certain embodiments of the invention, such new compounds exhibit affinity for the ORL-1 receptor, and also for one or more of the μ, κ or δ receptors. In a particular

embodiment, a new compound of the invention exhibits affinity for both the ORL-1 receptor and the μ receptor. In another embodiment, a new compound of the invention acts as an ORL-1 receptor agonist and as a μ receptor agonist. In another embodiment, a new compound of the invention acts as an ORL-1 receptor partial agonist and as a μ receptor agonist. In another embodiment, a new compound of the invention acts as an ORL-1 receptor partial agonist and as a μ receptor antagonist. In another embodiment, a new compound of the invention acts as an ORL-1 receptor antagonist and as a μ receptor agonist.

Certain new compounds of the invention can be used to treat an animal suffering from chronic or acute pain.

It is a further object of the invention to provide methods of treating chronic or acute pain in an animal by administering one or more Substituted-Quinoxaline-Type Piperidine Compounds of the invention to an animal in need of such treatment. In certain embodiments, such new Substituted-Quinoxaline-Type Piperidine Compounds effectively treat chronic or acute pain in the animal, while producing fewer or reduced side effects compared to previously available compounds.

The invention encompasses compounds of Formula (I) and Formula (II):



(I) (II)

and pharmaceutically acceptable derivatives thereof wherein:

Y_1 is O or S;

Q is selected from fused benzo or (5- or 6-membered)heteroaryl;

each R_2 is independently selected from:

(a) -halo, -CN, -NO_2, -OT_3, -$C(=O)T_3$, -$C(=O)OT_3$, -$C(=O)N(T_1)(T_2)$, -$S(=O)_3H$, -$S(=O)T_3$, -$S(=O)_2T_3$, -$S(=O)_2N(T_1)(T_2)$, -$N(T_1)(T_2)$, -$N(T_3)C(=O)T_3$, -$N(T_3)C(=O)N(T_1)(T_2)$, -$N(T_3)S(=O)_2T_3$, or -$N(T_3)S(=O)_2N(T_1)(T_2)$; or

(b) -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_7)cycloalkyl, -(C_1-C_6)alkoxy, -(C_6-C_{14})bicycloalkyl, -(C_8-C_{20})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_7-C_{14})bicycloalkenyl, -(C_8-C_{20})tricycloalkenyl, -(5- or 6-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_8 groups; or

(c) -phenyl, -naphthalenyl, -(C_{14})aryl, or -(5- or 6-membered)heteroaryl, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_7 groups;

a is an integer selected from 0, 1 or 2;

the dashed line in the 6-membered, nitrogen-containing ring that is fused to the Q group denotes the presence or absence of a bond, and when that dashed line denotes the presence of a bond then R_3 and one R_4 are absent;

R_3 is selected from:

(a) -H; or

(b) -(C_1-C_4)alkyl which is unsubstituted or substituted with 1, 2 or 3 groups independently selected from -OH, -(C_1-C_4)alkoxy, -$N(R_6)_2$, -$C(=O)OR_9$, or -$C(=O)N(R_6)_2$; or

(c) -(C_3-C_7)cycloalkyl which is unsubstituted or substituted with 1, 2 or 3 groups independently selected from -OH, -(C_1-C_4)alkyl, -(C_1-C_4)alkoxy, -$N(R_6)_2$, -$C(=O)OR_9$, or -$C(=O)N(R_6)_2$;

each R_4 is independently selected from:

(a) -H; or

(b) -halo, -CN, or -NO_2; or

(c) -X, -CH_2X, -CH_2CH_2X, -(C_1-C_6)alkyl-X, -(5- or 6-membered)heterocycle-X, -(5- or 6-membered)heterocycle-(C_1-C_6)alkyl-X, or -(5- or 6-membered)heterocycle-(C_1-C_6)alkyl-R_8; or

(d) -C(=Y)CN, -C(=Y)X, -$C(=Y)T_3$, -C(=Y)YX, -$C(=Y)YT_3$, -$C(=Y)N(T_1)(T_2)$, -$C(=Y)N(R_9)CN$, -$C(=Y)N(R_9)X$, -$C(=Y)N(R_9)CH_2CH_2N(T_1)(T_2)$, -$C(=Y)N(R_9)YH$, -$C(=Y)N(R_9)YX$, -$C(=Y)N(R_9)YCH_2X$, -$C(=Y)N(R_9)YCH_2CH_2X$, or -$C(=Y)N(R_9)S(=O)_2T_3$; or

(e) -N(R_9)X, -N(R_9)-CH_2X, -N(R_9)-CH_2CH_2X, -N(R_9)-CH_2CH_2N(R_9)X, -N(R_9)CH_2CH_2N(T_1)(T_2), -N(R_9)CH_2C(=Y)X, -N((C_1-C_6)alkyl-C(=O)OR_9)$_2$, -N(R_9)CH_2N(R_9)C(=N(R_{12}))N(R_{12})$_2$, -N(R_9)-CH_2CH_2N(R_9)C(=N(R_{12}))N(R_{12})$_2$, -N(T_1)(T_2), -N(T_3)C(=Y)T_3, -N(T_3)C(=Y)YT_3, -N(T_3)C(=Y)N(T_1)(T_2), -N(T_3)S(=O)$_2$$T_3$, or -N($T_3$)S(=O)$_2$N($T_1$)($T_2$); or

(f) -YH, -CH_2YH, -CH_2CH_2YH, -YX, or -YT_3; or

(g) -S(=O)T_3, -S(=O)$_2$$T_3$, -S(=O)N($T_1$)($T_2$), -S(=O)$_2$N($T_1$)($T_2$), -S(=O)X, or -S(=O)$_2$X;

X is:

(a) -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_1-C_6)alkoxy, -(C_3-C_7)cycloalkyl, -(C_6-C_{14})bicycloalkyl, -(C_8-C_{20})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_7-C_{14})bicycloalkenyl, -(C_8-C_{20})tricycloalkenyl, -(5- or 6-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_8 groups; or

(b) -phenyl, -benzyl, -naphthalenyl, -(C_{14})aryl, -(C_1-C_6)alkyl-(5- or 6-membered)heteroaryl or -(5- or 6-membered)heteroaryl, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_7 groups;

each Y is independently selected from O or S;

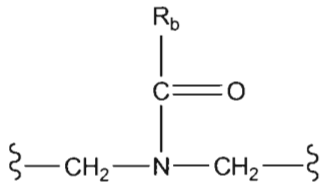
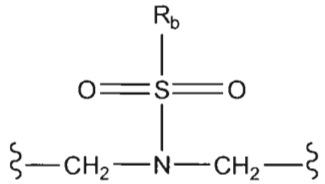
A and B are independently selected from:

(a) -H, -CN, -C(=O)OT_3, or -C(=O)N(T)$_1$(T_2); or

(b) -(C_3-C_{12})cycloalkyl, -(C_3-C_{12})cycloalkoxy, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, or -(C_1-C_6)alkoxy, each of which is unsubstituted or substituted with 1 or 2 substituents independently selected from -OH, -S(=O)$_2$$NH_2$, -N($R_6$)$_2$, =N$R_6$, -C(=O)O$T_3$, -CON($R_6$)$_2$, -N($R_6$)C(=O)$R_9$, and -(5- or 6-membered)heterocycle, or 1, 2 or 3 independently selected -halo; or

(c) A-B can together form a (C_2-C_6)bridge, which is unsubstituted or substituted with 1, 2, 3, 4, 5, 6, 7 or 8 substituents independently selected from -OH, -(C_1-C_4)alkyl, -halo, and -C(halo)$_3$, and which bridge optionally contains -HC=CH- or -O- within the (C_2-C_6)bridge; wherein the 6-membered, nitrogen-containing ring that is fused to the Q group can be in the *endo*- or *exo*- configuration with respect to the A-B bridge; or

(d) A-B can together form a -CH_2-N(R_a)-CH_2- bridge, a


bridge, or a

bridge;

wherein the 6-membered, nitrogen-containing ring that is fused to the Q group can be in the *endo*- or *exo*- configuration with respect to the A-B bridge;

R_a is selected from -H, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -CH_2-C(=O)-R_c, -(CH_2)-C(=O)-OR_c, -(CH_2)-C(=O)-$N(R_c)_2$, -(CH_2)$_2$-O-R_c, -(CH_2)$_2$-S(=O)$_2$-$N(R_c)_2$, R_c, or -(CH_2)$_7$-$N(R_c)$S(=O)$_2$-R_c;

R_b is selected from:

(a) -H, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(3- to 7-membered)heterocycle, -$N(R_c)_2$, -$N(R_c)$-(C_3-C_7)cycloalkyl, or -$N(R_c)$-(3- to 7-membered)heterocycle; or

(b) -phenyl, -naphthalenyl, or-(5- or 6-membered)heteroaryl, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_7 groups; or

(c) -$N(R_c)$-phenyl, -$N(R_c)$-naphthalenyl, -$N(R_c)$-(C_{14})aryl, or -$N(R_c)$-(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_7 groups;

each R_c is independently selected from -H or -(C_1-C_4)alkyl;

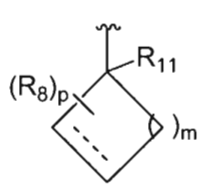
Z is -[(C_1-C_{10})alkyl optionally substituted by R_1]$_h$-, wherein h is 0 or 1; [(C_2-C_{10})alkenyl optionally substituted by R_1]; or -(C_1-C_{10})alkyl-NR_6C(=Y)-;

each R_1 is independently selected from:

(a) -H, -halo, -CN, -OH, -CH_2OH, -CH_2CH_2OH, -NO_2, -$N(R_6)_2$, -S(=O)NH_2, -S(=O)$_2NH_2$, -C(=O)OV_1, or -C(=O)CN; or

(b) -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -O(C_1-C_6)alkyl, -(C_3-C_7)cycloalkoxy, -(C_6-C_{14})bicycloalkyl, -(C_8-C_{20})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_7-C_{14})bicycloalkenyl, -(C_8-C_{20})tricycloalkenyl, -(3- to 7-membered)heterocycle, -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_8 groups; or

(c)



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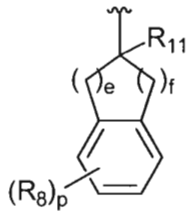
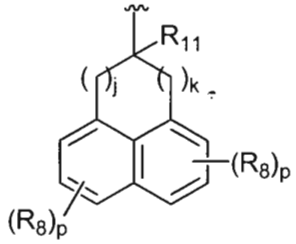


, or



;

(i) (ii) (iii)

; or

(d) -phenyl, -naphthalenyl, -(C_{14})aryl, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with an R_7 group; or

-Z-R_1 is 3,3-diphenylpropyl- optionally substituted at the 3 carbon of the propyl with -CN, -C(=O)N(R_6)$_2$, -C(=O)OV_1, or -tetrazolyl; or

-Z-R_1 is -(C_1-C_4)alkyl substituted with tetrazolyl;

each R_6 is independently selected from -H, -(C_1-C_6)alkyl, or -(C_3-C_7)cycloalkyl, or two R_6 groups attached to the same nitrogen atom can together form a 5- to 8-membered ring, wherein the number of atoms in the ring includes the nitrogen atom, and in which one of the 5- to 8-membered ring carbon atoms is optionally replaced by O, S, or N(T_3);

each R_7 is independently selected from -(C_1-C_4)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -OR_9, -SR_9, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -CN, -halo, -N_3, -NO_2, -CH=N(R_9), -N(R_9)$_2$, -N(R_9)OH, -N(R_9)S(=O)R_{12}, -N(R_9)S(=O)$_2R_{12}$, -N(R_9)C(=O)R_{12}, -N(R_9)C(=O)N(T_1)(T_2), -N(R_9)C(=O)OR_{12}, -C(=O)R_9, -C(=O)N(T_1)(T_2), -C(=O)OR_9, -OC(=O)R_9, -OC(=O)N(T_1)(T_2), -OC(=O)OR_9, -S(=O)R_9, or -S(=O)$_2R_9$;

each R_8 is independently selected from -(C_1-C_4)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(5- or 6-membered)heteroaryl, -phenyl, -(C_1-C_6)alkylCOOR_9, -OR_9, -SR_9, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -CN, =O, =S, -halo, -N_3, -NO_2, -CH=N(R_9), -NR_9(C_1-C_6)alkylCOOR_9, -N(R_9)$_2$, -N(R_9)OH, -N(R_9)S(=O)R_{12}, -N(R_9)S(=O)$_2R_{12}$, -N(R_9)C(=O)R_{12}, -N(R_9)C(=O)N(T_1)(T_2), -N(R_9)C(=O)OR_{12}, , -C(=O)R_9, -C(=O)-C(=O)OR_9, -C(=O)N(T_1)(T_2), -C(=O)OR_9, -OC(=O)R_9, -OC(=O)N(T_1)(T_2), -OC(=O)OR_9, -S(=O)R_9, or -S(=O)$_2R_9$;

each R_9 is independently selected from -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_1-C_6)alkoxy, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -benzyl, -(3- to

6-membered)heterocycle, -(5- to 10-membered)heteroaryl, -C(halo)$_3$, -CH(halo)$_2$, or -CH$_2$(halo);

if h is 0, then R_{11} can be selected from -H, -CN, -C(=O)OR$_9$, or -C(=O)N(R$_6$)$_2$ or R_{11} can be -(C$_1$-C$_4$)alkyl which is unsubstituted or substituted with -OH, -(C$_1$-C$_4$)alkoxy, -N(R$_6$)$_2$, -C(=O)OR$_9$, or -C(=O)N(R$_6$)$_2$;

if h is 1, then R_{11} can be selected from -H, -CN, -OH, -halo, -C(=O)OR$_9$, or -C(=O)N(R$_6$)$_2$ or R_{11} can be -(C$_1$-C$_4$)alkyl which is unsubstituted or substituted with -OH, -(C$_1$-C$_4$)alkoxy, -N(R$_6$)$_2$, -C(=O)OR$_9$, or -C(=O)N(R$_6$)$_2$;

otherwise, where Z is -(C$_1$-C$_{10}$)alkyl-NR$_6$C(=Y)-, then R_{11} can be selected from -H, -CN, -C(=O)OR$_9$, or -C(=O)N(R$_6$)$_2$ or R_{11} can be -(C$_1$-C$_4$)alkyl which is unsubstituted or substituted with -OH, -(C$_1$-C$_4$)alkoxy, -N(R$_6$)$_2$, -C(=O)OR$_9$, or -C(=O)N(R$_6$)$_2$;

each R_{12} is independently selected from -H or -(C$_1$-C$_4$)alkyl;

m is an integer selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 11;

e and f are each an integer independently selected from 0, 1, 2, 3, 4, or 5 provided that $2 \leq (e + f) \leq 5$;

j and k are each an integer independently selected from 0, 1, 2, 3, or 4 provided that $1 \leq (j + k) \leq 4$;

each p is an integer independently selected from 0, 1, 2, 3, or 4;

each T_1, T_2, and T_3 is independently -H or -(C$_1$-C$_{10}$)alkyl which is unsubstituted or substituted with 1, 2 or 3 independently selected R_8 groups and, optionally, in which any -(C$_1$-C$_{10}$)alkyl carbon atom except the carbon atom bonded directly to the atom to which T_1, T_2, or T_3 is attached is independently replaced by O, S, or N(R$_6$), or T_1 and T_2 can together form a 5- to 8-membered ring where the number of atoms in the ring includes the nitrogen atom to which T_1 and T_2 are bonded, said 5- to 8-membered ring is unsubstituted or substituted with 1, 2 or 3 independently selected R_8 groups and, optionally, any carbon atom in said 5- to 8-membered ring is independently replaced by O, S, or N(R$_6$);

each V_1 is independently selected from -H, -(C$_1$-C$_6$)alkyl, -(C$_3$-C$_7$)cycloalkyl, -phenyl, or -benzyl; and

each halo is independently selected from -F, -Cl, -Br, or -I.

A compound of Formula (I) or Formula (II) or a pharmaceutically acceptable derivative thereof (a "Substituted-Quinoxaline-Type Piperidine Compound") is useful, *e.g.*, as an analgesic, anti-inflammatory, diuretic, anesthetic agent, neuroprotective agent, anti-hypertensive, an anxiolytic agent, an agent for appetite control, hearing regulator, anti-tussive, anti-asthmatic, modulator of locomotor activity, modulator of learning and memory, regulator of neurotransmitter release, regulator of hormone release, kidney function modulator, anti-depressant, agent to treat memory loss due to Alzheimer's disease and/or other dementias, anti-epileptic, anti-convulsant, agent to treat withdrawal from alcohol, agent to treat withdrawal from drug(s) of addiction, agent to control water balance, agent to control sodium excretion, and/or agent to control arterial blood pressure disorder(s).

A Substituted-Quinoxaline-Type Piperidine Compound is useful for treating and/or preventing pain, anxiety, cough, diarrhea, high blood pressure, epilepsy, anorexia/cachexia, urinary incontinence, drug abuse, a memory disorder, obesity, constipation, depression, dementia, or Parkinsonism (each being a "Condition") in an animal.

The invention also relates to compositions comprising an effective amount of a Substituted-Quinoxaline-Type Piperidine Compound and a pharmaceutically acceptable carrier or excipient. The compositions are useful for treating or preventing a Condition in an animal.

The invention further relates to methods for treating a Condition, comprising administering to an animal in need thereof an effective amount of a Substituted-Quinoxaline-Type Piperidine Compound.

The invention further relates to methods for preventing a Condition, comprising administering to an animal in need thereof an effective amount of a Substituted-Quinoxaline-Type Piperidine Compound.

The invention further relates to the use of a Substituted-Quinoxaline-Type Piperidine Compound, *e.g.*, of Formulas (I) and/or (II), for the manufacture of a medicament useful for treating a Condition.

The invention further relates to the use of a Substituted-Quinoxaline-Type Piperidine Compound, *e.g.*, of Formulas (I) and/or (II), for the manufacture of a medicament useful for preventing a Condition.

The invention still further relates to methods for inhibiting ORL-1 receptor function in a cell, comprising contacting a cell capable of expressing the ORL-1 receptor with an ORL-1 receptor function inhibiting amount of a Substituted-Quinoxaline-Type Piperidine Compound.

The invention still further relates to methods for activating ORL-1 receptor function in a cell, comprising contacting a cell capable of expressing the ORL-1 receptor with an ORL-1 receptor function activating amount of a Substituted-Quinoxaline-Type Piperidine Compound.

The invention still further relates to methods for preparing a composition, comprising the step of admixing a Substituted-Quinoxaline-Type Piperidine Compound and a pharmaceutically acceptable carrier or excipient.

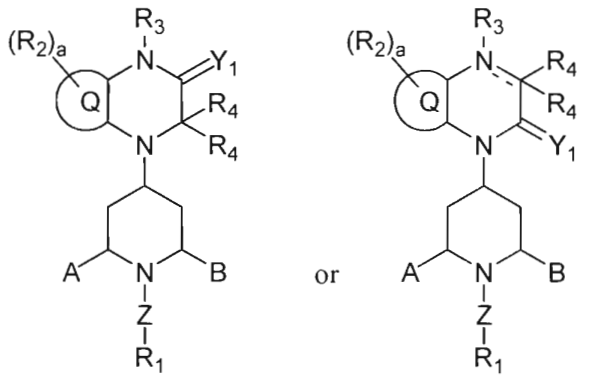
The invention still further relates to a kit comprising a container containing an effective amount of a Substituted-Quinoxaline-Type Piperidine Compound.

The invention also provides novel intermediates for use in making the Substituted-Quinoxaline-Type Piperidine Compounds.

The invention can be understood more fully by reference to the following detailed description and illustrative examples, which are intended to exemplify non-limiting embodiments of the invention. Other objects and advantages of the invention will become apparent from the following detailed description thereof.

4. DETAILED DESCRIPTION OF THE INVENTION

The invention encompasses compounds of Formula (I.1) and Formula (II.1):



(I.1) (II.1)

or a pharmaceutically acceptable derivative thereof wherein:

Y_1 is O or S;

Q is selected from fused benzo or (5- or 6-membered)heteroaryl;

each R_2 is independently selected from:

(a) -halo, -CN, $-NO_2$, $-OT_3$, $-C(O)T_3$, $-C(O)OT_3$, $-C(O)N(T_1)(T_2)$, $-S(O)_3H$, $-S(O)T_3$, $-S(O)_2T_3$, $-S(O)_2N(T_1)(T_2)$, $-N(T_1)(T_2)$, $-N(T_3)C(O)T_3$, $-N(T_3)C(O)N(T_1)(T_2)$, $-N(T_3)S(O)_2T_3$, or $-N(T_3)S(O)_2N(T_1)(T_2)$; or

(b) $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_3-C_7)$cycloalkyl, $-(C_6-C_{14})$bicycloalkyl, $-(C_8-C_{20})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_7-C_{14})$bicycloalkenyl, $-(C_8-C_{20})$tricycloalkenyl, -(5- or 6-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with 1, 2 or 3 R_8 groups; or

(c) -phenyl, -naphthalenyl, $-(C_{14})$aryl, or -(5- or 6-membered)heteroaryl, each of which is unsubstituted or substituted with 1, 2 or 3 R_7 groups;

a is an integer from 0 to 2;

the dashed line in the fused piperazine ring denotes the presence or absence of a bond, and when that dashed line denotes the presence of a bond then R_3 and one R_4 are absent;

R_3 is independently selected from -H or $-(C_1-C_4)$alkyl which is unsubstituted or substituted with 1,2, or 3 of -OH, $-(C_1-C_4)$alkoxy, $-N(R_6)_2$, $-C(O)OR_9$, or $-C(O)N(R_6)_2$;

each R_4 is independently selected from:

(a) -H; or

(b) -halo, -CN, or $-NO_2$; or

(c) -X, $-CH_2X$, or $-CH_2CH_2X$; or

(d) -C(Y)CN, -C(Y)X, $-C(Y)T_3$, -C(Y)YX, $-C(Y)YT_3$, $-C(Y)N(T_1)(T_2)$, $-C(Y)N(R_9)CN$, $-C(Y)N(R_9)X$, $-C(Y)N(R_9)YH$, $-C(Y)N(R_9)YX$, $-C(Y)N(R_9)YCH_2X$, $-C(Y)N(R_9)YCH_2CH_2X$, or $-C(Y)N(R_9)S(O)_2T_3$; or

(e) $-N(R_9)X$, $-N(R_9)-CH_2X$, $-N(R_9)-CH_2CH_2X$, $-N(R_9)CH_2N(R_9)C(=N(R_{12}))N(R_{12})_2$, $-N(R_9)-CH_2CH_2N(R_9)C(=N(R_{12}))N(R_{12})_2$, $-N(T_1)(T_2)$, $-N(T_3)C(Y)T_3$, $-N(T_3)C(Y)YT_3$, $-N(T_3)C(Y)N(T_1)(T_2)$, $-N(T_3)S(O)_2T_3$, or $-N(T_3)S(O)_2N(T_1)(T_2)$; or

(f) -YH, $-CH_2YH$, $-CH_2CH_2YH$, -YX, or $-YT_3$; or

(g) $-S(O)T_3$, $-S(O)_2T_3$, $-S(O)N(T_1)(T_2)$, $-S(O)_2N(T_1)(T_2)$, -S(O)X, or $-S(O)_2X$;

X is:

(a) -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_7)cycloalkyl, -(C_6-C_{14})bicycloalkyl, -(C_8-C_{20})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_7-C_{14})bicycloalkenyl, -(C_8-C_{20})tricycloalkenyl, -(5- or 6-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with 1, 2 or 3 R_8 groups; or

(b) -phenyl, -naphthalenyl, -(C_{14})aryl, or -(5- or 6-membered)heteroaryl, each of which is unsubstituted or substituted with 1, 2 or 3 R_7 groups;

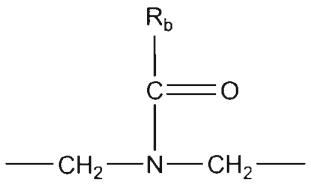
each Y is independently selected from O or S;

A and B are independently selected from:

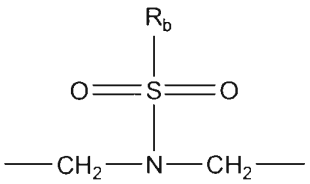
(a) -H, -CN, -C(O)OT_3, -C(O)N(T)$_1$(T_2), -(C_3-C_{12})cycloalkyl, -(C_3-C_{12})cycloalkoxy, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, or -(C_2-C_6)alkynyl, each of which -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl or -(C_2-C_6)alkynyl is unsubstituted or substituted with 1 or 2 substituents selected from -OH, -S(O)$_2$$NH_2$, -N($R_6$)$_2$, =N$R_6$, -C(O)$OT_3$, -CON($R_6$)$_2$, -N($R_6$)C(O)$R_9$ and -(5- or 6-membered)heterocycle or from 1 to 3 independently selected -halo; or

(b) A-B can together form a (C_2-C_6)bridge, which is unsubstituted or optionally substituted with from 1 to 3 -OH or optionally contains -HC=CH- within the (C_2-C_6)bridge; or

(c) A-B can together form a -CH_2-N(R_a)-CH_2- bridge, a



bridge, or a



bridge;

R_a is selected from -H, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -CH_2-C(O)-R_c, -(CH_2)-C(O)-OR_c, -(CH_2)-C(O)-N(R_c)$_2$, -(CH_2)$_2$-O-R_c, -(CH_2)$_2$-S(O)$_2$-N(R_c)$_2$, R_c, or -(CH_2)$_2$-N(R_c)S(O)$_2$-R_c;

R_b is selected from:

(a) -H, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(3- to 7-membered)heterocycle, -N(R_c)$_2$, -N(R_c)-(C_3-C_7)cycloalkyl, or -N(R_c)-(3- to 7-membered)heterocycle; or

(b) -phenyl, -naphthalenyl, or-(5- or 6-membered)heteroaryl, each of which is unsubstituted or substituted with 1, 2 or 3 R_7 groups; or

(c) -N(R_c)-phenyl, -N(R_c)-naphthalenyl, -N(R_c)-(C_{14})aryl, or -N(R_c)-(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with 1, 2 or 3 R_7 groups;

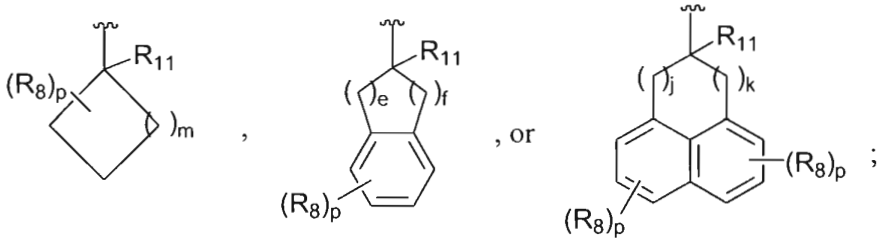
each R_c is independently selected from -H or -(C_1-C_4)alkyl;

Z is -[(C_1-C_{10})alkyl]$_h$-, wherein h is 0 or 1; or -(C_1-C_{10})alkyl-$NR_6C(=Y)$-;

R_1 is selected from:

(a) -H, -halo, -CN, -OH, $-CH_2OH$, $-CH_2CH_2OH$, $-NO_2$, $-N(R_6)_2$, $-S(O)NH_2$, $-S(O)_2NH_2$, $-C(O)OV_1$, or -C(O)CN; or

(b) -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -O(C_1-C_6)alkyl, -(C_3-C_7)cycloalkoxy, -(C_6-C_{14})bicycloalkyl, -(C_8-C_{20})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_7-C_{14})bicycloalkenyl, -(C_8-C_{20})tricycloalkenyl, -(3- to 7-membered)heterocycle, -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with an R_8 group, or



(i) (ii) (iii) or

(c) -phenyl, -naphthalenyl, -(C_{14})aryl, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with an R_7 group; or

-Z-R_1 is 3,3-diphenylpropyl- optionally substituted at the 3 carbon of the propyl with -CN, $-C(O)N(R_6)_2$, $-C(O)OV_1$, or -tetrazolyl; or

-Z-R_1 is -(C_1-C_4)alkyl substituted with tetrazolyl;

each R_6 is independently selected from -H, -(C_1-C_6)alkyl, or -(C_3-C_7)cycloalkyl, or two R_6 groups attached to the same nitrogen atom can form a 5- to 8-membered ring, the number of atoms in the ring including the nitrogen atom, in which one of the ring carbon atoms is optionally replaced by O, S, or N(T_3);

each R_7 is independently selected from -(C_1-C_4)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -OR_9, -SR_9, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -CN, -halo, -N_3, -NO_2, -CH=N(R_9), -N(R_9)$_2$, -N(R_9)OH, -N(R_9)S(O)R_{12}, -N(R_9)S(O)$_2R_{12}$, -N(R_9)C(O)R_{12}, -N(R_9)C(O)N(T_1)(T_2), -N(R_9)C(O)OR_{12}, -C(O)R_9, -C(O)N(T_1)(T_2), -C(O)OR_9, -OC(O)R_9, -OC(O)N(T_1)(T_2), -OC(O)OR_9, -S(O)R_9, or -S(O)$_2R_9$;

each R_8 is independently selected from -(C_1-C_4)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -OR_9, -SR_9, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -CN, =O, =S, -halo, -N_3, -NO_2, -CH=N(R_9), -N(R_9)$_2$, -N(R_9)OH, -N(R_9)S(O)R_{12}, -N(R_9)S(O)$_2R_{12}$, -N(R_9)C(O)R_{12}, -N(R_9)C(O)N(T_1)(T_2), -N(R_9)C(O)OR_{12}, -C(O)R_9, -C(O)N(T_1)(T_2), -C(O)OR_9, -OC(O)R_9, -OC(O)N(T_1)(T_2), -OC(O)OR_9, -S(O)R_9, or -S(O)$_2R_9$;

each R_9 is independently selected from -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -benzyl, -(3- to 6-membered)heterocycle, -C(halo)$_3$, -CH(halo)$_2$, or -CH_2(halo);

if h is 0, R_{11} is selected from -H, -C(O)OR_9, or -C(O)N(R_6)$_2$ or -(C_1-C_4)alkyl which is unsubstituted or substituted with -OH, -(C_1-C_4)alkoxy, -N(R_6)$_2$, -C(O)OR_9, or -C(O)N(R_6)$_2$;

if h is 1, R_{11} is selected from -H, -OH, -halo, -C(O)OR_9, or -C(O)N(R_6)$_2$ or -(C_1-C_4)alkyl which is unsubstituted or substituted with -OH, -(C_1-C_4)alkoxy, -N(R_6)$_2$, -C(O)OR_9, or -C(O)N(R_6)$_2$;

each R_{12} is independently selected from -H or -(C_1-C_4)alkyl;

m is an integer from 1 to 7;

e and f are independently an integer from 0 to 5 provided that $2 \leq (e + f) \leq 5$;

j and k are independently an integer from 0 to 4 provided that $1 \leq (j + k) \leq 4$;

each p is independently 0 or 1;

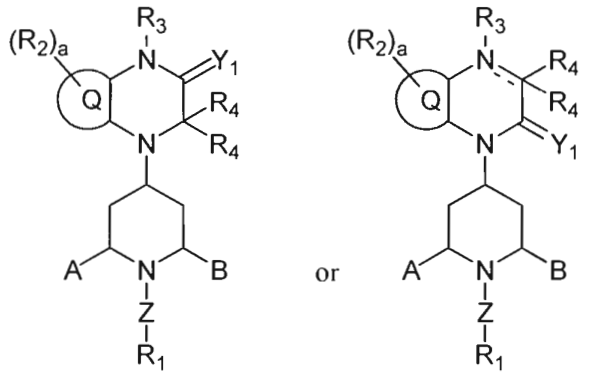
each T_1, T_2, and T_3 is independently -H or -(C_1-C_{10})alkyl which is unsubstituted or substituted with 1, 2 or 3 R_8 groups and, optionally, in which any -(C_1-C_{10})alkyl carbon atom except the carbon atom bonded directly to the atom to which T_1, T_2, or T_3 is attached is independently replaced by O, S, or N(R_6), or T_1 and T_2 together can form a 5- to 8-membered ring where the number of atoms in the ring includes the nitrogen atom to which T_1 and T_2 are bonded, said 5- to 8-membered ring is unsubstituted or substituted with 1, 2 or 3 R_8 groups

and, optionally, any carbon atom in said 5- to 8-membered ring is independently replaced by O, S, or $N(R_6)$;

each V_1 is independently selected from -H, -$(C_1$-$C_6)$alkyl, -$(C_3$-$C_7)$cycloalkyl, -phenyl, or -benzyl; and

each halo is independently selected from -F, -Cl, -Br, or -I.

The invention encompasses compounds of Formula (I.2) and Formula (II.2):



(I.2) (II.2)

or a pharmaceutically acceptable derivative thereof wherein:

Y_1 is O or S;

Q is selected from fused benzo or (5- or 6-membered)heteroaryl;

each R_2 is independently selected from:

(a) -halo, -CN, -NO_2, -OT_3, -$C(O)T_3$, -$C(O)OT_3$, -$C(O)N(T_1)(T_2)$, -$S(O)_3H$, -$S(O)T_3$, -$S(O)_2T_3$, -$S(O)_2N(T_1)(T_2)$, -$N(T_1)(T_2)$, -$N(T_3)C(O)T_3$, -$N(T_3)C(O)N(T_1)(T_2)$, -$N(T_3)S(O)_2T_3$, or -$N(T_3)S(O)_2N(T_1)(T_2)$; or

(b) -$(C_1$-$C_6)$alkyl, -$(C_2$-$C_6)$alkenyl, -$(C_2$-$C_6)$alkynyl, -(C_1-$C_6)$alkoxy, -$(C_3$-$C_7)$cycloalkyl, -$(C_6$-$C_{14})$bicycloalkyl, -$(C_8$-$C_{20})$tricycloalkyl, -$(C_5$-$C_{10})$cycloalkenyl, -$(C_7$-$C_{14})$bicycloalkenyl, -$(C_8$-$C_{20})$tricycloalkenyl, -(5- or 6-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_8 groups; or

(c) -phenyl, -naphthalenyl, -(C_{14})aryl, or -(5- or 6-membered)heteroaryl, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_7 groups;

a is an integer selected from 0, 1 or 2;

the dashed line in the fused piperazine ring denotes the presence or absence of a bond, and when that dashed line denotes the presence of a bond then R_3 and one R_4 are absent;

R_3 is selected from -H, -(C_1-C_4)alkyl which is unsubstituted or substituted with 1,2, or 3 of independently selected -OH, -(C_1-C_4)alkoxy, -$N(R_6)_2$, -$C(O)OR_9$, or -$C(O)N(R_6)_2$, or -(C_3-C_7)cycloalkyl which is unsubstituted or substituted with 1,2, or 3 of independently selected -OH, -(C_1-C_4)alkyl, -(C_1-C_4)alkoxy, -$N(R_6)_2$, -$C(O)OR_9$, or -$C(O)N(R_6)_2$;

each R_4 is independently selected from:

(a) -H; or

(b) -halo, -CN, or -NO_2; or

(c) -X, -CH_2X, or -CH_2CH_2X; or

(d) -C(Y)CN, -C(Y)X, -$C(Y)T_3$, -C(Y)YX, -$C(Y)YT_3$, -$C(Y)N(T_1)(T_2)$, -$C(Y)N(R_9)CN$, -$C(Y)N(R_9)X$, -$C(Y)N(R_9)YH$, -$C(Y)N(R_9)YX$, -$C(Y)N(R_9)YCH_2X$, -$C(Y)N(R_9)YCH_2CH_2X$, or -$C(Y)N(R_9)S(O)_2T_3$; or

(e) -$N(R_9)X$, -$N(R_9)$-CH_2X, -$N(R_9)$-CH_2CH_2X, -$N(R_9)CH_2N(R_9)C(=N(R_{12}))N(R_{12})_2$, -$N(R_9)$-$CH_2CH_2N(R_9)C(=N(R_{12}))N(R_{12})_2$, -$N(T_1)(T_2)$, -$N(T_3)C(Y)T_3$, -$N(T_3)C(Y)YT_3$, -$N(T_3)C(Y)N(T_1)(T_2)$, -$N(T_3)S(O)_2T_3$, or -$N(T_3)S(O)_2N(T_1)(T_2)$; or

(f) -YH, -CH_2YH, -CH_2CH_2YH, -YX, or -YT_3; or

(g) -$S(O)T_3$, -$S(O)_2T_3$, -$S(O)N(T_1)(T_2)$, -$S(O)_2N(T_1)(T_2)$, -S(O)X, or -$S(O)_2X$;

X is:

(a) -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_1-C_6)alkoxy, -(C_3-C_7)cycloalkyl, -(C_6-C_{14})bicycloalkyl, -(C_8-C_{20})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_7-C_{14})bicycloalkenyl, -(C_8-C_{20})tricycloalkenyl, -(5- or 6-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_8 groups; or

(b) -phenyl, -naphthalenyl, -(C_{14})aryl, or -(5- or 6-membered)heteroaryl, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_7 groups;

each Y is independently selected from O or S;

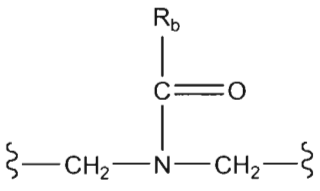
A and B are independently selected from:

(a) -H, -CN, $-C(O)OT_3$, $-C(O)N(T)_1(T_2)$, $-(C_3-C_{12})$cycloalkyl, $-(C_3-C_{12})$cycloalkoxy, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl or $-(C_1-C_6)$alkoxy, each of which $-(C_3-C_{12})$cycloalkyl, $-(C_3-C_{12})$cycloalkoxy, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl or $-(C_2-C_6)$alkynyl is unsubstituted or substituted with 1 or 2 substituents independently selected from -OH, $-S(O)_2NH_2$, $-N(R_6)_2$, $=NR_6$, $-C(O)OT_3$, $-CON(R_6)_2$, $-N(R_6)C(O)R_9$ and -(5- or 6-membered)heterocycle or 1, 2 or 3 independently selected -halo; or

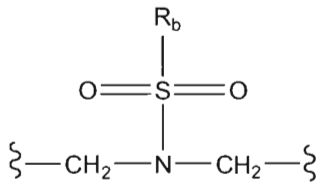
(b) A-B can together form a (C_2-C_6)bridge, which is unsubstituted or substituted with 1, 2 or 3 -OH groups, and which bridge optionally contains -HC=CH- within the (C_2-C_6)bridge; wherein the piperazine ring that is fused to the Q group can be in the endo- or exo- configuration with respect to the A-B bridge;

or

(c) A-B can together form a $-CH_2-N(R_a)-CH_2-$ bridge, a



bridge, or a



bridge;

wherein the piperazine ring that is fused to the Q group can be in the endo- or exo-configuration with respect to the A-B bridge;

R_a is selected from -H, $-(C_1-C_6)$alkyl, $-(C_3-C_7)$cycloalkyl, $-CH_2-C(O)-R_c$, $-(CH_2)-C(O)-OR_c$, $-(CH_2)-C(O)-N(R_c)_2$, $-(CH_2)_2-O-R_c$, $-(CH_2)_2-S(O)_2-N(R_c)_2$, R_c, or $-(CH_2)_2-N(R_c)S(O)_2-R_c$;

R_b is selected from:

(a) -H, $-(C_1-C_6)$alkyl, $-(C_3-C_7)$cycloalkyl, -(3- to 7-membered)heterocycle, $-N(R_c)_2$, $-N(R_c)-(C_3-C_7)$cycloalkyl, or $-N(R_c)-$(3- to 7-membered)heterocycle; or

(b) -phenyl, -naphthalenyl, or-(5- or 6-membered)heteroaryl, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_7 groups; or

(c) $-N(R_c)$-phenyl, $-N(R_c)$-naphthalenyl, $-N(R_c)-(C_{14})$aryl, or $-N(R_c)-$(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_7 groups;

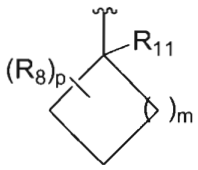
each R_c is independently selected from -H or $-(C_1-C_4)$alkyl;

Z is -[(C_1-C_{10})alkyl optionally substituted by R_1]$_h$-, wherein h is 0 or 1; or -(C_1-C_{10})alkyl-$NR_6C(=Y)$-;

each R_1 is independently selected from:

(a) -H, -halo, -CN, -OH, $-CH_2OH$, $-CH_2CH_2OH$, $-NO_2$, $-N(R_6)_2$, $-S(O)NH_2$, $-S(O)_2NH_2$, $-C(O)OV_1$, or -C(O)CN; or

(b) -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -O(C_1-C_6)alkyl, -(C_3-C_7)cycloalkoxy, -(C_6-C_{14})bicycloalkyl, -(C_8-C_{20})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_7-C_{14})bicycloalkenyl, -(C_8-C_{20})tricycloalkenyl, -(3- to 7-membered)heterocycle, -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_8 groups; or



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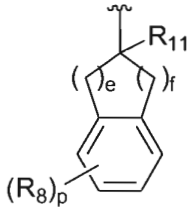

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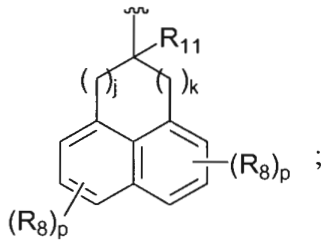


;

(i) (ii) (iii) ; or

(d) -phenyl, -naphthalenyl, -(C_{14})aryl, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with an R_7 group; or

-Z-R_1 is 3,3-diphenylpropyl- optionally substituted at the 3 carbon of the propyl with -CN, $-C(O)N(R_6)_2$, $-C(O)OV_1$, or -tetrazolyl; or

-Z-R_1 is -(C_1-C_4)alkyl substituted with tetrazolyl;

each R_6 is independently selected from -H, -(C_1-C_6)alkyl, or -(C_3-C_7)cycloalkyl, or two R_6 groups attached to the same nitrogen atom can together form a 5- to 8-membered ring, wherein the number of atoms in the ring includes the nitrogen atom, and in which one of the 5- to 8-membered ring carbon atoms is optionally replaced by O, S, or $N(T_3)$;

each R_7 is independently selected from -(C_1-C_4)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, $-OR_9$, $-SR_9$, $-C(halo)_3$, $-CH(halo)_2$, $-CH_2(halo)$, -CN, -halo, $-N_3$, $-NO_2$, $-CH=N(R_9)$, $-N(R_9)_2$, $-N(R_9)OH$, $-N(R_9)S(O)R_{12}$, $-N(R_9)S(O)_2R_{12}$, $-N(R_9)C(O)R_{12}$, $-N(R_9)C(O)N(T_1)(T_2)$, $-N(R_9)C(O)OR_{12}$, $-C(O)R_9$, $-C(O)N(T_1)(T_2)$, $-C(O)OR_9$, $-OC(O)R_9$, $-OC(O)N(T_1)(T_2)$, $-OC(O)OR_9$, $-S(O)R_9$, or $-S(O)_2R_9$;

each R_8 is independently selected from -(C_1-C_4)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, (C_1-C_6)alkylCOOR$_9$, -OR$_9$, -SR$_9$, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -CN, =O, =S, -halo, -N_3, -NO_2, -CH=N(R$_9$), -N(R$_9$)(C_1-C_6)alkylCOOR$_9$, -N(R$_9$)$_2$, -N(R$_9$)OH, -N(R$_9$)S(O)R$_{12}$, -N(R$_9$)S(O)$_2$R$_{12}$, -N(R$_9$)C(O)R$_{12}$, -N(R$_9$)C(O)N(T$_1$)(T$_2$), -N(R$_9$)C(O)OR$_{12}$, -C(O)R$_9$, -C(O)N(T$_1$)(T$_2$), -C(O)OR$_9$, -OC(O)R$_9$, -OC(O)N(T$_1$)(T$_2$), -OC(O)OR$_9$, -S(O)R$_9$, or -S(O)$_2$R$_9$;

each R_9 is independently selected from -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -benzyl, -(3- to 6-membered)heterocycle, -C(halo)$_3$, -CH(halo)$_2$, or -CH_2(halo);

if h is 0, then R_{11} can be selected from -H, -C(O)OR$_9$, or -C(O)N(R$_6$)$_2$ or R_{11} can be -(C_1-C_4)alkyl which is unsubstituted or substituted with -OH, -(C_1-C_4)alkoxy, -N(R$_6$)$_2$, -C(O)OR$_9$, or -C(O)N(R$_6$)$_2$;

if h is 1, then R_{11} can be selected from -H, -OH, -halo, -C(O)OR$_9$, or -C(O)N(R$_6$)$_2$ or R_{11} can be -(C_1-C_4)alkyl which is unsubstituted or substituted with -OH, -(C_1-C_4)alkoxy, -N(R$_6$)$_2$, -C(O)OR$_9$, or -C(O)N(R$_6$)$_2$;

otherwise, where Z is -(C_1-C_{10})alkyl-NR$_6$C(=Y)-, then R_{11} can be selected from -H, -C(O)OR$_9$, or -C(O)N(R$_6$)$_2$ or R_{11} can be -(C_1-C_4)alkyl which is unsubstituted or substituted with -OH, -(C_1-C_4)alkoxy, -N(R$_6$)$_2$, -C(O)OR$_9$, or -C(O)N(R$_6$)$_2$;

each R_{12} is independently selected from -H or -(C_1-C_4)alkyl;

m is an integer selected from 0, 1, 2, 3, 4, 5, 6 or 7;

e and f are each an integer independently selected from 0, 1, 2, 3, 4 or 5 provided that $2 \leq (e + f) \leq 5$;

j and k are each an integer independently selected from 0, 1, 2, 3 or 4 provided that $1 \leq (j + k) \leq 4$;

each p is an integer independently selected from 0 or 1;

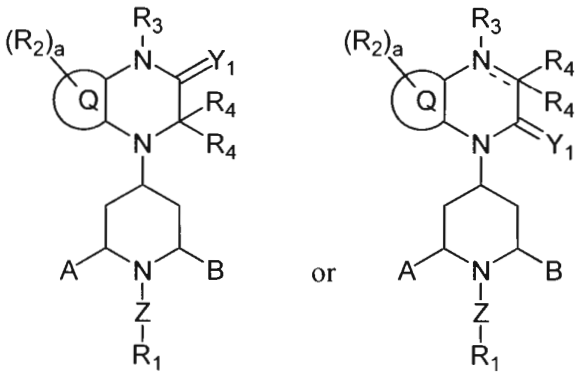
each T_1, T_2, and T_3 is independently -H or -(C_1-C_{10})alkyl which is unsubstituted or substituted with 1, 2 or 3 independently selected R_8 groups and, optionally, in which any -(C_1-C_{10})alkyl carbon atom except the carbon atom bonded directly to the atom to which T_1, T_2, or T_3 is attached is independently replaced by O, S, or N(R$_6$), or T_1 and T_2 can together form a 5- to 8-membered ring where the number of atoms in the ring includes the nitrogen atom to which T_1 and T_2 are bonded, said 5- to 8-membered ring is unsubstituted or substituted with 1, 2 or 3

independently selected R_8 groups and, optionally, any carbon atom in said 5- to 8-membered ring is independently replaced by O, S, or $N(R_6)$;

each V_1 is independently selected from -H, -$(C_1$-$C_6)$alkyl, -$(C_3$-$C_7)$cycloalkyl, -phenyl, or -benzyl; and

each halo is independently selected from -F, -Cl, -Br, or -I.

The invention encompasses compounds of Formula (I.3) and Formula (II.3):



(I.3) (II.3)

or a pharmaceutically acceptable derivative thereof wherein:

Y_1 is O or S;

Q is selected from fused benzo or (5- or 6-membered)heteroaryl;

each R_2 is independently selected from:

(a) -halo, -CN, -NO_2, -OT_3, -$C(O)T_3$, -$C(O)OT_3$, -$C(O)N(T_1)(T_2)$, -$S(O)_3H$, -$S(O)T_3$, -$S(O)_2T_3$, -$S(O)_2N(T_1)(T_2)$, -$N(T_1)(T_2)$, -$N(T_3)C(O)T_3$, -$N(T_3)C(O)N(T_1)(T_2)$, -$N(T_3)S(O)_2T_3$, or -$N(T_3)S(O)_2N(T_1)(T_2)$; or

(b) -$(C_1$-$C_6)$alkyl, -$(C_2$-$C_6)$alkenyl, -$(C_2$-$C_6)$alkynyl, -(C_1-$C_6)$alkoxy, -$(C_3$-$C_7)$cycloalkyl, -$(C_6$-$C_{14})$bicycloalkyl, -$(C_8$-$C_{20})$tricycloalkyl, -$(C_5$-$C_{10})$cycloalkenyl, -$(C_7$-$C_{14})$bicycloalkenyl, -$(C_8$-$C_{20})$tricycloalkenyl, -(5- or 6-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_8 groups; or

(c) -phenyl, -naphthalenyl, -(C_{14})aryl, or -(5- or 6-membered)heteroaryl, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_7 groups;

a is an integer selected from 0, 1 or 2;

the dashed line in the fused piperazine ring denotes the presence or absence of a bond, and when that dashed line denotes the presence of a bond then R_3 and one R_4 are absent;

R_3 is selected from -H, -(C_1-C_4)alkyl which is unsubstituted or substituted with 1,2, or 3 of independently selected -OH, -(C_1-C_4)alkoxy, -$N(R_6)_2$, -$C(O)OR_9$, or -$C(O)N(R_6)_2$, or -(C_3-C_7)cycloalkyl which is unsubstituted or substituted with 1,2, or 3 of independently selected -OH, -(C_1-C_4)alkyl, -(C_1-C_4)alkoxy, -$N(R_6)_2$, -$C(O)OR_9$, or -$C(O)N(R_6)_2$;

each R_4 is independently selected from:

(a) -H; or

(b) -halo, -CN, or -NO_2; or

(c) -X, -CH_2X, or -CH_2CH_2X; or

(d) -C(Y)CN, -C(Y)X, -$C(Y)T_3$, -C(Y)YX, -$C(Y)YT_3$, -$C(Y)N(T_1)(T_2)$, -$C(Y)N(R_9)CN$, -$C(Y)N(R_9)X$, -$C(Y)N(R_9)YH$, -$C(Y)N(R_9)YX$, -$C(Y)N(R_9)YCH_2X$, -$C(Y)N(R_9)YCH_2CH_2X$, or -$C(Y)N(R_9)S(O)_2T_3$; or

(e) -$N(R_9)X$, -$N(R_9)$-CH_2X, -$N(R_9)$-CH_2CH_2X, -$N(R_9)CH_2N(R_9)C(=N(R_{12}))N(R_{12})_2$, -$N(R_9)$-$CH_2CH_2N(R_9)C(=N(R_{12}))N(R_{12})_2$, -$N(T_1)(T_2)$, -$N(T_3)C(Y)T_3$, -$N(T_3)C(Y)YT_3$, -$N(T_3)C(Y)N(T_1)(T_2)$, -$N(T_3)S(O)_2T_3$, or -$N(T_3)S(O)_2N(T_1)(T_2)$; or

(f) -YH, -CH_2YH, -CH_2CH_2YH, -YX, or -YT_3; or

(g) -$S(O)T_3$, -$S(O)_2T_3$, -$S(O)N(T_1)(T_2)$, -$S(O)_2N(T_1)(T_2)$, -S(O)X, or -$S(O)_2X$;

X is:

(a) -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_1-C_6)alkoxy, -(C_3-C_7)cycloalkyl, -(C_6-C_{14})bicycloalkyl, -(C_8-C_{20})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_7-C_{14})bicycloalkenyl, -(C_8-C_{20})tricycloalkenyl, -(5- or 6-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_8 groups; or

(b) -phenyl, -naphthalenyl, -(C_{14})aryl, or -(5- or 6-membered)heteroaryl, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_7 groups;

each Y is independently selected from O or S;

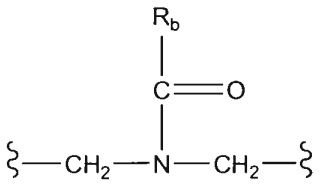
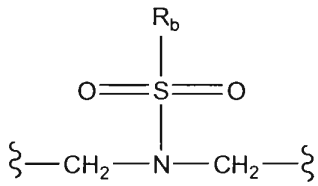
A and B are independently selected from:

(a) -H, -CN, -C(O)OT$_3$, -C(O)N(T)$_1$(T$_2$), -(C$_3$-C$_{12}$)cycloalkyl, -(C$_3$-C$_{12}$)cycloalkoxy, -(C$_1$-C$_6$)alkyl, -(C$_2$-C$_6$)alkenyl, -(C$_2$-C$_6$)alkynyl or -(C$_1$-C$_6$)alkoxy, each of which -(C$_3$-C$_{12}$)cycloalkyl, -(C$_3$-C$_{12}$)cycloalkoxy, -(C$_1$-C$_6$)alkyl, -(C$_2$-C$_6$)alkenyl or -(C$_2$-C$_6$)alkynyl is unsubstituted or substituted with 1 or 2 substituents independently selected from -OH, -S(O)$_2$NH$_2$, -N(R$_6$)$_2$, =NR$_6$, -C(O)OT$_3$, -CON(R$_6$)$_2$, -N(R$_6$)C(O)R$_9$ and -(5- or 6-membered)heterocycle or 1, 2 or 3 independently selected -halo; or

(b) A-B can together form a (C$_2$-C$_6$)bridge, which is unsubstituted or substituted with 1, 2 or 3 -OH groups, and which bridge optionally contains -HC=CH- or -O- within the (C$_2$-C$_6$)bridge; wherein the piperazine ring that is fused to the Q group can be in the endo- or exo- configuration with respect to the A-B bridge;

or

(c) A-B can together form a -CH$_2$-N(R$_a$)-CH$_2$- bridge, a

 bridge, or a  bridge;

wherein the piperazine ring that is fused to the Q group can be in the endo- or exo-configuration with respect to the A-B bridge;

R$_a$ is selected from -H, -(C$_1$-C$_6$)alkyl, -(C$_3$-C$_7$)cycloalkyl, -CH$_2$-C(O)-R$_c$, -(CH$_2$)-C(O)-OR$_c$, -(CH$_2$)-C(O)-N(R$_c$)$_2$, -(CH$_2$)$_2$-O-R$_c$, -(CH$_2$)$_2$-S(O)$_2$-N(R$_c$)$_2$, R$_c$, or -(CH$_2$)$_2$-N(R$_c$)S(O)$_2$-R$_c$;

R$_b$ is selected from:

(a) -H, -(C$_1$-C$_6$)alkyl, -(C$_3$-C$_7$)cycloalkyl, -(3- to 7-membered)heterocycle, -N(R$_c$)$_2$, -N(R$_c$)-(C$_3$-C$_7$)cycloalkyl, or -N(R$_c$)-(3- to 7-membered)heterocycle; or

(b) -phenyl, -naphthalenyl, or-(5- or 6-membered)heteroaryl, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R$_7$ groups; or

(c) -N(R$_c$)-phenyl, -N(R$_c$)-naphthalenyl, -N(R$_c$)-(C$_{14}$)aryl, or -N(R$_c$)-(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R$_7$ groups;

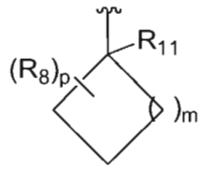
each R$_c$ is independently selected from -H or -(C$_1$-C$_4$)alkyl;

Z is -[(C_1-C_{10})alkyl optionally substituted by R_1]$_h$-, wherein h is 0 or 1; or -(C_1-C_{10})alkyl-$NR_6C(=Y)$-;

each R_1 is independently selected from:

(a) -H, -halo, -CN, -OH, $-CH_2OH$, $-CH_2CH_2OH$, $-NO_2$, $-N(R_6)_2$, $-S(O)NH_2$, $-S(O)_2NH_2$, $-C(O)OV_1$, or -C(O)CN; or

(b) -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -O(C_1-C_6)alkyl, -(C_3-C_7)cycloalkoxy, -(C_6-C_{14})bicycloalkyl, -(C_8-C_{20})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_7-C_{14})bicycloalkenyl, -(C_8-C_{20})tricycloalkenyl, -(3- to 7-membered)heterocycle, -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_8 groups; or



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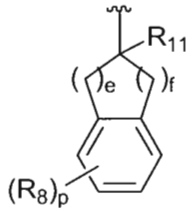
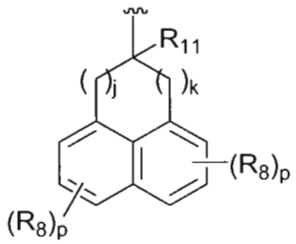


, or


;

(i) (ii) (iii)

; or

(d) -phenyl, -naphthalenyl, -(C_{14})aryl, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with an R_7 group; or

-Z-R_1 is 3,3-diphenylpropyl- optionally substituted at the 3 carbon of the propyl with -CN, $-C(O)N(R_6)_2$, $-C(O)OV_1$, or -tetrazolyl; or

-Z-R_1 is -(C_1-C_4)alkyl substituted with tetrazolyl;

each R_6 is independently selected from -H, -(C_1-C_6)alkyl, or -(C_3-C_7)cycloalkyl, or two R_6 groups attached to the same nitrogen atom can together form a 5- to 8-membered ring, wherein the number of atoms in the ring includes the nitrogen atom, and in which one of the 5- to 8-membered ring carbon atoms is optionally replaced by O, S, or $N(T_3)$;

each R_7 is independently selected from -(C_1-C_4)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, $-OR_9$, $-SR_9$, $-C(halo)_3$, $-CH(halo)_2$, $-CH_2(halo)$, -CN, -halo, $-N_3$, $-NO_2$, $-CH=N(R_9)$, $-N(R_9)_2$, $-N(R_9)OH$, $-N(R_9)S(O)R_{12}$, $-N(R_9)S(O)_2R_{12}$, $-N(R_9)C(O)R_{12}$, $-N(R_9)C(O)N(T_1)(T_2)$, $-N(R_9)C(O)OR_{12}$, $-C(O)R_9$, $-C(O)N(T_1)(T_2)$, $-C(O)OR_9$, $-OC(O)R_9$, $-OC(O)N(T_1)(T_2)$, $-OC(O)OR_9$, $-S(O)R_9$, or $-S(O)_2R_9$;

each R_8 is independently selected from -(C_1-C_4)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, (C_1-C_6)alkylCOOR_9, -OR_9, -SR_9, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -CN, =O, =S, -halo, -N_3, -NO_2, -CH=N(R_9), -N(R_9)(C_1-C_6)alkylCOOR_9, -N(R_9)$_2$, -N(R_9)OH, -N(R_9)S(O)R_{12}, -N(R_9)S(O)$_2R_{12}$, -N(R_9)C(O)R_{12}, -N(R_9)C(O)N(T_1)(T_2), -N(R_9)C(O)OR_{12}, -C(O)R_9, -C(O)N(T_1)(T_2), -C(O)OR_9, -OC(O)R_9, -OC(O)N(T_1)(T_2), -OC(O)OR_9, -S(O)R_9, or -S(O)$_2R_9$;

each R_9 is independently selected from -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -benzyl, -(3- to 6-membered)heterocycle, -C(halo)$_3$, -CH(halo)$_2$, or -CH_2(halo);

if h is 0, then R_{11} can be selected from -H, -C(O)OR_9, or -C(O)N(R_6)$_2$ or R_{11} can be -(C_1-C_4)alkyl which is unsubstituted or substituted with -OH, -(C_1-C_4)alkoxy, -N(R_6)$_2$, -C(O)OR_9, or -C(O)N(R_6)$_2$;

if h is 1, then R_{11} can be selected from -H, -OH, -halo, -C(O)OR_9, or -C(O)N(R_6)$_2$ or R_{11} can be -(C_1-C_4)alkyl which is unsubstituted or substituted with -OH, -(C_1-C_4)alkoxy, -N(R_6)$_2$, -C(O)OR_9, or -C(O)N(R_6)$_2$;

otherwise, where Z is -(C_1-C_{10})alkyl-NR_6C(=Y)-, then R_{11} can be selected from -H, -C(O)OR_9, or -C(O)N(R_6)$_2$ or R_{11} can be -(C_1-C_4)alkyl which is unsubstituted or substituted with -OH, -(C_1-C_4)alkoxy, -N(R_6)$_2$, -C(O)OR_9, or -C(O)N(R_6)$_2$;

each R_{12} is independently selected from -H or -(C_1-C_4)alkyl;

m is an integer selected from 0, 1, 2, 3, 4, 5, 6 or 7;

e and f are each an integer independently selected from 0, 1, 2, 3, 4 or 5 provided that $2 \leq (e + f) \leq 5$;

j and k are each an integer independently selected from 0, 1, 2, 3 or 4 provided that $1 \leq (j + k) \leq 4$;

each p is an integer independently selected from 0 or 1;

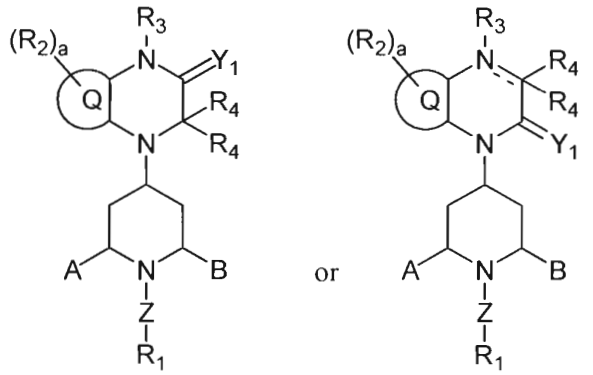
each T_1, T_2, and T_3 is independently -H or -(C_1-C_{10})alkyl which is unsubstituted or substituted with 1, 2 or 3 independently selected R_8 groups and, optionally, in which any -(C_1-C_{10})alkyl carbon atom except the carbon atom bonded directly to the atom to which T_1, T_2, or T_3 is attached is independently replaced by O, S, or N(R_6), or T_1 and T_2 can together form a 5- to 8-membered ring where the number of atoms in the ring includes the nitrogen atom to which T_1 and T_2 are bonded, said 5- to 8-membered ring is unsubstituted or substituted with 1, 2 or 3

independently selected R_8 groups and, optionally, any carbon atom in said 5- to 8-membered ring is independently replaced by O, S, or $N(R_6)$;

each V_1 is independently selected from -H, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -phenyl, or -benzyl; and

each halo is independently selected from -F, -Cl, -Br, or -I.

The invention encompasses compounds of Formula (I.4) and Formula (II.4):



(I.4) (II.4)

or a pharmaceutically acceptable derivative thereof wherein:

Y_1 is O or S;

Q is selected from fused benzo or (5- or 6-membered)heteroaryl;

each R_2 is independently selected from:

(a) -halo, -CN, -NO_2, -OT_3, -C(=O)T_3, -C(=O)OT_3, -C(=O)$N(T_1)(T_2)$, -$S(=O)_3H$, -S(=O)T_3, -$S(=O)_2T_3$, -$S(=O)_2N(T_1)(T_2)$, -$N(T_1)(T_2)$, -$N(T_3)$C(=O)T_3, -$N(T_3)$C(=O)$N(T_1)(T_2)$, -$N(T_3)S(=O)_2T_3$, or -$N(T_3)S(=O)_2N(T_1)(T_2)$; or

(b) -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_1-C_6)alkoxy, -(C_3-C_7)cycloalkyl, -(C_6-C_{14})bicycloalkyl, -(C_8-C_{20})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_7-C_{14})bicycloalkenyl, -(C_8-C_{20})tricycloalkenyl, -(5- or 6-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_8 groups; or

(c) -phenyl, -naphthalenyl, -(C_{14})aryl, or -(5- or 6-membered)heteroaryl, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_7 groups;

a is an integer selected from 0, 1 or 2;

the dashed line in the 6-membered, nitrogen-containing ring that is fused to the Q group denotes the presence or absence of a bond, and when that dashed line denotes the presence of a bond then R_3 and one R_4 are absent;

R_3 is selected from:

(a) -H; or

(b) -(C_1-C_4)alkyl which is unsubstituted or substituted with 1, 2 or 3 groups independently selected from -OH, -(C_1-C_4)alkoxy, -$N(R_6)_2$, -C(=O)OR_9, or -C(=O)$N(R_6)_2$; or

(c) -(C_3-C_7)cycloalkyl which is unsubstituted or substituted with 1, 2 or 3 groups independently selected from -OH, -(C_1-C_4)alkyl, -(C_1-C_4)alkoxy, -$N(R_6)_2$, -C(=O)OR_9, or -C(=O)$N(R_6)_2$;

each R_4 is independently selected from:

(a) -H; or

(b) -halo, -CN, or -NO_2; or

(c) -X, -(C_1-C_6)alkyl-X, -(5- or 6-membered)heterocycle-X, or -(5- or 6-membered)heterocycle-(C_1-C_6)alkyl-X; or

(d) -C(=Y)CN, -C(=Y)X, -C(=Y)T_3, -C(=Y)YX, -C(=Y)YT_3, -C(=Y)$N(T_1)(T_2)$, -C(=Y)$N(R_9)$CN, -C(=Y)$N(R_9)$X, -C(=Y)$N(R_9)$YH, -C(=Y)$N(R_9)$YX, -C(=Y)$N(R_9)YCH_2X$, -C(=Y)$N(R_9)YCH_2CH_2X$, or -C(=Y)$N(R_9)S(=O)_2T_3$; or

(e) -$N(R_9)$X, -$N(R_9)$-CH_2X, -$N(R_9)$-CH_2CH_2X, -$N(R_9)CH_2N(R_9)C(=N(R_{12}))N(R_{12})_2$, -$N(R_9)$-$CH_2CH_2N(R_9)C(=N(R_{12}))N(R_{12})_2$, -$N(T_1)(T_2)$, -$N(T_3)C(=Y)T_3$, -$N(T_3)C(=Y)YT_3$, -$N(T_3)C(=Y)N(T_1)(T_2)$, -$N(T_3)S(=O)_2T_3$, or -$N(T_3)S(=O)_2N(T_1)(T_2)$; or

(f) -YH, -CH_2YH, -CH_2CH_2YH, -YX, or -YT_3; or

(g) -S(=O)T_3, -$S(=O)_2T_3$, -S(=O)$N(T_1)(T_2)$, -$S(=O)_2N(T_1)(T_2)$, -S(=O)X, or -$S(=O)_2$X;

X is:

(a) -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_1-C_6)alkoxy, -(C_3-C_7)cycloalkyl, -(C_6-C_{14})bicycloalkyl, -(C_8-C_{20})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_7-C_{14})bicycloalkenyl, -(C_8-C_{20})tricycloalkenyl, -(5- or 6-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_8 groups; or

(b) -phenyl, -naphthalenyl, -(C_{14})aryl, or -(5- or 6-membered)heteroaryl, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_7 groups;

each Y is independently selected from O or S;

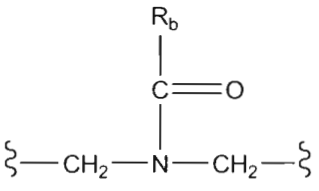
A and B are independently selected from:

(a) -H, -CN, -C(=O)OT_3, or -C(=O)N$(T)_1(T_2)$; or

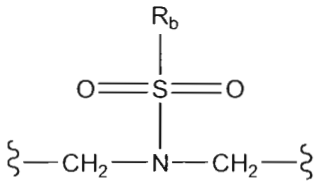
(b) -(C_3-C_{12})cycloalkyl, -(C_3-C_{12})cycloalkoxy, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, or -(C_1-C_6)alkoxy, each of which is unsubstituted or substituted with 1 or 2 substituents independently selected from -OH, -S(=O)$_2NH_2$, -N$(R_6)_2$, =NR_6, -C(=O)OT_3, -CON$(R_6)_2$, -N(R_6)C(=O)R_9, and -(5- or 6-membered)heterocycle, or 1, 2 or 3 independently selected -halo; or

(c) A-B can together form a (C_2-C_6)bridge, which is unsubstituted or substituted with 1, 2, 3, 4, 5, 6, 7 or 8 substituents independently selected from -OH, -(C_1-C_4)alkyl, -halo, and -C(halo)$_3$, and which bridge optionally contains -HC=CH- or -O- within the (C_2-C_6)bridge; wherein the 6-membered, nitrogen-containing ring that is fused to the Q group can be in the *endo*- or *exo*- configuration with respect to the A-B bridge; or

(d) A-B can together form a -CH_2-N(R_a)-CH_2- bridge, a



bridge, or a



bridge;

wherein the 6-membered, nitrogen-containing ring that is fused to the Q group can be in the *endo*- or *exo*- configuration with respect to the A-B bridge;

R_a is selected from -H, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -CH_2-C(=O)-R_c, -(CH_2)-C(=O)-OR_c, -(CH_2)-C(=O)-N$(R_c)_2$, -(CH_2)$_2$-O-R_c, -(CH_2)$_2$-S(=O)$_2$-N$(R_c)_2$, R_c, or -(CH_2)$_2$-N(R_c)S(=O)$_2$-R_c;

R_b is selected from:

(a) -H, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(3- to 7-membered)heterocycle, -N$(R_c)_2$, -N(R_c)-(C_3-C_7)cycloalkyl, or -N(R_c)-(3- to 7-membered)heterocycle; or

(b) -phenyl, -naphthalenyl, or-(5- or 6-membered)heteroaryl, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_7 groups; or

(c) -N(R_c)-phenyl, -N(R_c)-naphthalenyl, -N(R_c)-(C_{14})aryl, or -N(R_c)-(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_7 groups;

each R_c is independently selected from -H or -(C_1-C_4)alkyl;

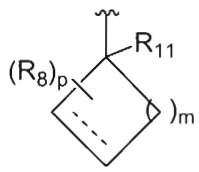
Z is -[(C_1-C_{10})alkyl optionally substituted by R_1]$_h$-, wherein h is 0 or 1; or -(C_1-C_{10})alkyl-$NR_6C(=Y)$-;

each R_1 is independently selected from:

(a) -H, -halo, -CN, -OH, -CH_2OH, -CH_2CH_2OH, -NO_2, -N(R_6)$_2$, -S(=O)NH_2, -S(=O)$_2NH_2$, -C(=O)OV_1, or -C(=O)CN; or

(b) -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -O(C_1-C_6)alkyl, -(C_3-C_7)cycloalkoxy, -(C_6-C_{14})bicycloalkyl, -(C_8-C_{20})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_7-C_{14})bicycloalkenyl, -(C_8-C_{20})tricycloalkenyl, -(3- to 7-membered)heterocycle, -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_8 groups; or

(c)



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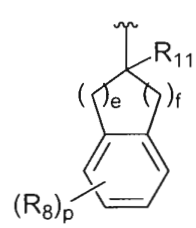
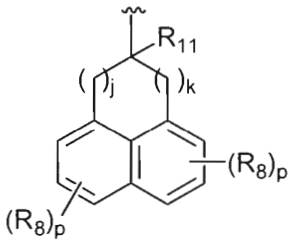


, or



;

(i) (ii) (iii) ; or

(d) -phenyl, -naphthalenyl, -(C_{14})aryl, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with an R_7 group; or

-Z-R_1 is 3,3-diphenylpropyl- optionally substituted at the 3 carbon of the propyl with -CN, -C(=O)N(R_6)$_2$, -C(=O)OV_1, or -tetrazolyl; or

-Z-R_1 is -(C_1-C_4)alkyl substituted with tetrazolyl;

each R_6 is independently selected from -H, -(C_1-C_6)alkyl, or -(C_3-C_7)cycloalkyl, or two R_6 groups attached to the same nitrogen atom can together form a 5- to 8-membered ring, wherein the number of atoms in the ring includes the nitrogen atom, and in which one of the 5- to 8-membered ring carbon atoms is optionally replaced by O, S, or N(T_3);

each R_7 is independently selected from -(C_1-C_4)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -OR_9, -SR_9, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -CN, -halo, -N_3, -NO_2, -CH=N(R_9), -N(R_9)$_2$, -N(R_9)OH, -N(R_9)S(=O)R_{12}, -N(R_9)S(=O)$_2R_{12}$, -N(R_9)C(=O)R_{12}, -N(R_9)C(=O)N(T_1)(T_2), -N(R_9)C(=O)OR_{12}, -C(=O)R_9, -C(=O)N(T_1)(T_2), -C(=O)OR_9, -OC(=O)R_9, -OC(=O)N(T_1)(T_2), -OC(=O)OR_9, -S(=O)R_9, or -S(=O)$_2R_9$;

each R_8 is independently selected from -(C_1-C_4)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(5- or 6-membered)heteroaryl, -(C_1-C_6)alkylCOOR_9, -OR_9, -SR_9, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -CN, =O, =S, -halo, -N_3, -NO_2, -CH=N(R_9), -N(R_9)(C_1-C_6)alkylCOOR_9, -N(R_9)$_2$, -N(R_9)OH, -N(R_9)S(=O)R_{12}, -N(R_9)S(=O)$_2R_{12}$, -N(R_9)C(=O)R_{12}, -N(R_9)C(=O)N(T_1)(T_2), -N(R_9)C(=O)OR_{12}, -C(=O)R_9, -C(=O)N(T_1)(T_2), -C(=O)OR_9, -OC(=O)R_9, -OC(=O)N(T_1)(T_2), -OC(=O)OR_9, -S(=O)R_9, or -S(=O)$_2R_9$;

each R_9 is independently selected from -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -benzyl, -(3- to 6-membered)heterocycle, -C(halo)$_3$, -CH(halo)$_2$, or -CH_2(halo);

if h is 0, then R_{11} can be selected from -H, -CN, -C(=O)OR_9, or -C(=O)N(R_6)$_2$ or R_{11} can be -(C_1-C_4)alkyl which is unsubstituted or substituted with -OH, -(C_1-C_4)alkoxy, -N(R_6)$_2$, -C(=O)OR_9, or -C(=O)N(R_6)$_2$;

if h is 1, then R_{11} can be selected from -H, -CN, -OH, -halo, -C(=O)OR_9, or -C(=O)N(R_6)$_2$ or R_{11} can be -(C_1-C_4)alkyl which is unsubstituted or substituted with -OH, -(C_1-C_4)alkoxy, -N(R_6)$_2$, -C(=O)OR_9, or -C(=O)N(R_6)$_2$;

otherwise, where Z is -(C_1-C_{10})alkyl-NR_6C(=Y)-, then R_{11} can be selected from -H, -CN, -C(=O)OR_9, or -C(=O)N(R_6)$_2$ or R_{11} can be -(C_1-C_4)alkyl which is unsubstituted or substituted with -OH, -(C_1-C_4)alkoxy, -N(R_6)$_2$, -C(=O)OR_9, or -C(=O)N(R_6)$_2$;

each R_{12} is independently selected from -H or -(C_1-C_4)alkyl;

m is an integer selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 11;

e and f are each an integer independently selected from 0, 1, 2, 3, 4, or 5 provided that $2 \leq (e + f) \leq 5$;

j and k are each an integer independently selected from 0, 1, 2, 3, or 4 provided that $1 \leq (j + k) \leq 4$;

each p is an integer independently selected from 0 or 1;

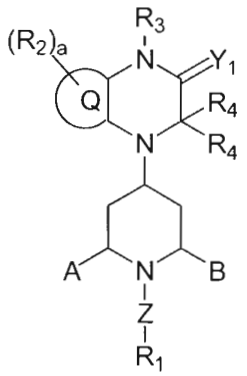
each T_1, T_2, and T_3 is independently -H or -(C_1-C_{10})alkyl which is unsubstituted or substituted with 1, 2 or 3 independently selected R_8 groups and, optionally, in which any -(C_1-C_{10})alkyl carbon atom except the carbon atom bonded directly to the atom to which T_1, T_2, or T_3 is attached is independently replaced by O, S, or N(R_6), or T_1 and T_2 can together form a 5- to 8-membered ring where the number of atoms in the ring includes the nitrogen atom to which T_1 and T_2 are bonded, said 5- to 8-membered ring is unsubstituted or substituted with 1, 2 or 3 independently selected R_8 groups and, optionally, any carbon atom in said 5- to 8-membered ring is independently replaced by O, S, or N(R_6);

each V_1 is independently selected from -H, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -phenyl, or -benzyl; and

each halo is independently selected from -F, -Cl, -Br, or -I.

4.1 Substituted-Quinoxaline-Type Piperidine Compounds of Formula (I)

As stated above, the invention encompasses Substituted-Quinoxaline-Type Piperidine Compounds of Formula (I):



(I)

or a pharmaceutically acceptable derivative thereof where R_1, R_2, R_3, R_4, Q, Y_1, Z, A, B, and a are defined above for the Substituted-Quinoxaline-Type Piperidine Compounds.

In one embodiment, Y_1 is O.

In another embodiment, Y_1 is S.

In another embodiment, A is H.

In another embodiment, B is H.

In another embodiment, a is 0 or 1.

In another embodiment, a is 0.

In another embodiment, a is 1.

In another embodiment, a is 2.

In another embodiment, h is 0.

In another embodiment, h is 1.

In another embodiment, h is 1 and Z is a $(C_1$-$C_3)$alkyl.

In another embodiment, h is 1, Z is a $(C_1$-$C_3)$alkyl, R_1 is phenyl, the $(C_1$-$C_3)$alkyl is substituted by another R_1, and the other R_1 is phenyl.

In another embodiment, R_1 is -$(C_1$-$C_6)$alkyl, -$(C_2$-$C_6)$alkenyl, -$(C_2$-$C_6)$alkynyl, -O$(C_1$-$C_6)$alkyl, -$(C_3$-$C_7)$cycloalkoxy, -$(C_6$-$C_{14})$bicycloalkyl, -$(C_8$-$C_{20})$tricycloalkyl, -$(C_5$-$C_{10})$cycloalkenyl, -$(C_7$-$C_{14})$bicycloalkenyl, -$(C_8$-$C_{20})$tricycloalkenyl, -(3- to 7-membered)heterocycle, -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_8 groups.

In another embodiment, R_1 is optionally substituted cyclooctyl.

In another embodiment, R_1 is optionally substituted cyclooctenyl.

In another embodiment, R_1 is optionally substituted anthryl.

In another embodiment, h is 0 and R_1 is optionally substituted cyclooctyl.

In another embodiment, h is 0 and R_1 is optionally substituted cyclooctenyl.

In another embodiment, h is 0 and R_1 is optionally substituted anthryl.

In another embodiment, Y_1 is O, A and B are each H, and a is 0 or 1.

In another embodiment, Y_1 is S, A and B are each H, and a is 0 or 1.

In another embodiment, Y_1 is O, A and B are each H, and a is 0.

In another embodiment, Y_1 is S, A and B are each H, and a is 0.

In another embodiment, Y_1 is O, A and B are each H, and a is 1.

In another embodiment, Y_1 is S, A and B are each H, and a is 1.

In another embodiment, R_3 is -H, -(C_1-C_4)alkyl, or -(C_3-C_7)cycloalkyl.

In another embodiment, R_3 is -H.

In another embodiment, R_3 is -(C_1-C_4)alkyl.

In another embodiment, R_3 is methyl, ethyl, n-propyl or *iso*-propyl, each optionally substituted with one -OH, -(C_1-C_4)alkoxy, -$N(R_6)_2$, -C(=O)OR_9, or -C(=O)$N(R_6)_2$ group.

In another embodiment, R_3 is -(C_3-C_7)cycloalkyl.

In another embodiment, R_3 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl, each optionally substituted with 1 or 2 -CH_3 groups.

In another embodiment, R_3 is cyclopentyl, cyclohexyl, or cycloheptyl, each optionally substituted with one -OH, -(C_1-C_4)alkyl, -(C_1-C_4)alkoxy, -$N(R_6)_2$, -C(=O)OR_9, or -C(=O)$N(R_6)_2$ group.

In another embodiment, R_{11} is not -COOH.

In another embodiment, Y_1 is O, A and B are each H, R_3 is -H, -(C_1-C_4)alkyl, or -(C_3-C_7)cycloalkyl, and a is 0 or 1.

In another embodiment, Y_1 is S, A and B are each H, R_3 is -H, -(C_1-C_4)alkyl, or -(C_3-C_7)cycloalkyl, and a is 0 or 1.

In another embodiment, Y_1 is O, A and B are each H, R_3 is -H, -(C_1-C_4)alkyl, or -(C_3-C_7)cycloalkyl, and a is 0.

In another embodiment, Y_1 is S, A and B are each H, R_3 is -H, -(C_1-C_4)alkyl, or -(C_3-C_7)cycloalkyl, and a is 0.

In another embodiment, Y_1 is O, A and B are each H, R_3 is -H, -(C_1-C_4)alkyl, or -(C_3-C_7)cycloalkyl, and a is 1.

In another embodiment, Y_1 is S, A and B are each H, R_3 is -H, -(C_1-C_4)alkyl, or -(C_3-C_7)cycloalkyl, and a is 1.

In another embodiment, each R_2 is independently selected from -halo, -OH, -NH_2, -CN, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(5- or 6-membered)heterocycle, -phenyl, -naphthalenyl or -(5- or 6-membered)heteroaryl.

In another embodiment, a is 2 and each R_2 is independently selected from -halo, -OH, -NH_2, -CN, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(5- or 6-membered)heterocycle, -phenyl, -naphthalenyl or -(5- or 6-membered)heteroaryl.

In another embodiment, a is 1 and R_2 is selected from -halo, -OH, -NH_2, -CN, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(5- or 6-membered)heterocycle, -phenyl, -naphthalenyl or -(5- or 6-membered)heteroaryl.

In another embodiment, a is 2 and each R_2 is independently selected from -halo, -OH, -NH_2, -CN, methyl, ethyl, n-propyl, *iso*-propyl, cyclopentyl, cyclohexyl, cycloheptyl, or phenyl.

In another embodiment, a is 1 and R_2 is selected from -halo, -OH, -NH_2, -CN, methyl, ethyl, n-propyl, *iso*-propyl, cyclopentyl, cyclohexyl, cycloheptyl, or phenyl.

In another embodiment, Q is selected from benzo, pyridino, pyrimidino, pyrazino, pyridazino, pyrrolino, imidazolino, pyrazolino, triazolino, furano, oxazolino, isoxazolino, oxadiazolino, thiopheno, thiazolino, isothiazolino, or thiadiazolino.

In another embodiment, Q is selected from benzo or pyridino.

In another embodiment, Q is benzo.

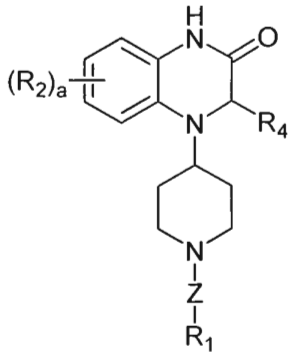
In another embodiment, Q is pyridino.

In another embodiment, Q is pyridino and the 2- and 3-positions of the pyridino are fused to the 6-membered, nitrogen-containing ring.

In another embodiment, each Y is O.

In another embodiment, each Y is S.

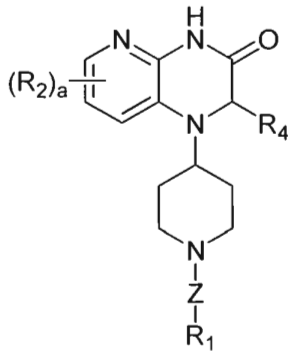
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (I) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IA):



(IA)

wherein R_1, R_2, R_4, Z and a are as defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formula (I).

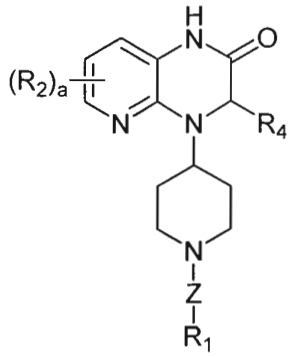
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (I) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IB):



(IB)

wherein R_1, R_2, R_4, Z and a are as defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formula (I).

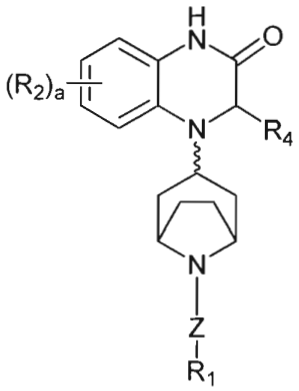
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (I) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IC):



(IC)

wherein R_1, R_2, R_4, Z and a are as defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formula (I).

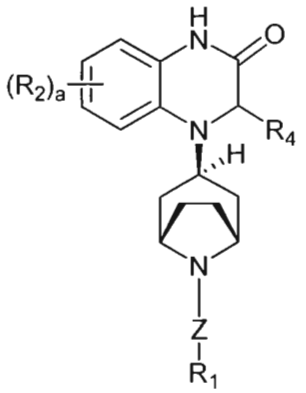
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (I) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (ID):



(ID)

wherein R_1, R_2, R_4, Z and a are as defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formula (I).

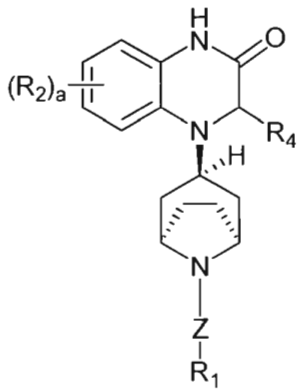
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (I) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (ID1):



(ID1)

i.e., a Substituted-Quinoxaline-Type Piperidine Compound of Formula (ID) wherein the 6-membered, nitrogen-containing ring that is fused to the benzo is in the *endo*- configuration with respect to the (-CH_2-CH_2-) bridge.

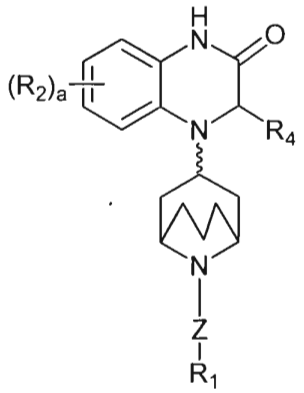
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (I) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (ID2):



(ID2)

i.e., a Substituted-Quinoxaline-Type Piperidine Compound of Formula (ID) wherein the 6-membered, nitrogen-containing ring that is fused to the benzo is in the *exo*- configuration with respect to the (-CH_2-CH_2-) bridge.

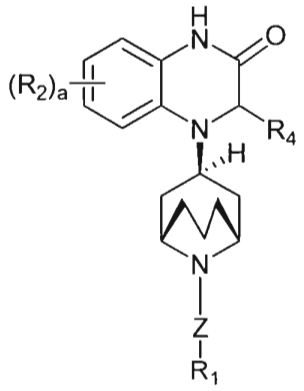
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (I) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IE):



(IE)

wherein R_1, R_2, R_4, Z and a are as defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formula (I).

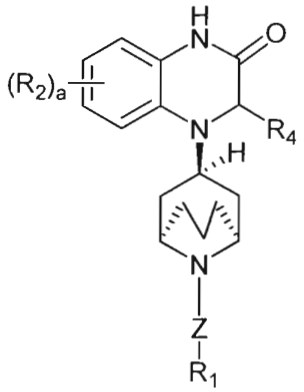
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (I) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IE1):



(IE1)

i.e., a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IE) wherein the 6-membered, nitrogen-containing ring that is fused to the benzo is in the *endo*- configuration with respect to the (-CH_2-CH_2-CH_2-) bridge.

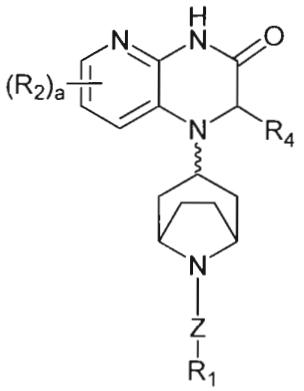
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (I) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IE2):



(IE2)

i.e., a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IE) wherein the 6-membered, nitrogen-containing ring that is fused to the benzo is in the *exo*- configuration with respect to the (-CH_2-CH_2-CH_2-) bridge.

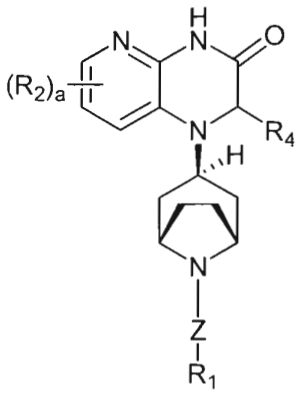
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (I) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IF):



(IF)

wherein R_1, R_2, R_4, Z and a are as defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formula (I).

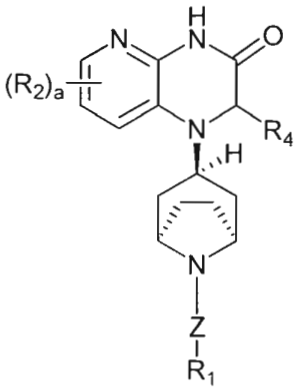
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (I) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IF1):



(IF1)

i.e., a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IF) wherein the 6-membered, nitrogen-containing ring that is fused to the pyridino is in the *endo*- configuration with respect to the (-CH_2-CH_2-) bridge.

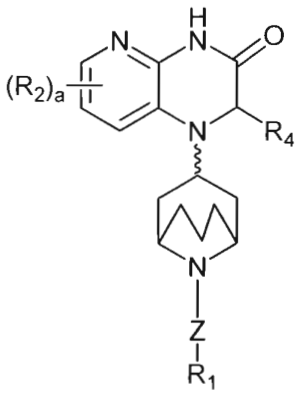
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (I) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IF2):



(IF2)

i.e., a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IF) wherein the 6-membered, nitrogen-containing ring that is fused to the pyridino is in the *exo*- configuration with respect to the (-CH_2-CH_2-) bridge.

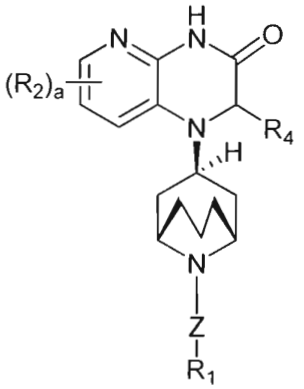
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (I) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IG):



(IG)

wherein R_1, R_2, R_4, Z and a are as defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formula (I).

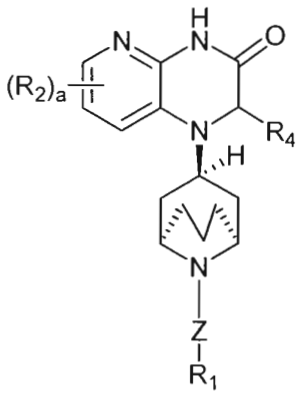
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (I) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IG1):



(IG1)

i.e., a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IG) wherein the 6-membered, nitrogen-containing ring that is fused to the pyridino is in the *endo*- configuration with respect to the (-CH_2-CH_2-CH_2-) bridge.

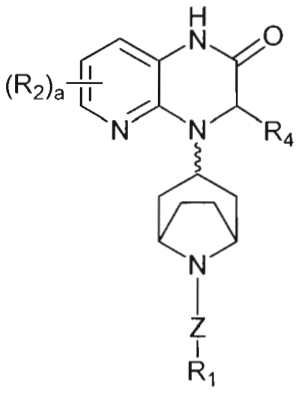
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (I) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IG2):



(IG2)

i.e., a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IG) wherein the 6-membered, nitrogen-containing ring that is fused to the pyridino is in the *exo*- configuration with respect to the (-CH_2-CH_2-CH_2-) bridge.

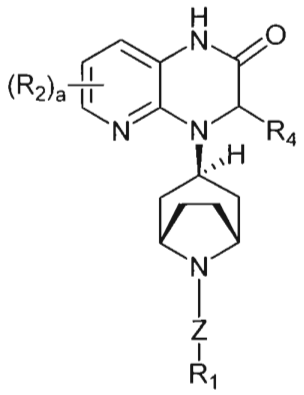
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (I) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IH):



(IH)

wherein R_1, R_2, R_4, Z and a are as defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formula (I).

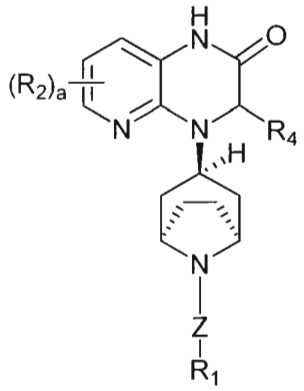
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (I) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IH1):



(IH1)

i.e., a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IH) wherein the 6-membered, nitrogen-containing ring that is fused to the pyridino is in the *endo*- configuration with respect to the (-CH_2-CH_2-) bridge.

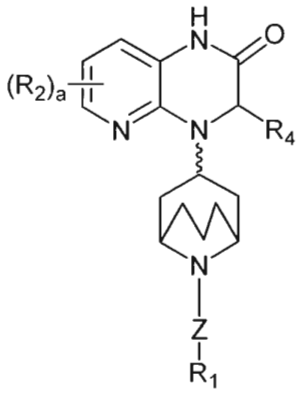
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (I) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IH2):



(IH2)

i.e., a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IH) wherein the 6-membered, nitrogen-containing ring that is fused to the pyridino is in the *exo*- configuration with respect to the (-CH_2-CH_2-) bridge.

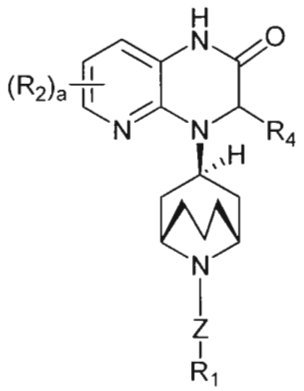
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (I) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IJ):



(IJ)

wherein R_1, R_2, R_4, Z and a are as defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formula (I).

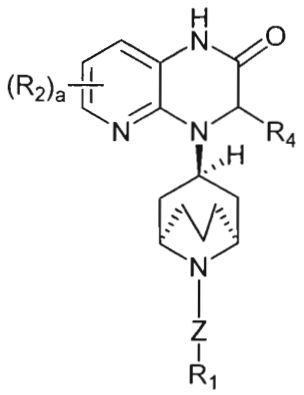
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (I) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IJ1):



(IJ1)

i.e., a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IJ) wherein the 6-membered, nitrogen-containing ring that is fused to the pyridino is in the *endo*- configuration with respect to the (-CH_2-CH_2-CH_2-) bridge.

In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (I) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IJ2):

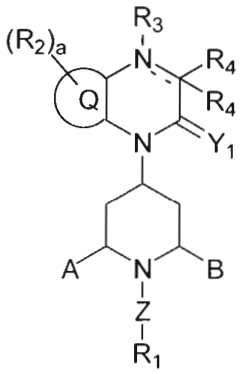


(IJ2)

i.e., a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IJ) wherein the 6-membered, nitrogen-containing ring that is fused to the pyridino is in the *exo*- configuration with respect to the (-CH_2-CH_2-CH_2-) bridge.

4.2 Substituted-Quinoxaline-Type Piperidine Compounds of Formula (II)

As stated above, the invention encompasses Substituted-Quinoxaline-Type Piperidine Compounds of Formula (II):



(II)

or a pharmaceutically acceptable derivative thereof where R_1, R_2, R_3, R_4, Q, Y_1, Z, A, B, a, and the dashed line are defined above for the Substituted-Quinoxaline-Type Piperidine Compounds.

In one embodiment, the dashed line (representing a bond) in the 6-membered, nitrogen-containing ring that is fused to the Q group is absent and R_3 is present.

In another embodiment, the dashed line (representing one bond of a double bond) in the 6-membered, nitrogen-containing ring that is fused to the Q group is present, and R_3 and one R_4 are absent.

In another embodiment, Y_1 is O.

In another embodiment, Y_1 is S.

In another embodiment, A is H.

In another embodiment, B is H.

In another embodiment, a is 0 or 1.

In another embodiment, a is 0.

In another embodiment, a is 1.

In another embodiment, a is 2.

In another embodiment, h is 0.

In another embodiment, h is 1.

In another embodiment, h is 1 and Z is a $(C_1$-$C_3)$alkyl.

In another embodiment, h is 1, Z is a $(C_1$-$C_3)$alkyl, R_1 is phenyl, the $(C_1$-$C_3)$alkyl is substituted by another R_1, and the other R_1 is phenyl.

In another embodiment, R_1 is -$(C_1$-$C_6)$alkyl, -$(C_2$-$C_6)$alkenyl, -$(C_2$-$C_6)$alkynyl, -O$(C_1$-$C_6)$alkyl, -$(C_3$-$C_7)$cycloalkoxy, -$(C_6$-$C_{14})$bicycloalkyl, -$(C_8$-$C_{20})$tricycloalkyl, -$(C_5$-$C_{10})$cycloalkenyl, -$(C_7$-$C_{14})$bicycloalkenyl, -$(C_8$-$C_{20})$tricycloalkenyl, -(3- to 7-membered)heterocycle, -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_8 groups.

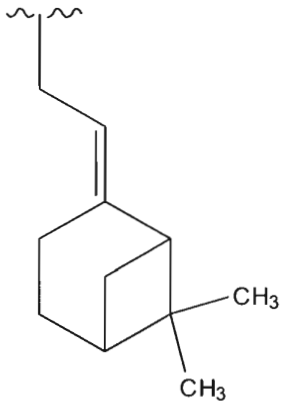
In another embodiment, h is 1 and Z is a $(C_2$-$C_{10})$alkenyl.

In another embodiment, h is 1 and Z is a $(C_2$-$C_6)$alkenyl.

In another embodiment, h is 1 and Z is a propenyl.

In another embodiment h is 1, Z is propenyl and R_1 is an optionally substituted -$(C_6$-$C_{14})$bicycloalkyl or -$(C_8$-$C_{20})$tricycloalkyl.

In another embodiment h is 1, and Z-R1 is



In another embodiment, R_1 is optionally substituted cyclooctyl.

In another embodiment, R_1 is optionally substituted cyclooctenyl.

In another embodiment, R_1 is optionally substituted anthryl.

In another embodiment, h is 0 and R_1 is optionally substituted cyclooctyl.

In another embodiment, h is 0 and R_1 is optionally substituted cycloundecyl.

In another embodiment, h is 0 and R_1 is optionally substituted cyclooctenyl.

In another embodiment, h is 0 and R_1 is optionally substituted anthryl.

In another embodiment, h is 0 and R_1 is optionally substituted -(C_6-C_{14})bicycloalkyl.

In another embodiment, h is 0 and R_1 is optionally substituted bicyclo[3.3.1]nonyl.

In another embodiment, h is 0 and R_1 is optionally substituted bicyclo[2.2.1.]hepyl.

In another embodiment, h is 0 and R_1 is optionally substituted -(C_8-C_{20})tricycloalkyl.

In another embodiment, h is 0 and R_1 is optionally substituted adamantyl.

In another embodiment, h is 0 and R_1 is optionally substituted noradamantyl.

In another embodiment, if Z is -[(C_1-C_{10})alkyl optionally substituted by R_1]$_h$ and h is 0 then R_4 is not COOH.

In another embodiment, Y_1 is O, A and B are each H, and a is 0 or 1.

In another embodiment, Y_1 is S, A and B are each H, and a is 0 or 1.

In another embodiment, Y_1 is O, A and B are each H, and a is 0.

In another embodiment, Y_1 is S, A and B are each H, and a is 0.

In another embodiment, Y_1 is O, A and B are each H, and a is 1.

In another embodiment, Y_1 is S, A and B are each H, and a is 1.

In another embodiment, the double bond in the 6-membered, nitrogen-containing ring that is fused to the Q group is present and R_3 is absent.

In another embodiment, R_3 is -H, -(C_1-C_4)alkyl, or -(C_3-C_7)cycloalkyl.

In another embodiment, R_3 is -H.

In another embodiment, R_3 is -(C_1-C_4)alkyl.

In another embodiment, R_3 is methyl, ethyl, n-propyl or *iso*-propyl, each optionally substituted with one -OH, -(C_1-C_4)alkoxy, -N(R_6)$_2$, -C(=O)OR_9, or -C(=O)N(R_6)$_2$ group.

In another embodiment, R_3 is -(C_3-C_7)cycloalkyl.

In another embodiment, R_3 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl, each optionally substituted with 1 or 2 -CH_3 groups.

In another embodiment, R_3 is cyclopentyl, cyclohexyl, or cycloheptyl, each optionally substituted with one -OH, -(C_1-C_4)alkyl, -(C_1-C_4)alkoxy, -N(R_6)$_2$, -C(=O)OR_9, or -C(=O)N(R_6)$_2$ group.

In another embodiment, R_{11} is not -COOH.

In another embodiment, Y_1 is O, A and B are each H, the double bond in the 6-membered, nitrogen-containing ring that is fused to the Q group is present, R_3 is absent, and a is 0 or 1.

In another embodiment, Y_1 is S, A and B are each H, the double bond in the 6-membered, nitrogen-containing ring that is fused to the Q group is present, R_3 is absent, and a is 0 or 1.

In another embodiment, Y_1 is O, A and B are each H, the double bond in the 6-membered, nitrogen-containing ring that is fused to the Q group is present, R_3 is absent, and a is 0.

In another embodiment, Y_1 is S, A and B are each H, the double bond in the 6-membered, nitrogen-containing ring that is fused to the Q group is present, R_3 is absent, and a is 0.

In another embodiment, Y_1 is O, A and B are each H, the double bond in the 6-membered, nitrogen-containing ring that is fused to the Q group is present, R_3 is absent, and a is 1.

In another embodiment, Y_1 is S, A and B are each H, the double bond in the 6-membered, nitrogen-containing ring that is fused to the Q group is present, R_3 is absent, and a is 1.

In another embodiment, Y_1 is O, A and B are each H, R_3 is -H, -(C_1-C_4)alkyl, or -(C_3-C_7)cycloalkyl, and a is 0 or 1.

In another embodiment, Y_1 is S, A and B are each H, R_3 is -H, -(C_1-C_4)alkyl, or -(C_3-C_7)cycloalkyl, and a is 0 or 1.

In another embodiment, Y_1 is O, A and B are each H, R_3 is -H, -(C_1-C_4)alkyl, or -(C_3-C_7)cycloalkyl, and a is 0.

In another embodiment, Y_1 is S, A and B are each H, R_3 is -H, -(C_1-C_4)alkyl, or -(C_3-C_7)cycloalkyl, and a is 0.

In another embodiment, Y_1 is O, A and B are each H, R_3 is -H, -(C_1-C_4)alkyl, or -(C_3-C_7)cycloalkyl, and a is 1.

In another embodiment, Y_1 is S, A and B are each H, R_3 is -H, -(C_1-C_4)alkyl, or -(C_3-C_7)cycloalkyl, and a is 1.

In another embodiment, each R_2 is independently selected from -halo, -OH, -NH_2, -CN, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(5- or 6-membered)heterocycle, -phenyl, -naphthalenyl or -(5- or 6-membered)heteroaryl.

In another embodiment, a is 2 and each R_2 is independently selected from -halo, -OH, -NH_2, -CN, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(5- or 6-membered)heterocycle, -phenyl, -naphthalenyl or -(5- or 6-membered)heteroaryl.

In another embodiment, a is 1 and R_2 is selected from -halo, -OH, -NH_2, -CN, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(5- or 6-membered)heterocycle, -phenyl, -naphthalenyl or -(5- or 6-membered)heteroaryl.

In another embodiment, a is 2 and each R_2 is independently selected from -halo, -OH, -NH_2, -CN, methyl, ethyl, n-propyl, *iso*-propyl, cyclopentyl, cyclohexyl, cycloheptyl, or phenyl.

In another embodiment, a is 1 and R_2 is selected from -halo, -OH, -NH_2, -CN, methyl, ethyl, n-propyl, *iso*-propyl, cyclopentyl, cyclohexyl, cycloheptyl, or phenyl.

In another embodiment, a is 1 and R_2 is selected from -halo, optionally -F.

In another embodiment, Q is selected from benzo, pyridino, pyrimidino, pyrazino, pyridazino, pyrrolino, imidazolino, pyrazolino, triazolino, furano, oxazolino, isoxazolino, oxadiazolino, thiopheno, thiazolino, isothiazolino, or thiadiazolino.

In another embodiment, Q is selected from benzo or pyridino.

In another embodiment, a is 1, Q is benzo or pyridino, and R_2 is attached at the 6-position of the benzo or pyridino, e.g., as illustrated for the -F substituted benzo of Substituted-Quinoxaline-Type Piperidine Compound 133.

In another embodiment, a is 1, Q is benzo or pyridino, R_2 is selected from -halo, optionally -F, and R_2 is attached at the 6-position of the benzo or pyridino, e.g., as illustrated for the -F substituted benzo of Substituted-Quinoxaline-Type Piperidine Compound 133.

In another embodiment, Q is benzo.

In another embodiment, Q is pyridino.

In another embodiment, Q is pyridino and the 2- and 3-positions of the pyridino are fused to the 6-membered, nitrogen-containing ring, e.g. as illustrated for compounds according to Formula (IIB).

In another embodiment, each Y is O.

In another embodiment, each Y is S.

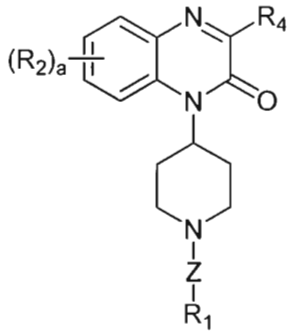
In another embodiment, the pharmaceutically acceptable derivative of compounds of Formula (II) is a pharmaceutically acceptable salt.

In another embodiment, the pharmaceutically acceptable salt is a hydrochloride salt.

In another embodiment, the pharmaceutically acceptable salt is a sodium salt.

In another embodiment, the pharmaceutically acceptable salt is a potassium salt.

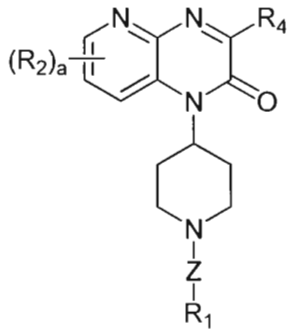
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIA):



(IIA)

wherein R_1, R_2, R_4, Z and a are as defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formula (II).

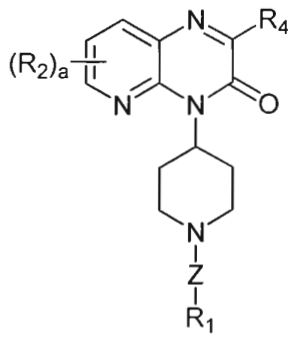
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIB):



(IIB)

wherein R_1, R_2, R_4, Z and a are as defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formula (II).

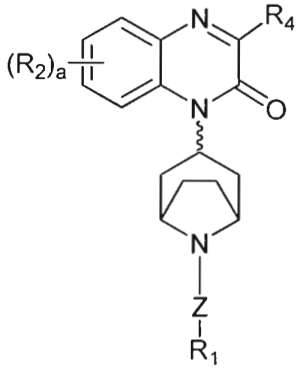
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIC):



(IIC)

wherein R_1, R_2, R_4, Z and a are as defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formula (II).

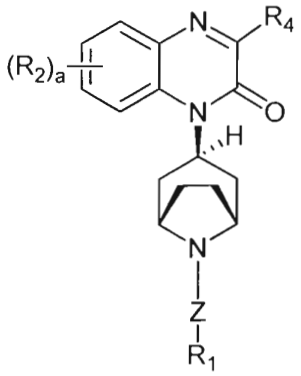
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IID):



(IID)

wherein R_1, R_2, R_4, Z and a are as defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formula (II).

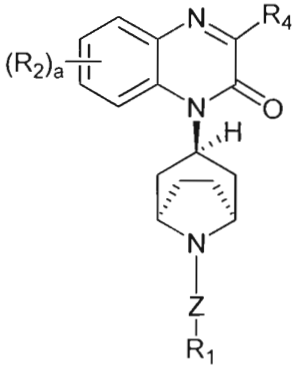
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IID1):



(IID1)

i.e., a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IID) wherein the 6-membered, nitrogen-containing ring that is fused to the benzo is in the *endo*- configuration with respect to the (-CH_2-CH_2-) bridge.

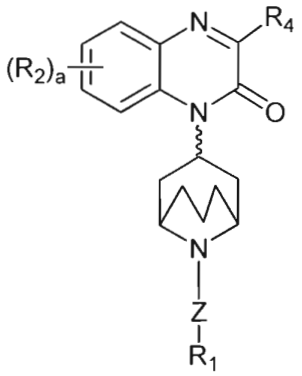
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IID2):



(IID2)

i.e., a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IID) wherein the 6-membered, nitrogen-containing ring that is fused to the benzo is in the *exo*- configuration with respect to the (-CH_2-CH_2-) bridge.

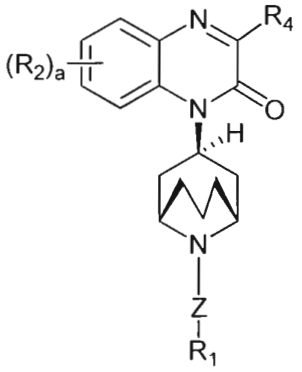
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIE):



(IIE)

wherein R_1, R_2, R_4, Z and a are as defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formula (II).

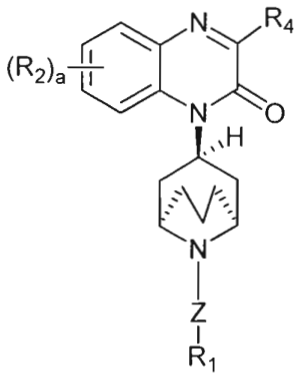
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIE1):



(IIE1)

i.e., a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIE) wherein the 6-membered, nitrogen-containing ring that is fused to the benzo is in the *endo*- configuration with respect to the (-CH_2-CH_2-CH_2-) bridge.

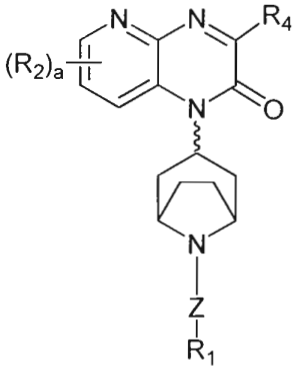
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIE2):



(IIE2)

i.e., a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIE) wherein the 6-membered, nitrogen-containing ring that is fused to the benzo is in the *exo*- configuration with respect to the (-CH_2-CH_2-CH_2-) bridge.

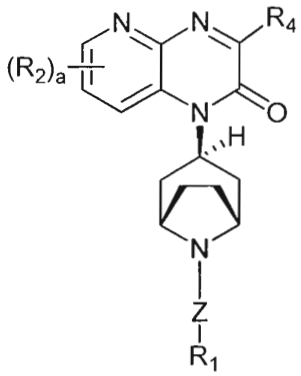
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIF):



(IIF)

wherein R_1, R_2, R_4, Z and a are as defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formula (II).

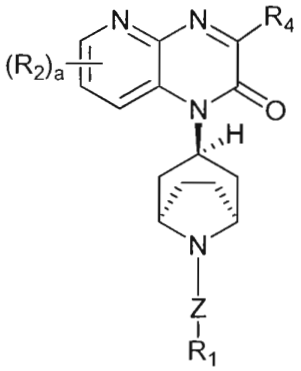
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIF1):



(IIF1)

i.e., a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIF) wherein the 6-membered, nitrogen-containing ring that is fused to the pyridino is in the *endo*- configuration with respect to the (-CH_2-CH_2-) bridge.

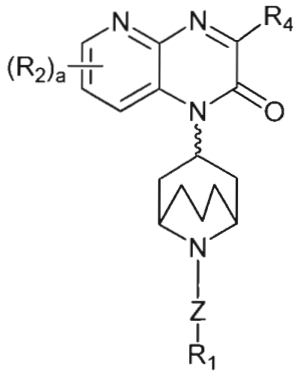
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIF2):



(IIF2)

i.e., a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIF) wherein the 6-membered, nitrogen-containing ring that is fused to the pyridino is in the *exo*- configuration with respect to the (-CH_2-CH_2-) bridge.

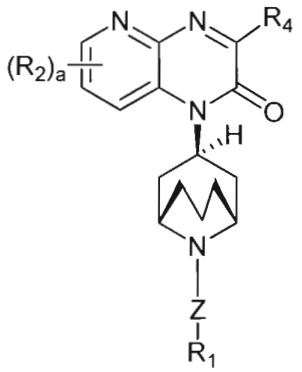
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIG):



(IIG)

wherein R_1, R_2, R_4, Z and a are as defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formula (II).

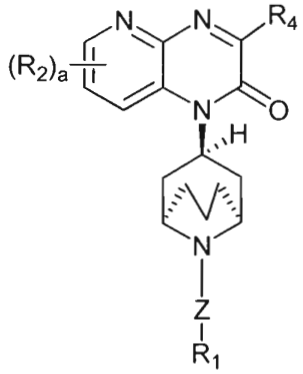
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIG1):



(IIG1)

i.e., a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIG) wherein the 6-membered, nitrogen-containing ring that is fused to the pyridino is in the *endo*- configuration with respect to the (-CH_2-CH_2-CH_2-) bridge.

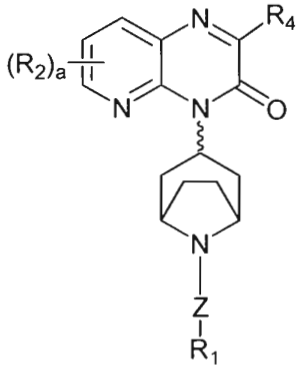
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIG2):



(IIG2)

i.e., a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIG) wherein the 6-membered, nitrogen-containing ring that is fused to the pyridino is in the *exo*- configuration with respect to the (-CH_2-CH_2-CH_2-) bridge.

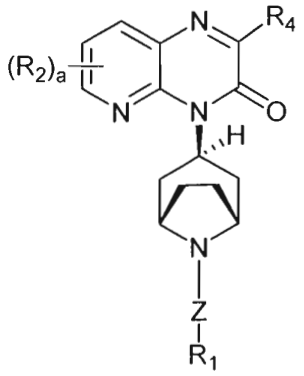
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIH):



(IIH)

wherein R_1, R_2, R_4, Z and a are as defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formula (II).

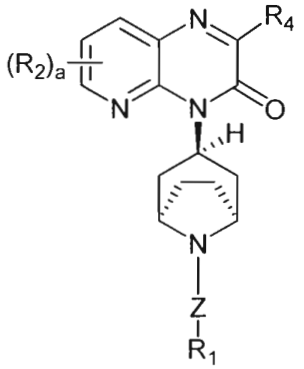
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIH1):



(IIH1)

i.e., a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIH) wherein the 6-membered, nitrogen-containing ring that is fused to the pyridino is in the *endo*- configuration with respect to the (-CH_2-CH_2-) bridge.

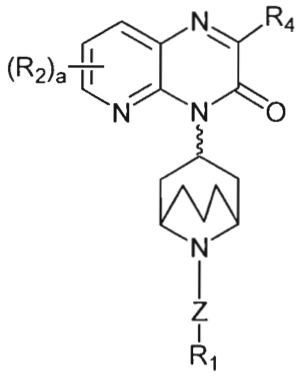
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIH2):



(IIH2)

i.e., a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIH) wherein the 6-membered, nitrogen-containing ring that is fused to the pyridino is in the *exo*- configuration with respect to the (-CH_2-CH_2-) bridge.

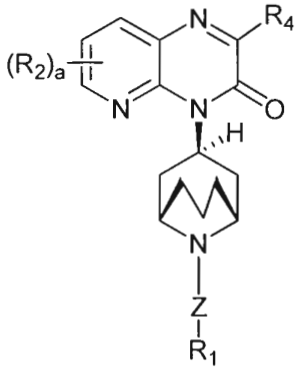
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIJ):



(IIJ)

wherein R_1, R_2, R_4, Z and a are as defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formula (II).

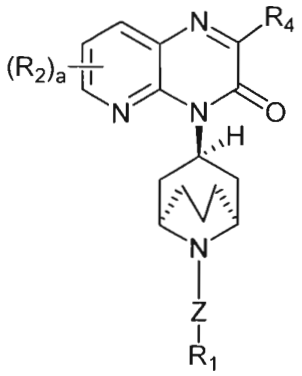
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIJ1):



(IIJ1)

i.e., a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIJ) wherein the 6-membered, nitrogen-containing ring that is fused to the pyridino is in the *endo*- configuration with respect to the (-CH_2-CH_2-CH_2-) bridge.

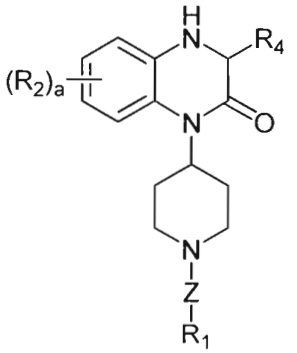
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIJ2):



(IIJ2)

i.e., a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIJ) wherein the 6-membered, nitrogen-containing ring that is fused to the pyridino is in the *exo*- configuration with respect to the (-CH_2-CH_2-CH_2-) bridge.

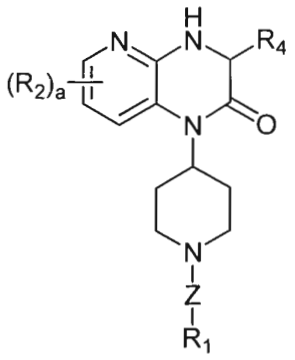
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIK):



(IIK)

wherein R_1, R_2, R_4, Z and a are as defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formula (II).

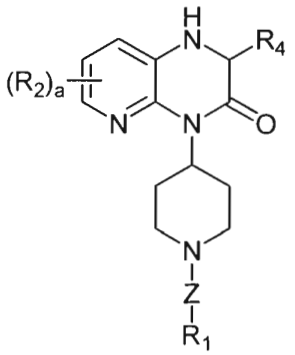
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIL):



(IIL)

wherein R_1, R_2, R_4, Z and a are as defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formula (II).

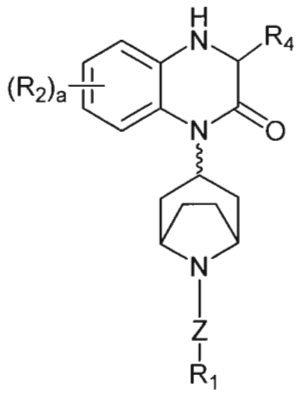
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIM):



(IIM)

wherein R_1, R_2, R_4, Z and a are as defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formula (II).

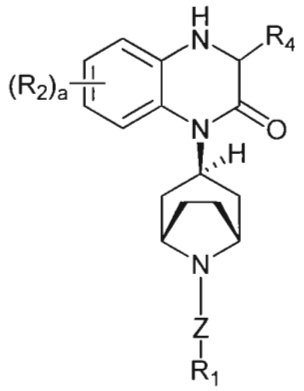
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIN):



(IIN)

wherein R_1, R_2, R_4, Z and a are as defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formula (II).

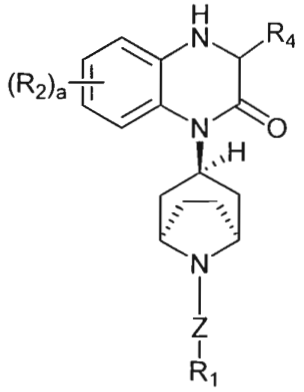
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIN1):



(IIN1)

i.e., a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIN) wherein the 6-membered, nitrogen-containing ring that is fused to the benzo is in the *endo*- configuration with respect to the (-CH_2-CH_2-) bridge.

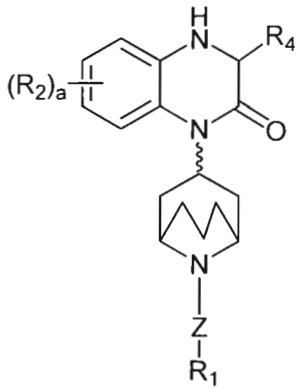
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIN2):



(IIN2)

i.e., a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIN) wherein the 6-membered, nitrogen-containing ring that is fused to the benzo is in the *exo*- configuration with respect to the (-CH_2-CH_2-) bridge.

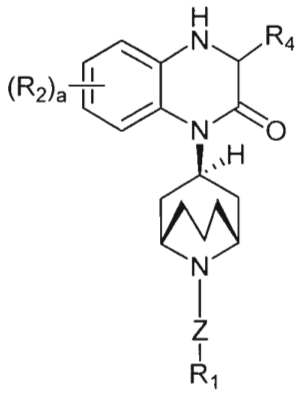
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIO):



(IIO)

wherein R_1, R_2, R_4, Z and a are as defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formula (II).

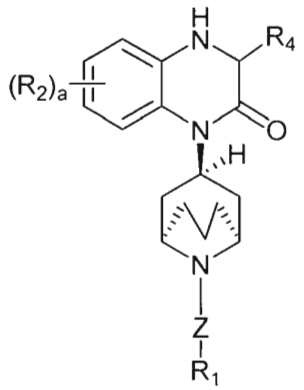
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIO1):



(IIO1)

i.e., a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIO) wherein the 6-membered, nitrogen-containing ring that is fused to the benzo is in the *endo*- configuration with respect to the (-CH_2-CH_2-CH_2-) bridge.

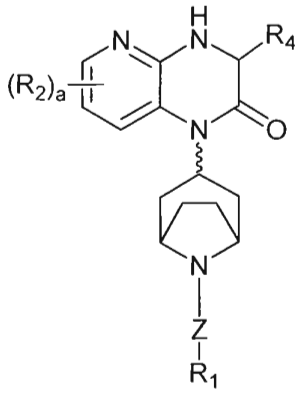
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIO2):



(IIO2)

i.e., a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIO) wherein the 6-membered, nitrogen-containing ring that is fused to the benzo is in the *exo*- configuration with respect to the (-CH_2-CH_2-CH_2-) bridge.

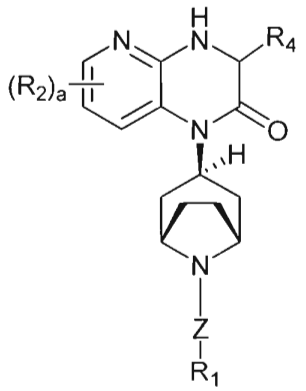
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIP):



(IIP)

wherein R_1, R_2, R_4, Z and a are as defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formula (II).

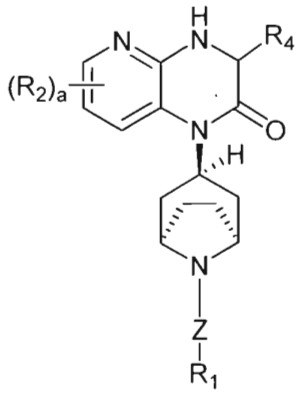
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIP1):



(IIP1)

i.e., a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIP) wherein the 6-membered, nitrogen-containing ring that is fused to the pyridino is in the *endo*- configuration with respect to the (-CH_2-CH_2-) bridge.

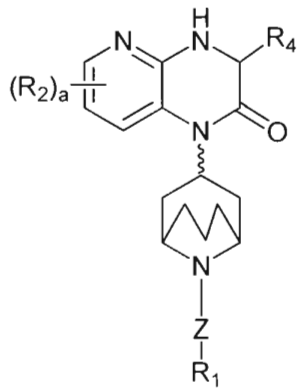
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIP2):



(IIP2)

i.e., a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIP) wherein the 6-membered, nitrogen-containing ring that is fused to the pyridino is in the *exo*- configuration with respect to the (-CH_2-CH_2-) bridge.

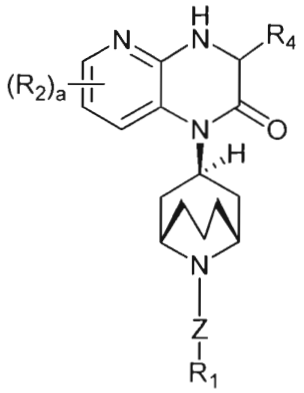
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIQ):



(IIQ)

wherein R_1, R_2, R_4, Z and a are as defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formula (II).

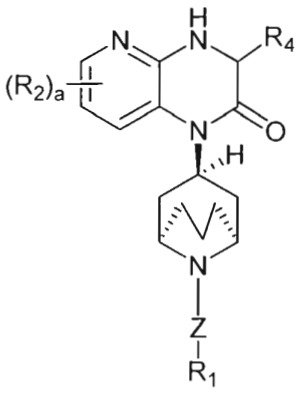
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIQ1):



(IIQ1)

i.e., a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIQ) wherein the 6-membered, nitrogen-containing ring that is fused to the pyridino is in the *endo*- configuration with respect to the (-CH_2-CH_2-CH_2-) bridge.

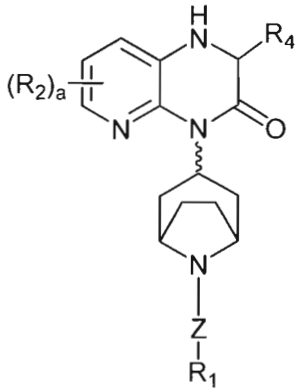
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIQ2):



(IIQ2)

i.e., a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIQ) wherein the 6-membered, nitrogen-containing ring that is fused to the pyridino is in the *exo*- configuration with respect to the (-CH_2-CH_2-CH_2-) bridge.

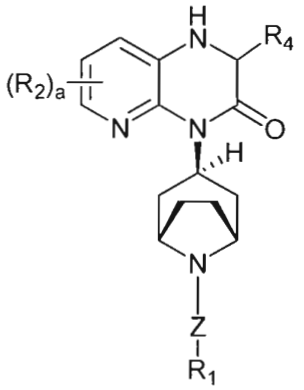
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIR):



(IIR)

wherein R_1, R_2, R_4, Z and a are as defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formula (II).

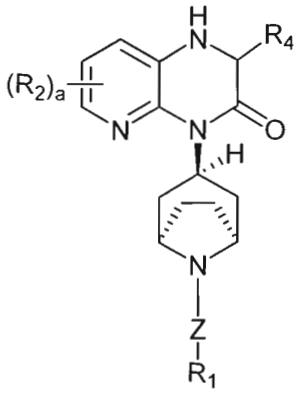
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIR1):



(IIR1)

i.e., a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIR) wherein the 6-membered, nitrogen-containing ring that is fused to the pyridino is in the *endo*- configuration with respect to the (-CH_2-CH_2-) bridge.

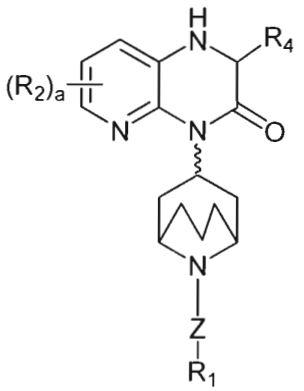
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIR2):



(IIR2)

i.e., a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIR) wherein the 6-membered, nitrogen-containing ring that is fused to the pyridino is in the *exo*- configuration with respect to the (-CH_2-CH_2-) bridge.

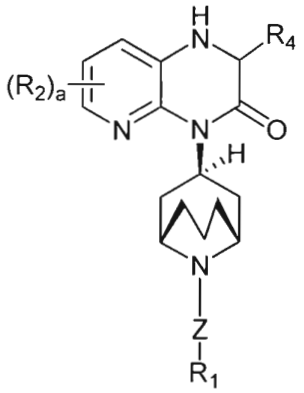
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIS):



(IIS)

wherein R_1, R_2, R_4, Z and a are as defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formula (II).

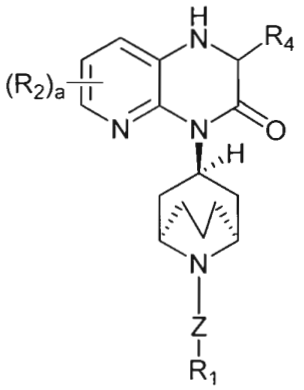
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIS1):



(IIS1)

i.e., a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIS) wherein the 6-membered, nitrogen-containing ring that is fused to the pyridino is in the *endo*- configuration with respect to the (-CH_2-CH_2-CH_2-) bridge.

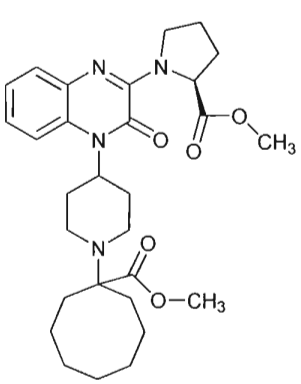
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIS2):



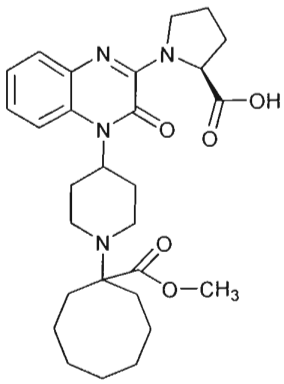
(IIS2)

i.e., a Substituted-Quinoxaline-Type Piperidine Compound of Formula (IIS) wherein the 6-membered, nitrogen-containing ring that is fused to the pyridino is in the *exo*- configuration with respect to the (-CH_2-CH_2-CH_2-) bridge.

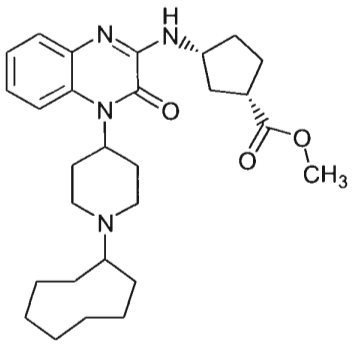
In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compound of Formula (II) is



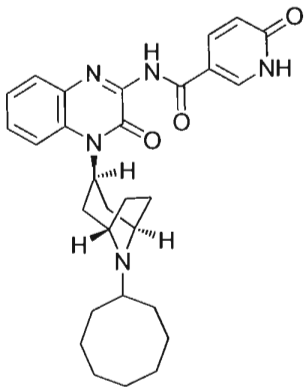
35 ,



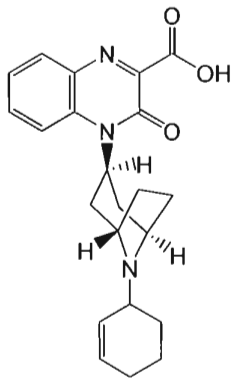
36 ,



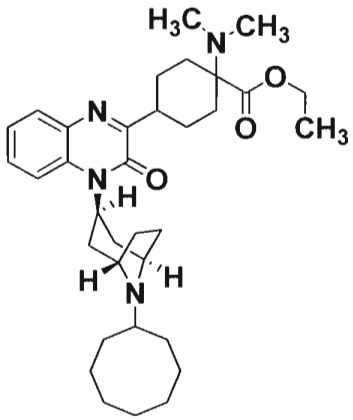
96 ,



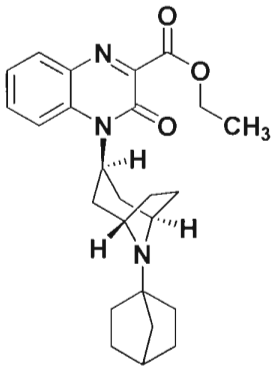
132 ,



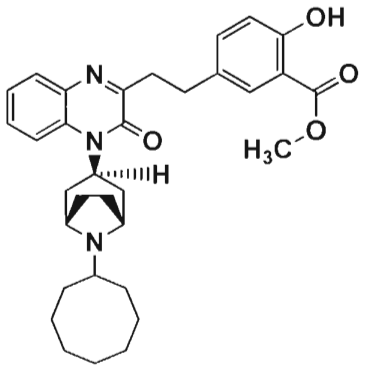
338 ,



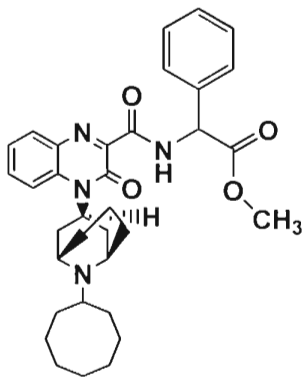
339 ,



341 ,



348 , or



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4.3 Definitions

As used in connection with the Substituted-Quinoxaline-Type Piperidine Compounds herein, the terms used herein having following meaning:

"-(C_1-C_{10})alkyl" means a straight chain or branched non-cyclic hydrocarbon having from 1 to 10 carbon atoms. Representative straight chain -(C_1-C_{10})alkyls include -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl, -n-hexyl, -n-heptyl, -n-octyl, -n-nonyl, and -n-decyl. A branched alkyl means that one or more straight chain -(C_1-C_8)alkyl groups, such as methyl, ethyl or propyl, replace one or both hydrogens in a -CH_2- group of a straight chain alkyl. A branched non-cyclic hydrocarbon means that one or more straight chain -(C_1-C_{10})alkyl groups, such as methyl, ethyl or propyl, replace one or both hydrogens in a -CH_2- group of a straight chain non-cyclic hydrocarbon. Representative branched -(C_1-C_{10})alkyls include -*iso*-propyl, -*sec*-butyl, -*iso*-butyl, -*tert*-butyl, -*iso*-pentyl, -neopentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-ethylbutyl, 2-ethylbutyl, 3-ethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,2-dimethylhexyl, 1,3-dimethylhexyl, 3,3-dimethylhexyl, 1,2-dimethylheptyl, 1,3-dimethylheptyl, and 3,3-dimethylheptyl.

"-(C_1-C_6)alkyl" means a straight chain or branched non-cyclic hydrocarbon having from 1 to 6 carbon atoms. Representative straight chain -(C_1-C_6)alkyls include -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl, and -n-hexyl. Representative branched -(C_1-C_6)alkyls include -*iso*-propyl, -*sec*-butyl, -*iso*-butyl, -*tert*-butyl, -*iso*-pentyl, -neopentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-ethylbutyl, 2-ethylbutyl, 3-ethylbutyl, 1,1-dimethtylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, and 3,3-dimethylbutyl.

"-(C_1-C_4)alkyl" means a straight chain or branched non-cyclic hydrocarbon having from 1 to 4 carbon atoms. Representative straight chain -(C_1-C_4)alkyls include -methyl, -ethyl, -n-propyl, and -n-butyl. Representative branched -(C_1-C_4)alkyls include -*iso*-propyl, -*sec*-butyl, -*iso*-butyl, and -*tert*-butyl.

"-(C_1-C_3)alkyl" means a straight chain or branched non-cyclic hydrocarbon having from 1 to 3 carbon atoms. Representative straight chain -(C_1-C_3)alkyls include -methyl, -ethyl, and -n-propyl. Representative branched -(C_1-C_3)alkyls include -*iso*-propyl.

"-(C_1-C_2)alkyl" means a straight chain non-cyclic hydrocarbon having 1 or 2 carbon atoms. Representative straight chain -(C_1-C_2)alkyls include -methyl and -ethyl.

"-(C_2-C_{10})alkenyl" means a straight chain or branched non-cyclic hydrocarbon having from 2 to 10 carbon atoms and including at least one carbon-carbon double bond. A branched alkenyl means that one or more straight chain -(C_1-C_8)alkyl groups, such as methyl, ethyl or propyl, replace one or both hydrogens in a -CH_2- or -CH= group of a straight chain alkenyl. Representative straight chain and branched (C_2-C_{10})alkenyls include -vinyl, -allyl, -1-butenyl, -2-butenyl, -*iso*-butylenyl, -1-pentenyl, -2-pentenyl, -3-methyl-1-butenyl, -2-methyl-2-butenyl, -2,3-dimethyl-2-butenyl, -1-hexenyl, -2-hexenyl, -3-hexenyl, -1-heptenyl, -2-heptenyl, -3-heptenyl, -1-octenyl, -2-octenyl, -3-octenyl, -1-nonenyl, -2-nonenyl, -3-nonenyl, -1-decenyl, -2-decenyl, -3-decenyl, and the like.

"-(C_2-C_6)alkenyl" means a straight chain or branched non-cyclic hydrocarbon having from 2 to 6 carbon atoms and including at least one carbon-carbon double bond. Representative straight chain and branched (C_2-C_6)alkenyls include -vinyl, -allyl, -1-butenyl, -2-butenyl, -*iso*-butylenyl, -1-pentenyl, -2-pentenyl, -3-methyl-1-butenyl, -2-methyl-2-butenyl, -2,3-dimethyl-2-butenyl, -1-hexenyl, 2-hexenyl, 3-hexenyl, and the like.

"-(C_2-C_{10})alkynyl" means a straight chain or branched non-cyclic hydrocarbon having from 2 to 10 carbon atoms and including at least one carbon-carbon triple bond. A branched alkynyl means that one or more straight chain -(C_1-C_8)alkyl groups, such as methyl, ethyl or propyl, replace one or both hydrogens in a -CH_2- group of a straight chain alkynyl. Representative straight chain and branched -(C_2-C_{10})alkynyls include -acetylenyl, -propynyl, -1-butynyl, -2-butynyl, -1-pentynyl, -2-pentynyl, -3-methyl-1-butynyl, -4-pentynyl, -1-hexynyl, -2-hexynyl, -5-hexynyl, -1-heptynyl, -2-heptynyl, -6-heptynyl, -1-octynyl, -2-octynyl, -7-octynyl, -1-nonynyl, -2-nonynyl, -8-nonynyl, -1-decynyl, -2-decynyl, -9-decynyl, and the like.

"-(C_2-C_6)alkynyl" means a straight chain or branched non-cyclic hydrocarbon having from 2 to 6 carbon atoms and including at least one carbon-carbon triple bond. Representative straight chain and branched (C_2-C_6)alkynyls include -acetylenyl, -propynyl, -1-butynyl, -2-butynyl, -1-pentynyl, -2-pentynyl, -3-methyl-1-butynyl, -4-pentynyl, -1-hexynyl, -2-hexynyl, -5-hexynyl, and the like.

"-(C_1-C_6)alkoxy" means a straight chain or branched non-cyclic hydrocarbon having one or more ether groups and from 1 to 6 carbon atoms. Representative straight chain and branched (C_1-C_6)alkoxys include -methoxy, -ethoxy, methoxymethyl, 2-methoxyethyl, -5-methoxypentyl, 3-ethoxybutyl and the like.

"-(C_3-C_{14})cycloalkyl" means a saturated monocyclic hydrocarbon having from 3 to 14 carbon atoms. Representative (C_3-C_{14})cycloalkyls are -cyclopropyl, -cyclobutyl, -cyclopentyl, -cyclohexyl, -cycloheptyl, -cyclooctyl, -cyclononyl, -cyclodecyl, cycloundecyl, and -cyclododecyl, and -cyclotetradecyl.

"-(C_3-C_{12})cycloalkyl" means a saturated monocyclic hydrocarbon having from 3 to 12 carbon atoms. Representative (C_3-C_{12})cycloalkyls are -cyclopropyl, -cyclobutyl, -cyclopentyl, -cyclohexyl, -cycloheptyl, -cyclooctyl, -cyclononyl, -cyclodecyl, cycloundecyl,and -cyclododecyl.

"-(C_6-C_{12})cycloalkyl" means a saturated monocyclic hydrocarbon having from 6 to 12 carbon atoms. Representative (C_6-C_{12})cycloalkyls are -cyclohexyl, -cycloheptyl, -cyclooctyl, -cyclononyl, -cyclodecyl, cycloundecyl,and -cyclododecyl.

"-(C_4-C_8)cycloalkyl" or "4- to 8-member cycloalkyl ring" means a saturated monocyclic hydrocarbon having from 4 to 8 carbon atoms. Representative -(C_4-C_8)cycloalkyls are -cyclobutyl, -cyclopentyl, -cyclohexyl, -cycloheptyl, and -cyclooctyl.

"-(C_3-C_8)cycloalkyl" means a saturated monocyclic hydrocarbon having from 3 to 8 carbon atoms. Representative (C_3-C_8)cycloalkyls include -cyclopropyl, -cyclobutyl, -cyclopentyl, -cyclohexyl, -cycloheptyl, and -cyclooctyl.

"-(C_3-C_7)cycloalkyl" means a saturated monocyclic hydrocarbon having from 3 to 7 carbon atoms. Representative (C_3-C_7)cycloalkyls include cyclopropyl, -cyclobutyl, -cyclopentyl, -cyclohexyl, -and cycloheptyl.

"-(C_6-C_{14})bicycloalkyl" means a bi-cyclic hydrocarbon ring system having from 6 to 14 carbon atoms and at least one saturated cyclic alkyl ring. Representative -(C_6-C_{14})bicycloalkyls include -indanyl, -norbornyl, -1,2,3,4-tetrahydronaphthalenyl, -5,6,7,8-tetrahydronaphthalenyl, -perhydronaphthalenyl, bicyclo[2.2.1]hexyl, bicyclo[2.2.1.]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.3.1]heptyl, bicyclo[3.2.1]octyl, bicyclo[3.3.1]nonyl, bicyclo[3.3.2]decyl, bicyclo[3.3.3]undecyl, bicyclo[4.2.2]decyl, bicyclo[4.3.2]undecyl, bicyclo[4.3.1]decyl, and the like.

"-(C_8-C_{20})tricycloalkyl" means a tri-cyclic hydrocarbon ring system having from 8 to 20 carbon atoms and at least one saturated cyclic alkyl ring. Representative -(C_8-C_{20})tricycloalkyls include -pyrenyl, -adamantyl, noradamantyl, -1,2,3,4-tetrahydroanthracenyl, -perhydroanthracenyl -aceanthrenyl, -1,2,3,4-tetrahydropenanthrenyl,

-5,6,7,8-tetrahydrophenanthrenyl, -perhydrophenanthrenyl, tetradecahydro-1*H*-cyclohepta[*a*]naphthalenyl, tetradecahydro-1*H*-cycloocta[*e*]indenyl, tetradecahydro-1*H*-cyclohepta[*e*]azulenyl, hexadecahydrocycloocta[*b*]naphthalenyl, hexadecahydrocyclohepta[*a*]heptalenyl, tricyclo-pentadecanyl, tricyclo-octadecanyl, tricyclo-nonadecanyl, tricyclo-icosanyl, and the like.

"-(C_3-C_{14})cycloalkenyl" means a cyclic non-aromatic hydrocarbon having at least one carbon-carbon double bond in the cyclic system and from 3 to 14 carbon atoms. Representative (C_3-C_{14})cycloalkenyls include -cyclopropenyl, -cyclobutenyl, -cyclopentenyl, -cyclopentadienyl, -cyclohexenyl, -cyclohexadienyl,-cycloheptenyl, -cycloheptadienyl, -cycloheptatrienyl, -cyclooctenyl, -cyclooctadienyl, -cyclooctatrienyl, -cyclooctatetraenyl, -cyclononenyl, -cyclononadienyl, -cyclodecenyl, -cyclodecadienyl, -cyclotetradecenyl, -cyclododecadienyl, and the like.

"-(C_5-C_{14})cycloalkenyl" means a cyclic non-aromatic hydrocarbon having at least one carbon-carbon double bond in the cyclic system and from 5 to 14 carbon atoms. Representative (C_5-C_{14})cycloalkenyls include -cyclopentenyl, -cyclopentadienyl, -cyclohexenyl, -cyclohexadienyl,-cycloheptenyl, -cycloheptadienyl, -cycloheptatrienyl, -cyclooctenyl, -cyclooctadienyl, -cyclooctatrienyl, -cyclooctatetraenyl, -cyclononenyl, -cyclononadienyl, -cyclodecenyl, -cyclodecadienyl, -cyclotetradecenyl, -cyclododecadienyl, and the like.

"-(C_6-C_{12})cycloalkenyl" means a cyclic non-aromatic hydrocarbon having at least one carbon-carbon double bond in the cyclic system and from 6 to 12 carbon atoms. Representative (C_6-C_{12})cycloalkenyls include -cyclohexenyl, -cyclohexadienyl,-cycloheptenyl, -cycloheptadienyl, -cycloheptatrienyl, -cyclooctenyl, -cyclooctadienyl, -cyclooctatrienyl, -cyclooctatetraenyl, -cyclononenyl, -cyclononadienyl, -cyclodecenyl, -cyclodecadienyl, -cyclododecadienyl, and the like.

"-(C_5-C_{10})cycloalkenyl" means a cyclic non-aromatic hydrocarbon having at least one carbon-carbon double bond in the cyclic system and from 5 to 10 carbon atoms. Representative (C_5-C_{10})cycloalkenyls include -cyclopentenyl, -cyclopentadienyl, -cyclohexenyl, -cyclohexadienyl,-cycloheptenyl, -cycloheptadienyl, -cycloheptatrienyl, -cyclooctenyl, -cyclooctadienyl, -cyclooctatrienyl, -cyclooctatetraenyl, -cyclononenyl, -cyclononadienyl, -cyclodecenyl, -cyclodecadienyl, and the like.

"-(C_5-C_8)cycloalkenyl" means a cyclic non-aromatic hydrocarbon having at least one carbon-carbon double bond in the cyclic system and from 5 to 8 carbon atoms. Representative (C_5-C_8)cycloalkenyls include -cyclopentenyl, -cyclopentadienyl, -cyclohexenyl, -cyclohexadienyl, -cycloheptenyl, -cycloheptadienyl, -cycloheptatrienyl, -cyclooctenyl, -cyclooctadienyl, -cyclooctatrienyl, -cyclooctatetraenyl, and the like.

"-(C_7-C_{14})bicycloalkenyl" means a bi-cyclic hydrocarbon ring system having at least one carbon-carbon double bond in each ring and from 7 to 14 carbon atoms. Representative -(C_7-C_{14})bicycloalkenyls include -bicyclo[3.2.0]hept-2-enyl, -indenyl, -pentalenyl, -naphthalenyl, -azulenyl, -heptalenyl, -1,2,7,8-tetrahydronaphthalenyl, norbornenyl, and the like.

"-(C_8-C_{20})tricycloalkenyl" means a tri-cyclic hydrocarbon ring system having at least one carbon-carbon double bond in each ring and from 8 to 20 carbon atoms. Representative -(C_8-C_{20})tricycloalkenyls include -anthracenyl, -phenanthrenyl, -phenalenyl, -acenaphthalenyl, as-indacenyl, s-indacenyl, 2,3,6,7,8,9,10,11-octahydro-1*H*-cycloocta[*e*]indenyl, 2,3,4,7,8,9,10,11-octahydro-1*H*-cyclohepta[a]naphthalenyl, 8,9,10,11-tetrahydro-7*H*-cyclohepta[*a*]naphthalenyl, 2,3,4,5,6,7,8,9,10,11,12,13-dodecahydro-1*H*-cyclohepta[*a*]heptalenyl, 1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-dicyclohepta[*a,c*]cyclooctenyl, 2,3,4,5,6,7,8,9,10,11,12,13-dodecahydro-1*H*-dibenzo[*a,d*]cyclononenyl, and the like.

"-(3- to 7-membered)heterocycle" or "-(3- to 7-membered)heterocyclo" means a 3- to 7-membered monocyclic heterocyclic ring which is either saturated, unsaturated non-aromatic, or aromatic. A 3-membered heterocycle can contain up to 1 heteroatom, a 4-membered heterocycle can contain up to 2 heteroatoms, a 5-membered heterocycle can contain up to 4 heteroatoms, a 6-membered heterocycle can contain up to 4 heteroatoms, and a 7-membered heterocycle can contain up to 5 heteroatoms. Each heteroatom is independently selected from nitrogen, which can be quaternized; oxygen; and sulfur, including sulfoxide and sulfone. The -(3- to 7-membered)heterocycle can be attached via a nitrogen or carbon atom. Representative -(3- to 7-membered)heterocycles include pyridyl, furyl, thiophenyl, pyrrolyl, oxazolyl, imidazolyl, thiazolidinyl, thiadiazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, triazinyl, morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, 2,3-dihydrofuranyl, dihydropyranyl, hydantoinyl, valerolactamyl, oxiranyl,

oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, dihydropyridinyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

"-(5- or 6-membered)heterocycle" or "-(5- or 6-membered)heterocyclo" means a 5- or 6-membered monocyclic heterocyclic ring which is either saturated, unsaturated non-aromatic, or aromatic. A 5-membered heterocycle can contain up to 4 heteroatoms and a 6-membered heterocycle can contain up to 4 heteroatoms. Each heteroatom is independently selected from nitrogen, which can be quaternized; oxygen; and sulfur, including sulfoxide and sulfone. The -(5- or 6-membered)heterocycle can be attached via a nitrogen or carbon atom. Representative -(5- or 6-membered)heterocycles include pyridyl, furyl, thiophenyl, pyrrolyl, oxazolyl, imidazolyl, thiazolidinyl, thiadiazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, triazinyl, morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, 2,3-dihydrofuranyl, dihydropyranyl, hydantoinyl, valerolactamyl, tetrahydrofuranyl, tetrahydropyranyl, dihydropyridinyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, tetrazolyl, and the like.

"-(3- to 5-membered)heterocycle" or "-(3- to 5-membered)heterocyclo" means a 3- to 5-membered monocyclic heterocyclic ring which is either saturated, unsaturated non-aromatic, or aromatic. A 3-membered heterocycle can contain up to 1 heteroatom, a 4-membered heterocycle can contain up to 2 heteroatoms, and a 5-membered heterocycle can contain up to 4 heteroatoms. Each heteroatom is independently selected from nitrogen, which can be quaternized; oxygen; and sulfur, including sulfoxide and sulfone. The -(3- to 5-membered)heterocycle can be attached via a nitrogen or carbon atom. Representative -(3- to 5-membered)heterocycles include furyl, thiophenyl, pyrrolyl, oxazolyl, imidazolyl, thiazolidinyl, thiadiazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, triazinyl, pyrrolidinonyl, pyrrolidinyl, 2,3-dihydrofuranyl, hydantoinyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrazolidinyl and the like.

"-(7- to 10-membered)bicycloheterocycle" or "-(7- to 10-membered)bicycloheterocyclo" means a 7- to 10-membered bicyclic, heterocyclic ring which is either saturated, unsaturated non-aromatic, or aromatic. A -(7- to 10-membered)bicycloheterocycle contains from 1 to 4 heteroatoms independently selected from nitrogen, which can be quaternized; oxygen; and sulfur, including sulfoxide and sulfone. The -(7- to 10-membered)bicycloheterocycle can be attached via a nitrogen or carbon atom. Representative -(7- to 10-membered)bicycloheterocycles include -quinolinyl, -isoquinolinyl, -

chromonyl, -coumarinyl, -indolyl, -indolizinyl, -benzo[b]furanyl, -benzo[b]thiophenyl, -indazolyl, -purinyl, -4H-quinolizinyl, -isoquinolyl, -quinolyl, -phthalazinyl, -naphthyridinyl, -carbazolyl, -β-carbolinyl, -indolinyl, -isoindolinyl, -1,2,3,4-tetrahydroquinolinyl, -1,2,3,4-tetrahydroisoquinolinyl, pyrrolopyrrolyl and the like.

"-(C_3-C_{12})cycloalkoxy" means a saturated monocyclic hydrocarbon having from 3 to 12 carbon atoms where at least one of the carbon atoms is replaced by an oxygen atom. Representative (C_3-C_{12})cycloalkoxy are -oxiranyl, -oxetanyl, -tetrahydrofuranyl, -tetrahydro-2H-pyranyl, -1,4-dioxanyl, -oxepanyl, -1,4-dioxepanyl, -oxocanyl, -1,5-dioxocanyl, -1,3,5-trioxocanyl, -oxonanyl, -1,5-dioxonanyl, -1,4,7-trioxonanyl, -oxacyclododecanyl, -1,7-dioxacyclododecanyl, and -1,5,9-trioxacyclododecanyl.

"-(C_3-C_7)cycloalkoxy " means a saturated monocyclic hydrocarbon having from 3 to 7 carbon atoms where at least one of the carbon atoms is replaced by an oxygen atom. Representative (C_3-C_7)cycloalkoxy are -oxiranyl, -oxetanyl, -tetrahydrofuranyl, -tetrahydro-2H-pyranyl, -1,4-dioxanyl, -oxepanyl, and -1,4-dioxepanyl.

"-(C_{14})aryl" means a 14-membered aromatic carbocyclic moiety such as -anthryl or -phenanthryl.

"-(5- to 10-membered)heteroaryl" means an aromatic heterocycle ring of 5 to 10 members, including both mono- and bicyclic ring systems, where at least one carbon atom of one or both of the rings is replaced with a heteroatom independently selected from nitrogen, oxygen, and sulfur, or at least two carbon atoms of one or both of the rings are replaced with a heteroatom independently selected from nitrogen, oxygen, and sulfur. In one embodiment, one of the -(5- to 10-membered)heteroaryl's rings contain at least one carbon atom. In another embodiment, both of the -(5- to 10-membered)heteroaryl's rings contain at least one carbon atom. Representative -(5- to 10-membered)heteroaryls include pyridyl, furyl, benzofuranyl, thiophenyl, benzothiophenyl, quinolinyl, isoquinolinyl, pyrrolyl, indolyl, oxazolyl, benzoxazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isoxazolyl, oxadiazolinyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidyl, pyrimidinyl, pyrazinyl, thiadiazolyl, triazinyl, thienyl, cinnolinyl, phthalazinyl, and quinazolinyl.

"-(5- or 6-membered)heteroaryl" means a monocyclic aromatic heterocycle ring of 5 or 6 members where at least one carbon atom is replaced with a heteroatom independently selected from nitrogen, oxygen, and sulfur. In one embodiment, one of the -(5- or 6-

membered)heteroaryl's ring contains at least one carbon atom. Representative -(5- or 6-membered)heteroaryls include pyridyl, furyl, pyrrolyl, oxazolyl, imidazolyl, thiazolyl, isoxazolyl, 1,2,3-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,3-triazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidyl, pyrazinyl, 1,2,3-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,5-triazinyl, and thiophenyl.

"-CH_2(halo)" means a methyl group where one of the hydrogens of the methyl group has been replaced with a halogen. Representative -CH_2(halo) groups include -CH_2F, -CH_2Cl, -CH_2Br, and -CH_2I.

"-CH(halo)$_2$" means a methyl group where two of the hydrogens of the methyl group have been replaced with a halogen. Representative -CH(halo)$_2$ groups include -CHF_2, -$CHCl_2$, -$CHBr_2$, -CHBrCl, -CHClI, and -CHI_2.

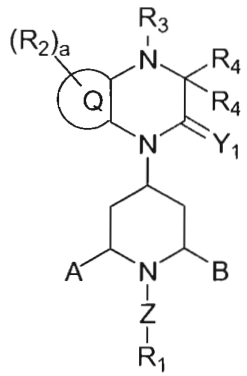
"-C(halo)$_3$" means a methyl group where each of the hydrogens of the methyl group has been replaced with a halogen. Representative -C(halo)$_3$ groups include -CF_3, -CCl_3, -CBr_3, and -CI_3.

"-Halogen" or "-halo" means -F, -Cl, -Br, or -I.

"Oxo", "=O", and the like as used herein mean an oxygen atom doubly bonded to carbon or another element.

"Thiooxo", "thioxo", "=S", and the like as used herein mean a sulfur atom doubly bonded to carbon or another element.

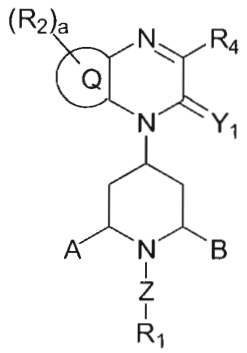
As used herein in connection with Formula (II), when the dashed line in the 6-membered, nitrogen-containing ring that is fused to the Q group is absent, then Formula (II) is understood to appear as follows



(II) ,

i.e., the 6-membered, nitrogen-containing ring that is fused to the Q group contains no double bond between the ring-carbon to which the R_4 groups are attached and the adjacent ring-nitrogen.

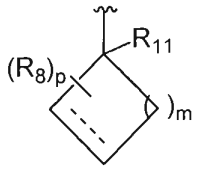
As used herein in connection with Formula (II), when the dashed line in the 6-membered, nitrogen-containing ring that is fused to the Q group indicates the presence of a bond, then Formula (II) is understood to appear as follows



(II) ,

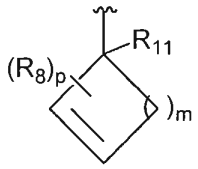
i.e., the 6-membered, nitrogen-containing ring that is fused to the Q group contains a double bond between the ring-carbon to which the R_4 group is attached and the adjacent ring-nitrogen.

As used herein in connection with the R_1 group



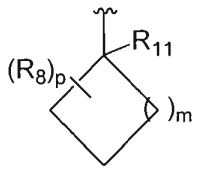
(i)

when the dashed line in the ring indicates the presence of a bond, then that group is understood to appear as follows



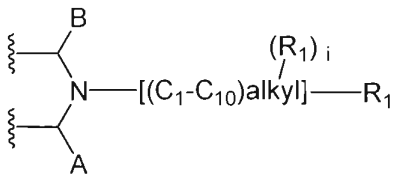
(i)

and when the dashed line in the ring indicates the absence of a bond, then that group is understood to appear as follows



(i)

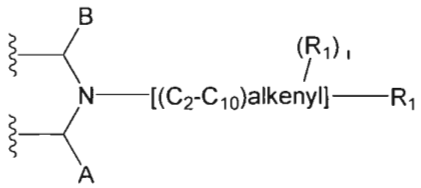
"-[(C_1-C_{10})alkyl optionally substituted by R_1]$_h$-" as used herein in connection with Z means that, when h is 0, Z is a bond. When h is 1, Z-R_1, as attached to the piperidine ring bearing A and B substituents, is



where; when i is 0, the (C_1-C_{10})alkyl is unsubstituted by an R_1 group at any position other than at the carbon atom furthest removed from the piperidine ring bearing A and B substituents; and, when i is 1, (*i.e.*, the (C_1-C_{10})alkyl is optionally substituted by R_1) the optionally substituted by R_1 (C_1-C_{10})alkyl is substituted by an R_1 group at the carbon atom furthest

removed from the piperidine ring bearing A and B substituents and substituted by another independently selected R_1 group at any carbon atom of the $(C_1$-$C_{10})$alkyl including at the carbon atom furthest removed from the piperidine ring bearing A and B substituents.

"-[$(C_2$-$C_{10})$alkenyl optionally substituted by R_1]-" as used herein in connection with Z means that the piperidine ring bearing A and B substituents, is

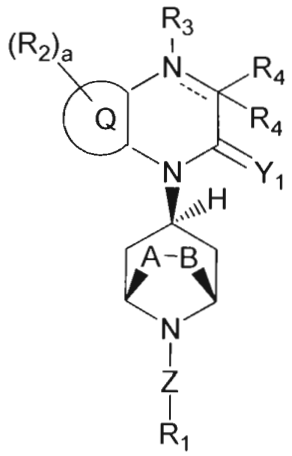


where; when i is 0, the $(C_2$-$C_{10})$alkenyl is unsubstituted by an R_1 group at any position other than at the carbon atom furthest removed from the piperidine ring bearing A and B substituents; and, when i is 1, (*i.e.*, the $(C_2$-$C_{10})$alkenyl is optionally substituted by R_1) the optionally substituted by R_1 $(C_2$-$C_{10})$alkenyl is substituted by an R_1 group at the carbon atom furthest removed from the piperidine ring bearing A and B substituents and substituted by another independently selected R_1 group at any carbon atom of the $(C_2$-$C_{10})$alkenyl including at the carbon atom furthest removed from the piperidine ring bearing A and B substituents.

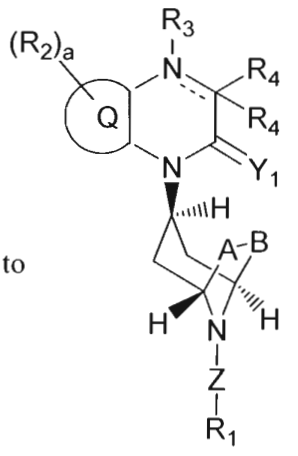
"$(C_2$-$C_6)$bridge" as used herein means a hydrocarbon chain containing 2 to 6 carbon atoms joining two atoms of the piperidine ring of Formula (I) or Formula (II) to form a fused bicyclic ring system. For example, compounds of the invention can comprise a $(C_2$-$C_6)$bridge joining positions 2 and 6 of the piperidine ring (A-B can together form a $(C_2$-$C_6)$bridge). Exemplary compounds of the invention include those with an unsubstituted (C_2)bridge, $-CH_2.CH_2-$, joining positions 2 and 6 of the piperidine ring (A-B can together form a (C_2)bridge); an unsubstituted (C_3)bridge, $-CH_2.CH_2.CH_2-$, joining positions 2 and 6 of the piperidine ring (A-B can together form a (C_3)bridge); an unsubstituted (C_4)bridge, $-CH_2.CH_2-CH_2.CH_2-$, joining positions 2 and 6 of the piperidine ring (A-B can together form a (C_4)bridge); an unsubstituted (C_5)bridge, $-CH_2.CH_2-CH_2.CH_2.CH_2-$, joining positions 2 and 6 of the piperidine ring (A-B can together form a (C_5)bridge); or an unsubstituted (C_6)bridge, $-CH_2.CH_2-CH_2.CH_2-CH_2.CH_2-$, joining positions 2 and 6 of the piperidine ring (A-B can together form a (C_6)bridge). Examples of compounds where A-B can together form a $(C_2$-$C_6)$bridge include compounds comprising the following ring systems: 8-aza-bicyclo[3.2.1]octane; 9-aza-bicyclo[3.3.1]nonane; 10-aza-bicyclo[4.3.1]decane; 11-aza-

bicyclo[5.3.1]undecane; and 12-aza-bicyclo[6.3.1]dodecane. Examples of a (C_2-C_6)bridge which optionally contains -HC=CH- within the (C_2-C_6)bridge include -HC=CH-, -CH_2-HC=CH-, -HC=CH-CH_2-, -CH_2-HC=CH-CH_2-, and the like. Examples of a (C_2-C_6)bridge which optionally contains -O- within the (C_2-C_6)bridge include -CH_2-O-CH_2- (containing 2 carbon atoms), -CH_2-O-CH_2-CH_2- and -CH_2-CH_2-O-CH_2- (each containing 3 carbon atoms), -CH_2-CH_2-O-CH_2-CH_2-, -CH_2-O-CH_2-CH_2-CH_2- and -CH_2-CH_2-CH_2-O-CH_2- (each containing 4 carbon atoms), and the like.

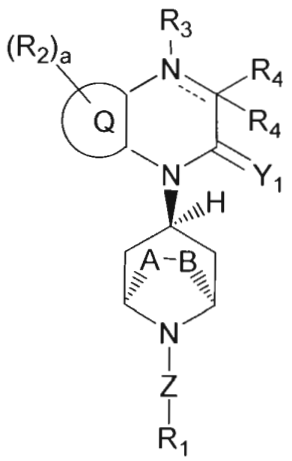
In compounds of the invention comprising a bridge joining positions 2 and 6 of the piperidine ring (*e.g.*, A-B can together form a (C_2-C_6)bridge), for, *e.g.*, a compound of Formula (II), the exemplary *endo* bridge



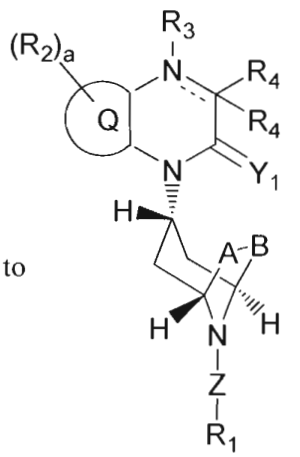
is equivalent to



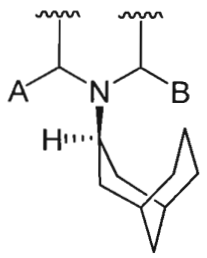
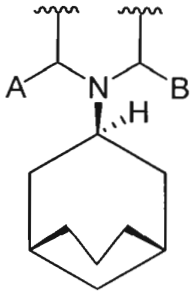
In compounds of the invention comprising a bridge joining positions 2 and 6 of the piperidine ring (*e.g.*, A-B can together form a (C_2-C_6)bridge), for, *e.g.*, a compound of Formula (II), the exemplary *exo* bridge

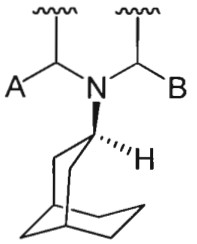
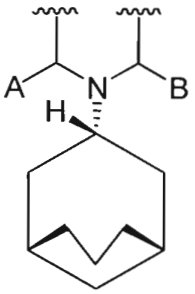


is equivalent to



In compounds of the invention where the -Z-R_1 group comprises a bicyclic group, that bicyclic group can have two orientations. For example, for a -Z-R_1 group that is a -(C_6-C_{14})bicycloalkyl, *e.g.*, bicyclo[3.3.1]nonanyl, attached directly to the piperidine ring nitrogen, the following orientations are possible:

endo:  or  ; or

exo:  or  .

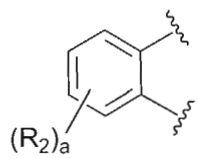
When a first group is "substituted with one or more" second groups, one or more hydrogen atoms of the first group is replaced with a corresponding number of second groups. When the number of second groups is two or greater, each second group can be the same or different.

In one embodiment, a first group is substituted with up to three second groups.

In another embodiment, a first group is substituted with one or two second groups.

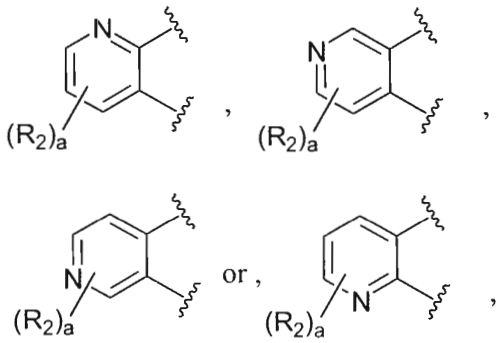
In another embodiment, a first group is substituted with only one second group.

The phrase "benzo", "benzo group" and the like, when used in connection with the optionally-substituted Q group, means

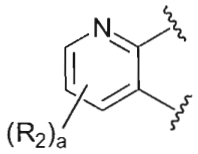


where R_2 and a are defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formulas (I) and (II).

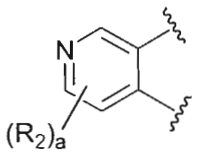
The phrase "pyridino", "pyridino group" and the like, when used in connection with the optionally-substituted Q group, means



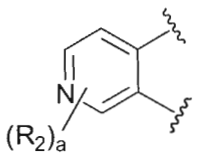
where R_2 and a are defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formulas (I) and (II). In one embodiment, the optionally-substituted pyridino Q group is



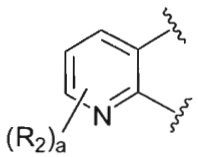
In another embodiment, the optionally-substituted pyridino Q group is



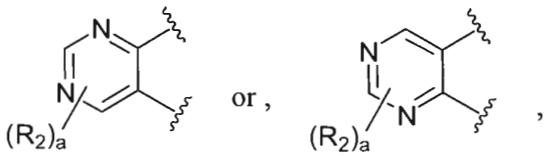
In another embodiment, the optionally-substituted pyridino Q group is



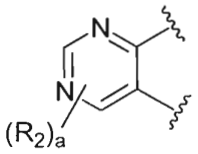
In another embodiment, the optionally-substituted pyridino Q group is



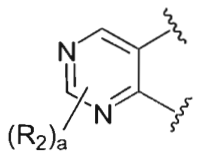
The phrase "pyrimidino", "pyrimidino group" and the like, when used in connection with the optionally-substituted Q group, means



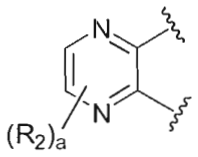
where R_2 and a are defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formulas (I) and (II). In one embodiment, the optionally-substituted pyrimidino Q group is



In another embodiment, the optionally-substituted pyrimidino Q group is

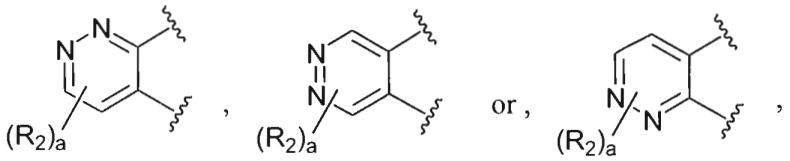


The phrase "pyrazino", "pyrazino group" and the like, when used in connection with the optionally-substituted Q group, means

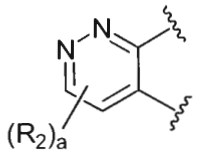


where R_2 and a are defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formulas (I) and (II).

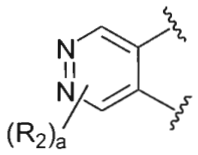
The phrase "pyridazino", "pyridazino group" and the like, when used in connection with the optionally-substituted Q group, means



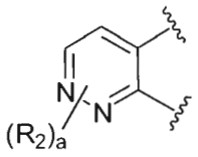
where R_2 and a are defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formulas (I) and (II). In one embodiment, the optionally-substituted pyridazino Q group is



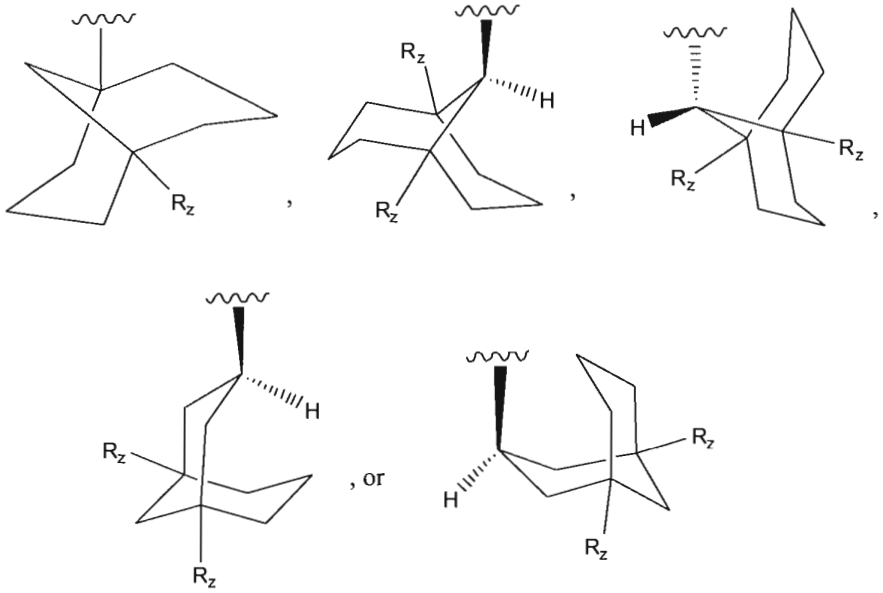
In another embodiment, the optionally-substituted pyridazino Q group is



In another embodiment, the optionally-substituted pyridazino Q group is

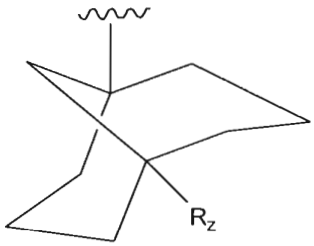


In one embodiment, the phrase "optionally substituted bicyclo[3.3.1]nonyl", when used in connection with the optionally-substituted R_1 group, means

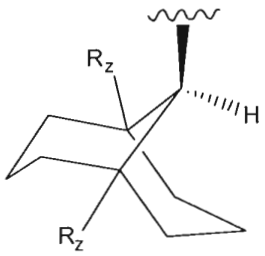


where R_z is defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formulas (I) and (II).

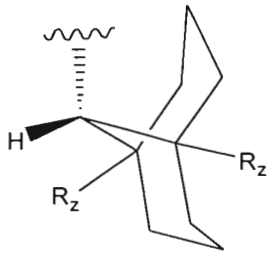
In one embodiment the optionally substituted bicyclo[3.3.1]nonyl is



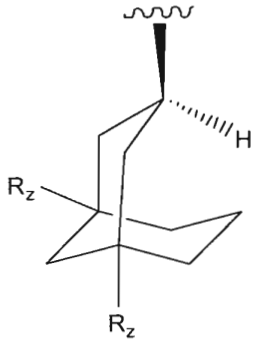
In another embodiment the optionally substituted bicyclo[3.3.1]nonyl is



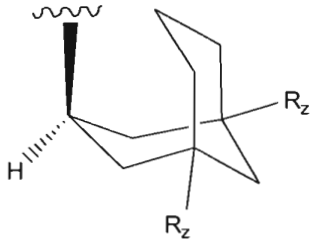
In another embodiment the optionally substituted bicyclo[3.3.1]nonyl is



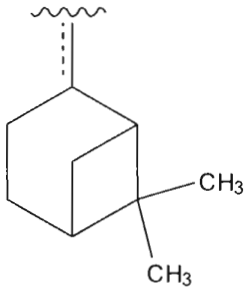
In another embodiment the optionally substituted bicyclo[3.3.1]nonyl is



In another embodiment the optionally substituted bicyclo[3.3.1]nonyl is

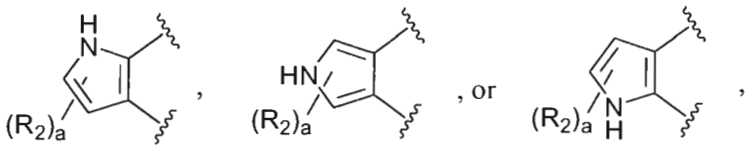


In one embodiment the phrase "optionally substituted -(C_6-C_{14})bicycloalkyl" means

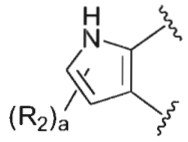


wherein the dashed line denotes the presence or absence of a bond.

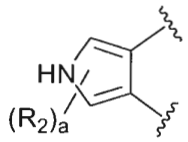
The phrase "pyrrolino", "pyrrolino group" and the like, when used in connection with the optionally-substituted Q group, means



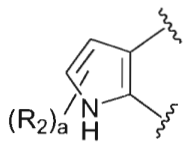
where R_2 and a are defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formulas (I) and (II). In one embodiment, the optionally-substituted pyrrolino Q group is



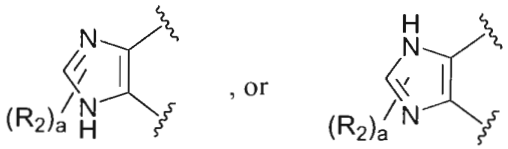
In another embodiment, the optionally-substituted pyrrolino Q group is



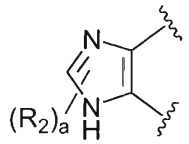
In another embodiment, the optionally-substituted pyrrolino Q group is



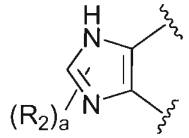
The phrase "imidazolino", "imidazolino group" and the like, when used in connection with the optionally-substituted Q group, means



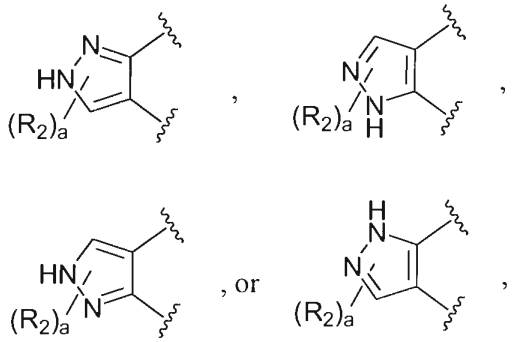
where R_2 and a are defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formulas (I) and (II). In one embodiment, the optionally-substituted imidazolino Q group is



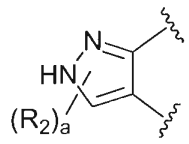
In another embodiment, the optionally-substituted imidazolino Q group is



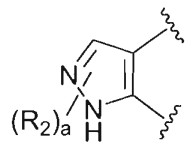
The phrase "pyrazolino", "pyrazolino group" and the like, when used in connection with the optionally-substituted Q group, means



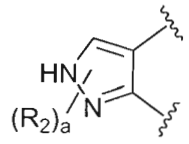
where R_2 and a are defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formulas (I) and (II). In one embodiment, the optionally-substituted pyrazolino Q group is



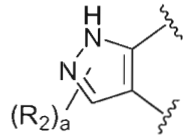
In another embodiment, the optionally-substituted pyrazolino Q group is



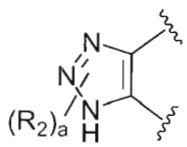
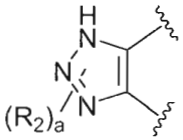
In another embodiment, the optionally-substituted pyrazolino Q group is



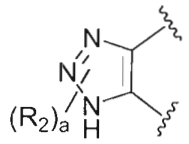
In another embodiment, the optionally-substituted pyrazolino Q group is



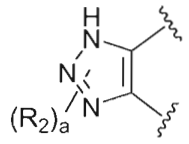
The phrase "triazolino", "triazolino group" and the like, when used in connection with the optionally-substituted Q group, means

 , or  ,

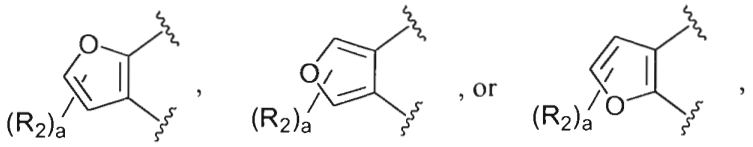
where R_2 and a are defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formulas (I) and (II). In one embodiment, the optionally-substituted triazolino Q group is



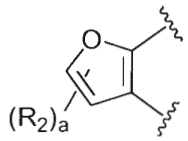
In another embodiment, the optionally-substituted triazolino Q group is



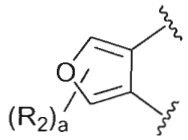
The phrase "furano", "furano group" and the like, when used in connection with the optionally-substituted Q group, means



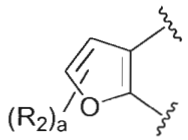
where R_2 and a are defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formulas (I) and (II). In one embodiment, the optionally-substituted furano Q group is



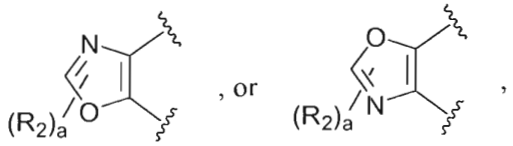
In another embodiment, the optionally-substituted furano Q group is



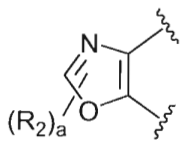
In another embodiment, the optionally-substituted furano Q group is



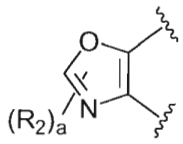
The phrase "oxazolino", "oxazolino group" and the like, when used in connection with the optionally-substituted Q group, means



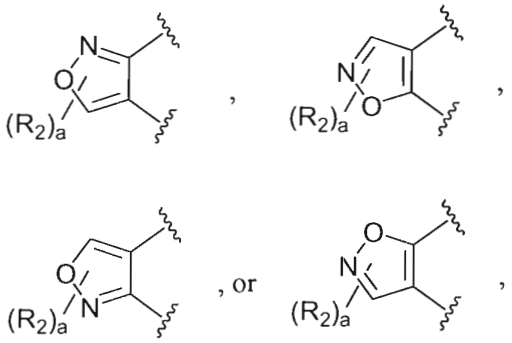
where R_2 and a are defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formulas (I) and (II). In one embodiment, the optionally-substituted oxazolino Q group is



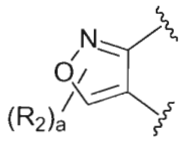
In another embodiment, the optionally-substituted oxazolino Q group is



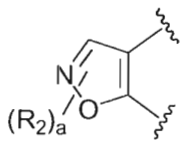
The phrase "isoxazolino", "isoxazolino group" and the like, when used in connection with the optionally-substituted Q group, means



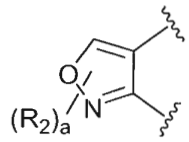
where R_2 and a are defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formulas (I) and (II). In one embodiment, the optionally-substituted isoxazolino Q group is



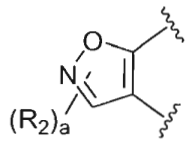
In another embodiment, the optionally-substituted isoxazolino Q group is



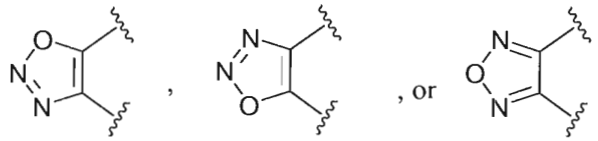
In another embodiment, the optionally-substituted isoxazolino Q group is



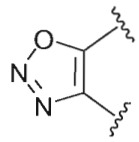
In another embodiment, the optionally-substituted isoxazolino Q group is



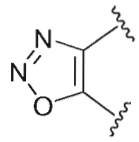
The phrase "oxadiazolino", "oxadiazolino group" and the like, when used in connection with the optionally-substituted Q group, means



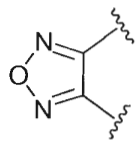
where R_2 and a are defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formulas (I) and (II). In one embodiment, the optionally-substituted oxadiazolino Q group is



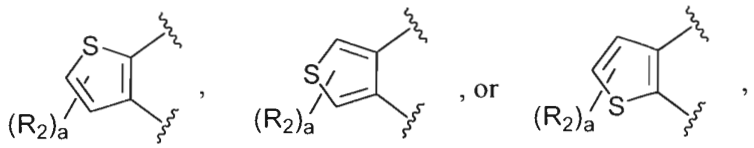
In another embodiment, the optionally-substituted oxadiazolino Q group is



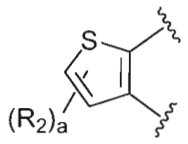
In another embodiment, the optionally-substituted oxadiazolino Q group is



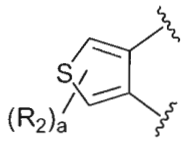
The phrase "thiopheno", "thiopheno group" and the like, when used in connection with the optionally-substituted Q group, means



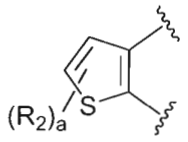
where R_2 and a are defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formulas (I) and (II). In one embodiment, the optionally-substituted thiopheno Q group is



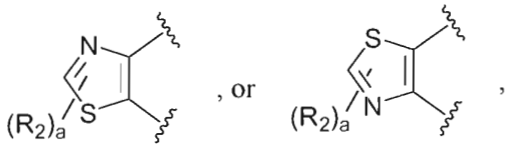
In another embodiment, the optionally-substituted thiopheno Q group is



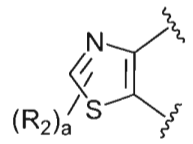
In another embodiment, the optionally-substituted thiopheno Q group is



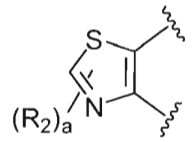
The phrase "thiazolino", "thiazolino group" and the like, when used in connection with the optionally-substituted Q group, means



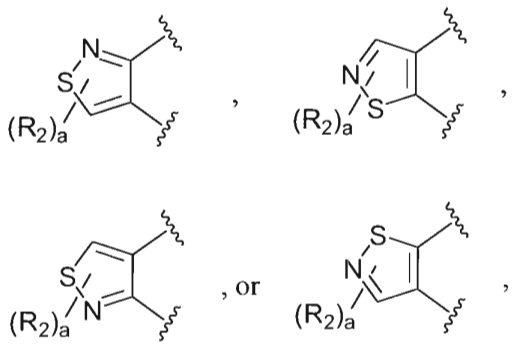
where R_2 and a are defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formulas (I) and (II). In one embodiment, the optionally-substituted thiazolino Q group is



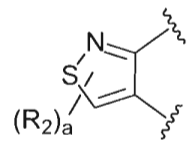
In another embodiment, the optionally-substituted thiazolino Q group is



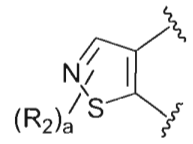
The phrase "isothiazolino", "isothiazolino group" and the like, when used in connection with the optionally-substituted Q group, means



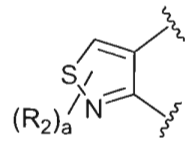
where R_2 and a are defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formulas (I) and (II). In one embodiment, the optionally-substituted isothiazolino Q group is



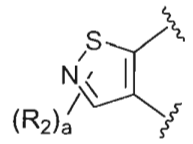
In another embodiment, the optionally-substituted isothiazolino Q group is



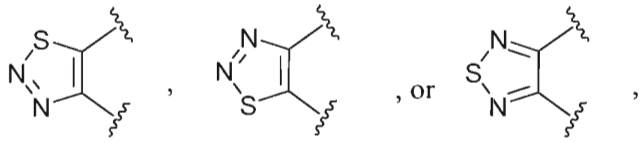
In another embodiment, the optionally-substituted isothiazolino Q group is



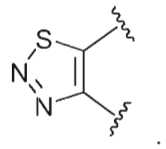
In another embodiment, the optionally-substituted isothiazolino Q group is



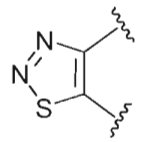
The phrase "thiadiazolino", "thiadiazolino group" and the like, when used in connection with the optionally-substituted Q group, means



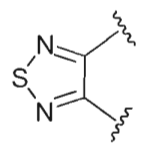
where R_2 and a are defined above for the Substituted-Quinoxaline-Type Piperidine Compounds of Formulas (I) and (II). In one embodiment, the optionally-substituted thiadiazolino Q group is



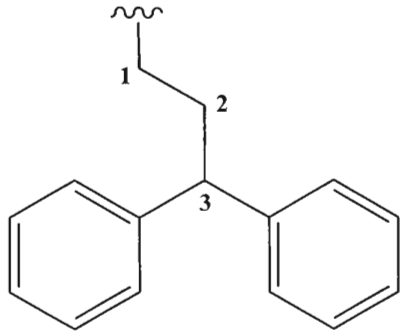
In another embodiment, the optionally-substituted thiadiazolino Q group is



In another embodiment, the optionally-substituted thiadiazolino Q group is

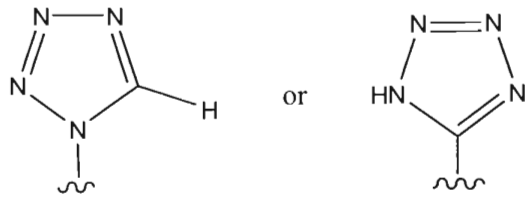


The phrase "3,3-diphenylpropyl-" and the like, when used in connection with the -Z-R_1 group, means

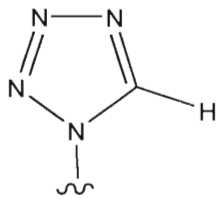


where the 3 carbon of the propyl is indicated by the number 3 in the structure above.

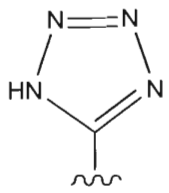
The phrase "tetrazolyl group" means



In one embodiment, the tetrazolyl group is



In another embodiment, the tetrazolyl group is



The term "animal" includes, but is not limited to, a human or a non-human animal, such as a companion animal or livestock, *e.g.*, a cow, monkey, baboon, chimpanzee, horse, sheep, pig, chicken, turkey, quail, cat, dog, mouse, rat, rabbit or guinea pig.

The phrase "pharmaceutically acceptable derivative", as used herein, includes any pharmaceutically acceptable salt, solvate, prodrug, radiolabeled, stereoisomer, enantiomer, diastereomer, other stereoisomeric form, racemic mixture, geometric isomer, and/or tautomer, *e.g.*, of a Substituted-Quinoxaline-Type Piperidine Compound of the invention. In one embodiment, the pharmaceutically acceptable derivative is a pharmaceutically acceptable salt, solvate, radiolabeled, stereoisomer, enantiomer, diastereomer, other stereoisomeric form, racemic mixture, geometric isomer, and/or tautomer, *e.g.*, of a Substituted-Quinoxaline-Type Piperidine Compound of the invention. In another embodiment, the pharmaceutically acceptable derivative is a pharmaceutically acceptable salt, *e.g.*, of a Substituted-Quinoxaline-Type Piperidine Compound of the invention.

The phrase "pharmaceutically acceptable salt", as used herein, is any pharmaceutically acceptable salt that can be prepared from a Substituted-Quinoxaline-Type Piperidine Compound including a salt formed from an acid and a basic functional group, such as a nitrogen group, of a Substituted-Quinoxaline-Type Piperidine Compound. Illustrative salts include, but are not limited, to sulfate, citrate, acetate, trifluoroacetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucoronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, and pamoate (*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. The term "pharmaceutically acceptable salt" also includes a salt prepared from a Substituted-Quinoxaline-Type Piperidine Compound having an acidic functional group, such as a carboxylic acid functional group, and a pharmaceutically acceptable inorganic or organic base. Suitable bases include, but are not limited to, hydroxides of alkali metals such as sodium, potassium, cesium, and lithium; hydroxides of alkaline earth metal such as calcium and magnesium; hydroxides of other metals, such as aluminum and zinc; ammonia and organic amines, such as unsubstituted or hydroxy-substituted mono-, di-, or trialkylamines; dicyclohexylamine; tributyl amine; pyridine; picoline; N-methyl,N-ethylamine; diethylamine; triethylamine; mono-, bis-, or tris-(2-hydroxy-(C_1-C_3)alkyl amines), such as mono-, bis-, or tris-(2-hydroxyethyl)amine, 2-hydroxy-*tert*-butylamine, or tris-(hydroxymethyl)methylamine, N,N-di-[(C_1-C_3)alkyl] -N-(hydroxy-(C_1-C_3)alkyl)-amines, such as N,N-dimethyl-N-(2-hydroxyethyl)amine, or tri-(2-hydroxyethyl)amine; N-methyl-D-glucamine; and amino acids such as arginine, lysine,

and the like. One skilled in the art will recognize that, *e.g.*, acid addition salts of a Substituted-Quinoxaline-Type Piperidine Compound can be prepared by reaction of the compounds with the appropriate acid via a variety of known methods.

The invention disclosed herein is also meant to encompass all solvates of the Substituted-Quinoxaline-Type Piperidine Compounds. "Solvates" are known in the art and are considered to be a combination, physical association and/or solvation of a Substituted-Quinoxaline-Type Piperidine Compound with a solvent molecule, *e.g.*, a disolvate, monosolvate or hemisolvate when the solvent molecule: Substituted-Quinoxaline-Type Piperidine Compound molecule ratio is 2:1, 1:1 or 1:2, respectively. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances, the solvate can be isolated, for example when one or more solvent molecules are incorporated into the crystal lattice of a crystalline solid. Thus, "solvate", as used herein, encompasses both solution-phase and isolatable solvates. A Substituted-Quinoxaline-Type Piperidine Compound of the invention can be present as a solvated form with a pharmaceutically acceptable solvent, such as water, methanol, ethanol, and the like, and it is intended that the invention include both solvated and unsolvated Substituted-Quinoxaline-Type Piperidine Compound forms. As "hydrate" relates to a particular subgroup of solvates, *i.e.*, where the solvent molecule is water, hydrates are included within the solvates of the invention. Preparation of solvates is known in the art. For example, M. Caira *et al.*, *J. Pharmaceut. Sci.*, 93(3):601-611 (2004), describes the preparation of solvates of fluconazole with ethyl acetate and with water. Similar preparations of solvates, hemisolvate, hydrates, and the like are described by E.C. van Tonder *et al.*, *AAPS Pharm. Sci. Tech.*, 5(1):Article 12 (2004), and A.L. Bingham *et al.*, *Chem. Commun.*, 603-604 (2001). A typical, non-limiting, process involves dissolving the Substituted-Quinoxaline-Type Piperidine Compound in a desired amount of the desired solvent (organic, water or mixtures thereof) at temperatures above about 20°C to about 25°C, cooling the solution at a rate sufficient to form crystals, and isolating the crystals by known methods, *e.g.*, filtration. Analytical techniques, for example, infrared spectroscopy, can be used to show the presence of the solvent in a crystal of the solvate.

The invention disclosed herein is also meant to encompass all prodrugs of the Substituted-Quinoxaline-Type Piperidine Compounds. "Prodrugs" are known in the art and, while not necessarily possessing any pharmaceutical activity as such, are considered to be any covalently bonded carrier(s) that releases the active parent drug *in vivo*. In general, such

prodrugs will be a functional derivative of a Substituted-Quinoxaline-Type Piperidine Compound of Formula (I) or Formula (II) which is readily convertible *in vivo*, *e.g.*, by being metabolized, into the required Substituted-Quinoxaline-Type Piperidine Compound of Formula (I) or Formula (II). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described in, for example, *Design of Prodrugs*, H. Bundgaard ed., Elsevier (1985); "Drug and Enzyme Targeting, Part A," K. Widder *et al.* eds., Vol. 112 in *Methods in Enzymology*, Academic Press (1985); Bundgaard, "Design and Application of Prodrugs," Chapter 5 (pp. 113-191) in *A Textbook of Drug Design and Development*, P. Krogsgaard-Larsen and H. Bundgaard eds., Harwood Academic Publishers (1991); Bundgaard *et al.*, *Adv. Drug Delivery Revs.* 8:1-38 (1992); Bundgaard *et al.*, *J. Pharmaceut. Sci.* 77:285 (1988); and Kakeya *et al.*, *Chem. Pharm. Bull.* 32:692 (1984).

In addition, one or more hydrogen, carbon or other atoms of a Substituted-Quinoxaline-Type Piperidine Compound can be replaced by an isotope of the hydrogen, carbon or other atoms. Such a "radiolabeled", "radiolabeled form", and the like of a Substituted-Quinoxaline-Type Piperidine Compound, each of which is encompassed by the invention, is useful as a research and/or diagnostic tool in metabolism pharmacokinetic studies and in binding assays. Examples of isotopes that can be incorporated into a Substituted-Quinoxaline-Type Piperidine Compound of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. Radiolabeled compounds of the invention can be prepared by methods known in the art. For example, tritiated compounds of Formula I can be prepared by introducing tritium into the particular compound of Formula I, for example, by catalytic dehalogenation with tritium. This method can include reacting a suitably halogen-substituted precursor of a compound of Formula (I) or Formula (II) with tritium gas in the presence of a suitable catalyst, for example, Pd/C, in the presence or absence of a base. Other suitable methods for preparing tritiated compounds can be found in Filer, *Isotopes in the Physical and Biomedical Sciences, Vol. 1, Labeled Compounds (Part A)*, Chapter 6 (1987). ^{14}C-labeled compounds can be prepared by employing starting materials having a ^{14}C carbon.

A Substituted-Quinoxaline-Type Piperidine Compound can contain one or more asymmetric centers and can thus give rise to enantiomers, diastereomers, and other stereoisomeric forms. The invention is also meant to encompass all such possible forms as

well as their racemic and resolved forms or any mixture thereof. When a Substituted-Quinoxaline-Type Piperidine Compound contains an olefinic double bond or other center of geometric asymmetry, and unless specified otherwise, it is intended to include all "geometric isomers", *e.g.*, both E and Z geometric isomers. All "tautomers", *e.g.*, ketone-enol, amide-imidic acid, lactam-lactim, enamine-imine, amine-imine, and enamine-enimine tautomers, are intended to be encompassed by the invention as well.

As used herein, the terms "stereoisomer", "stereoisomeric form", and the like are general terms for all isomers of individual molecules that differ only in the orientation of their atoms in space. It includes enantiomers and isomers of compounds with more than one chiral center that are not mirror images of one another ("diastereomers").

The term "chiral center" refers to a carbon atom to which four different groups are attached.

The term "enantiomer" or "enantiomeric" refers to a molecule that is nonsuperimposeable on its mirror image and hence optically active where the enantiomer rotates the plane of polarized light in one direction and its mirror image rotates the plane of polarized light in the opposite direction.

The term "racemic" refers to a mixture of equal parts of enantiomers which is optically inactive.

The term "resolution" refers to the separation or concentration or depletion of one of the two enantiomeric forms of a molecule.

Optical isomers of a Substituted-Quinoxaline-Type Piperidine Compound can be obtained by known techniques such as chiral chromatography or formation of diastereomeric salts from an optically active acid or base.

The phrase "effective amount", when used in connection with a Substituted-Quinoxaline-Type Piperidine Compound, means an amount effective for: (a) treating or preventing a Condition; (b) detectably inhibiting ORL-1 receptor function in a cell; or (c) detectably activating ORL-1 receptor function in a cell.

The phrase "effective amount", when used in connection with a second therapeutic agent means an amount for providing the therapeutic effect of the therapeutic agent.

The terms "modulate", "modulating", and the like as used herein with respect to the ORL-1 receptor mean the mediation of a pharmacodynamic response (*e.g.*, analgesia) in an animal from (i) inhibiting or activating the receptor, or (ii) directly or indirectly affecting the normal regulation of the receptor activity. Compounds that modulate the receptor activity include agonists, partial agonists, antagonists, mixed agonists/antagonists, mixed partial agonists/antagonists and compounds which directly or indirectly affect regulation of the receptor activity.

As used herein, a compound that binds to a receptor and mimics the regulatory effect(s) of an endogenous ligand is defined as an "agonist". As used herein, a compound that binds to a receptor and is only partly effective as an agonist is defined as a "partial agonist". As used herein, a compound that binds to a receptor but produces no regulatory effect, but rather blocks binding of another agent to the receptor is defined as an "antagonist". (*See* Ross and Kenakin, *Pharmacodynamics: Mechanisms of Drug Action and the Relationship Between Drug Concentration and Effect*, Chapter 2 in *Goodman & Gilman's The Pharmacological Basis of Therapeutics* 31-32 (J.G. Hardman, L.E. Limbird and A.Goodman-Gilman eds., 10th ed 2001).

The term "MeOH" means methanol, *i.e.*, methyl alcohol.

The term "EtOH" means ethanol, *i.e.*, ethyl alcohol.

The term "Et_2O" means diethyl ether, *i.e.*, ethoxyethane.

The term "THF" means tetrahydrofuran.

The term "DMF" means *N,N*-dimethylformamide.

The term "DCM" means methylene chloride, *i.e.*, dichloromethane or CH_2Cl_2.

The term "DCE" means dichloroethane.

The term "EtOAc" means ethyl acetate.

The term "MeCN" means acetonitrile.

The term "DMSO" means dimethylsulfoxide, *i.e.*, methylsulfinylmethane.

The term "AcOH" means acetic acid.

The term "NH_4Cl" means ammonium chloride.

The term "NH_4OH" means ammonium hydroxide.

The term "TEA" means triethylamine.

The term "TMA" means trimethylamine.

The term "DIEA" means *N,N*-di-*iso*-propylethylamine or *N*-ethyl-*N*-*iso*-propylpropan-2-amine.

The term "NaH" means sodium hydride.

The term "DMAP" means 4-dimethylaminopyridine.

The term "HOBT" means 1-hydroxybenzotriazole.

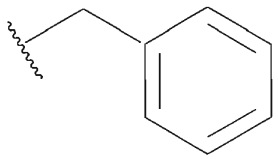
The term "WSCI" means a water soluble carbodiimide, for example, *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide.

The term "DIC" means 1,3-diisopropylcarbodiimide, *i.e.*, *N,N'*-methanediylidenedipropan-2-amine.

The term "TMSCl" means trimethylsilylchloride or $(CH_3)_3SiCl$.

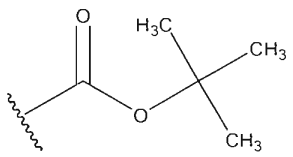
The term "TFFA" means trifluoroacetic anhydride or 2,2,2-trifluoroacetic anhydride.

The term "Bn" means benzyl or



.

The term "BOC" means *tert*-butyloxycarbonyl or



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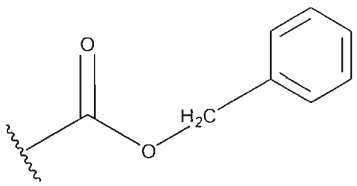
The term "CBZ" means benzyloxycarbonyl or



.

The term "IBD" means inflammatory-bowel disease.

The term "IBS" means irritable-bowel syndrome.

The term "ALS" means amyotrophic lateral sclerosis.

The phrases "treatment of", "treating", and the like include the amelioration or cessation of a Condition or a symptom thereof. In one embodiment, treating includes inhibiting, for example, decreasing the overall frequency of episodes of a Condition or a symptom thereof.

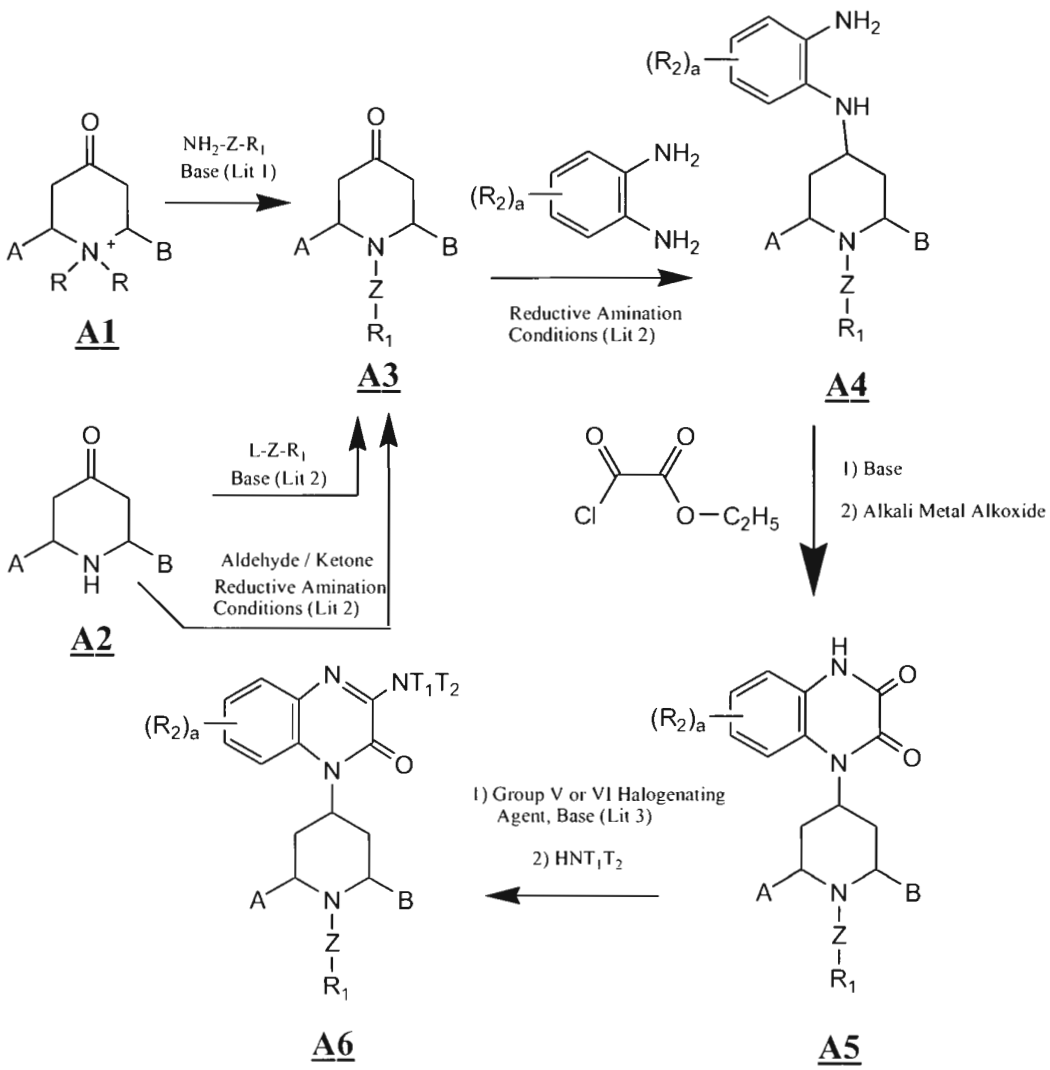
The phrases "prevention of", "preventing", and the like include the avoidance of the onset of a Condition or a symptom thereof.

A "disorder" includes, but is not limited to, the Conditions defined above.

4.4 Methods for Making the Substituted-Quinoxaline-Type Piperidine Compounds

The Substituted-Quinoxaline-Type Piperidine Compounds can be made using conventional organic synthesis, in view of the present disclosure, and including the following illustrative methods shown in the schemes below where R_1, R_2, R_3, R_4, T_1, T_2, T_3, Q, Y_1, Y, Z, A, B, a, and the dashed line are defined above, L is a halogen leaving group such as Br or I, L' is F or Cl, R is -(C_1-C_4)alkyl or -CF_3, R' is -(C_1-C_4)alkyl, and u is the integer 1 or 2.

Scheme A

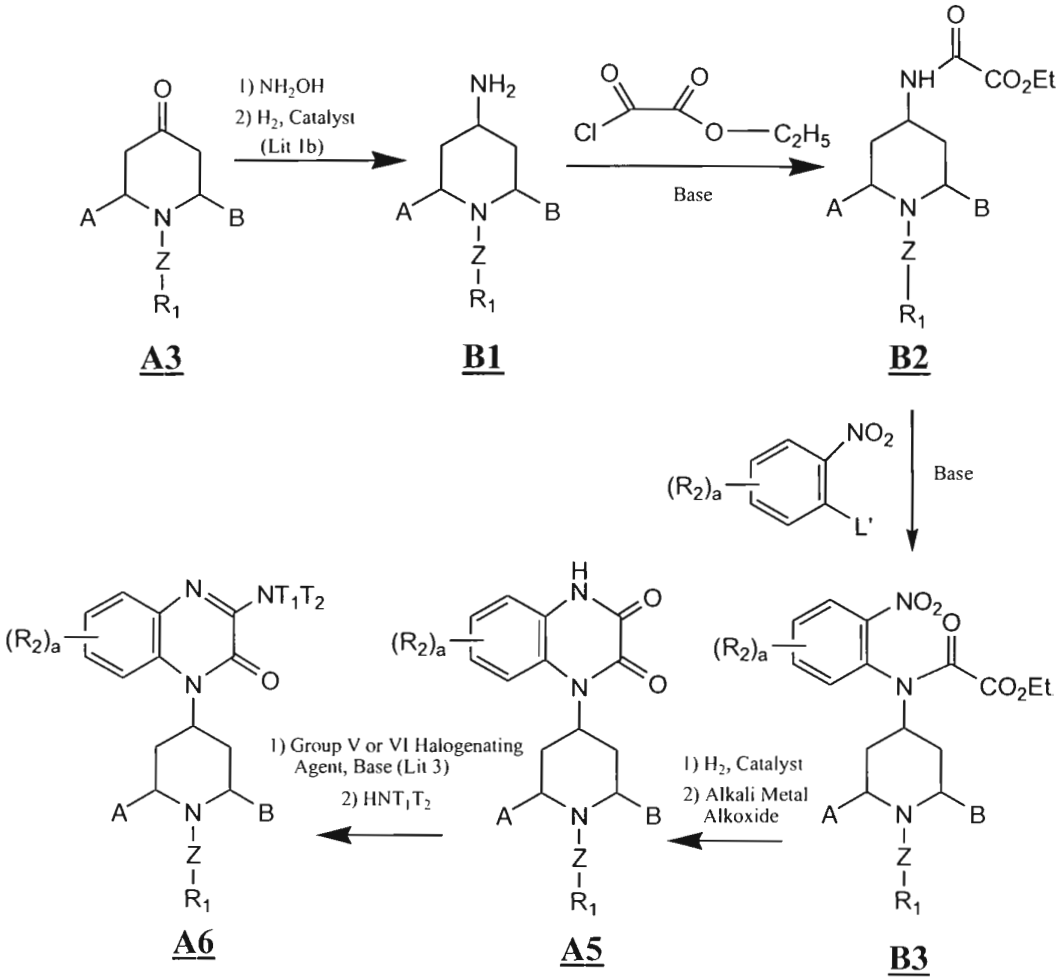


In Scheme A and the other schemes, "Lit 1" refers to the procedures described in the publications D.A. Tortolini and M. A. Poss, *Org. Lett.* 1:1261 (1999) and/or International PCT Publication No. WO 2005/075459 A1 of Euro-Celtique S.A., "Lit 2" refers to the procedures described in U.S. Patent No. 6,635,653 by Goehring *et al.*, and "Lit 3" refers to the procedures described in the publication J. Dudash *et al.*, *Bioorg. Med. Chem. Let.*, 15(21):4793-4796 (2005).

Compounds of formula **A1** and **A2** are commercially available or can be prepared by methods known to the art.

A piperidinium salt of structure **A1** can be reacted with a primary amine in a suitable solvent such as ethanol under reflux conditions in the presence of a base such as potassium carbonate as described in reference "Lit 1" to provide the 1-(substituted)piperidine-4-one compound **A3**. As described in reference "Lit 2," compound **A3** can also be prepared by alkylation of a piperidine-4-one of structure **A2** with an alkyl bromide or alkyl iodide in a suitable solvent such as dimethyl formamide, acetonitrile or dimethyl sulfoxide in the presence of an inorganic base such as potassium carbonate or an organic base such as diisopropylethylamine. As described in reference "Lit 2," compound **A3** can also be prepared by reductive amination of compound **A2** with an aldehyde or ketone using either sodium triacetoxyborohydride or sodium cyanoborohydride in a suitable solvent such as dichloromethane or methanol, respectively. Compound **A3** can then be reductively aminated with a substituted or unsubstituted 1,2-phenylenediamine using sodium triacetoxyborohydride or sodium cyanoborohydride in a suitable solvent such as dichloromethane or methanol, respectively, to provide compound **A4**, as described in reference "Lit 2." Compound **A4** can be dissolved in a suitable solvent such as toluene and reacted with ethyl 2-chloro-2-oxoacetate in the presence of a base such as triethylamine followed by treatment with an alkali metal alkoxide such as sodium ethoxide in a suitable solvent such as methanol or ethanol to provide compound **A5**. Compound **A5** can be dissolved in a suitable solvent such as toluene and, as described in reference "Lit 3," reacted with a group V or VI halogenating agent, such as thionyl chloride, phosphorus oxychloride or phosphorus pentachloride, and a base such as diisopropylethylamine in which an intermediate, believed to comprise a 3-chloroquinoxalin-2-one, is formed then reacted with the desired amine, *e.g.*, HNT_1T_2, to give compound **A6**, as shown in Scheme A.

Scheme B

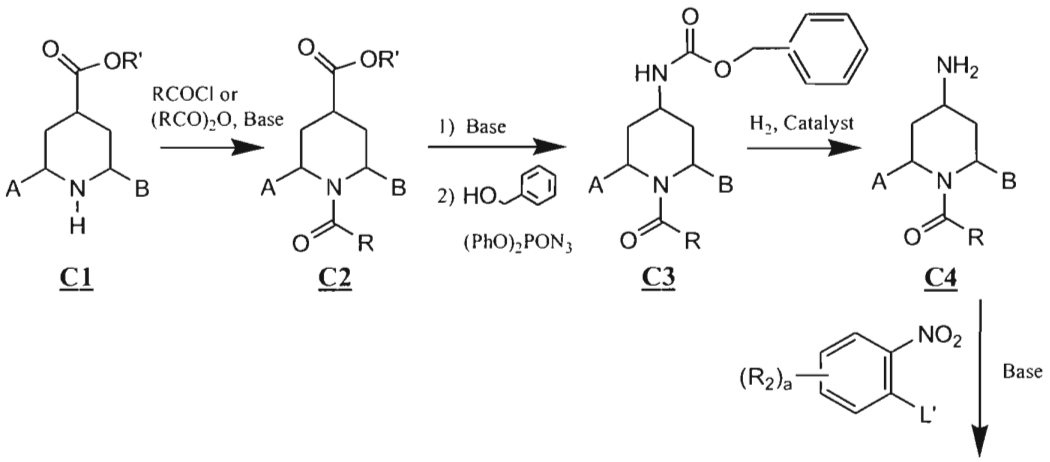


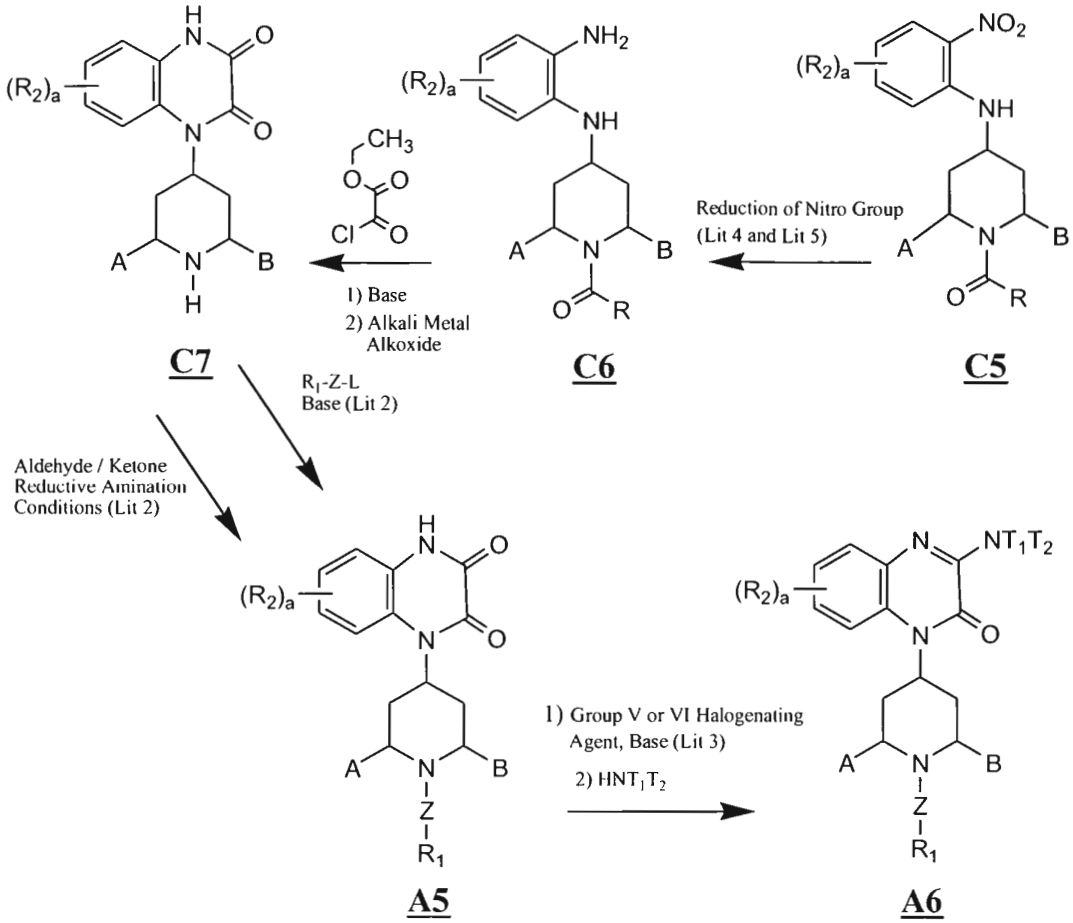
In Scheme B and the other schemes, "Lit 1b" refers to the procedures described in International PCT Publication No. WO 2005/075459 A1 of Euro-Celtique S.A.

As described in reference "Lit 1b," compound **A3** can be reacted with 50% aqueous hydroxylamine in a suitable solvent such as hexanes to provide an intermediate hydroxylamine which can be converted to an oxime by dehydration in a suitable solvent such as toluene under reflux conditions using a Dean-Stark apparatus. The oxime intermediate can be reduced to the primary amine compound **B1** by catalytic hydrogenation using a catalyst such as rhodium on alumina in a suitable solvent such as ethanol under a hydrogen atmosphere at a pressure of 1atm or greater in a suitable apparatus such as a Parr Hydrogenator according to reference "Lit 1b." Compound **B1** can be reacted with ethyl 2-chloro-2-oxoacetate in the presence of a base such as triethylamine to provide compound **B2**. Compound **B2** can be reacted with a

substituted or unsubstituted 2-halo-1-nitrobenzene (where the halo is fluoride or chloride) in the presence of a base such as potassium carbonate in a suitable solvent such as acetonitrile under reflux conditions to provide compound **B3**. Compound **B3** can be treated with a hydrogenation catalyst such as Raney nickel in a suitable solvent such as ethanol under a hydrogen atmosphere, and the product immediately treated with an alkali metal alkoxide such as sodium ethoxide in a suitable solvent such as methanol or ethanol to provide compound **A5**, which can be converted to compound **A6** as described in Scheme A.

Scheme C



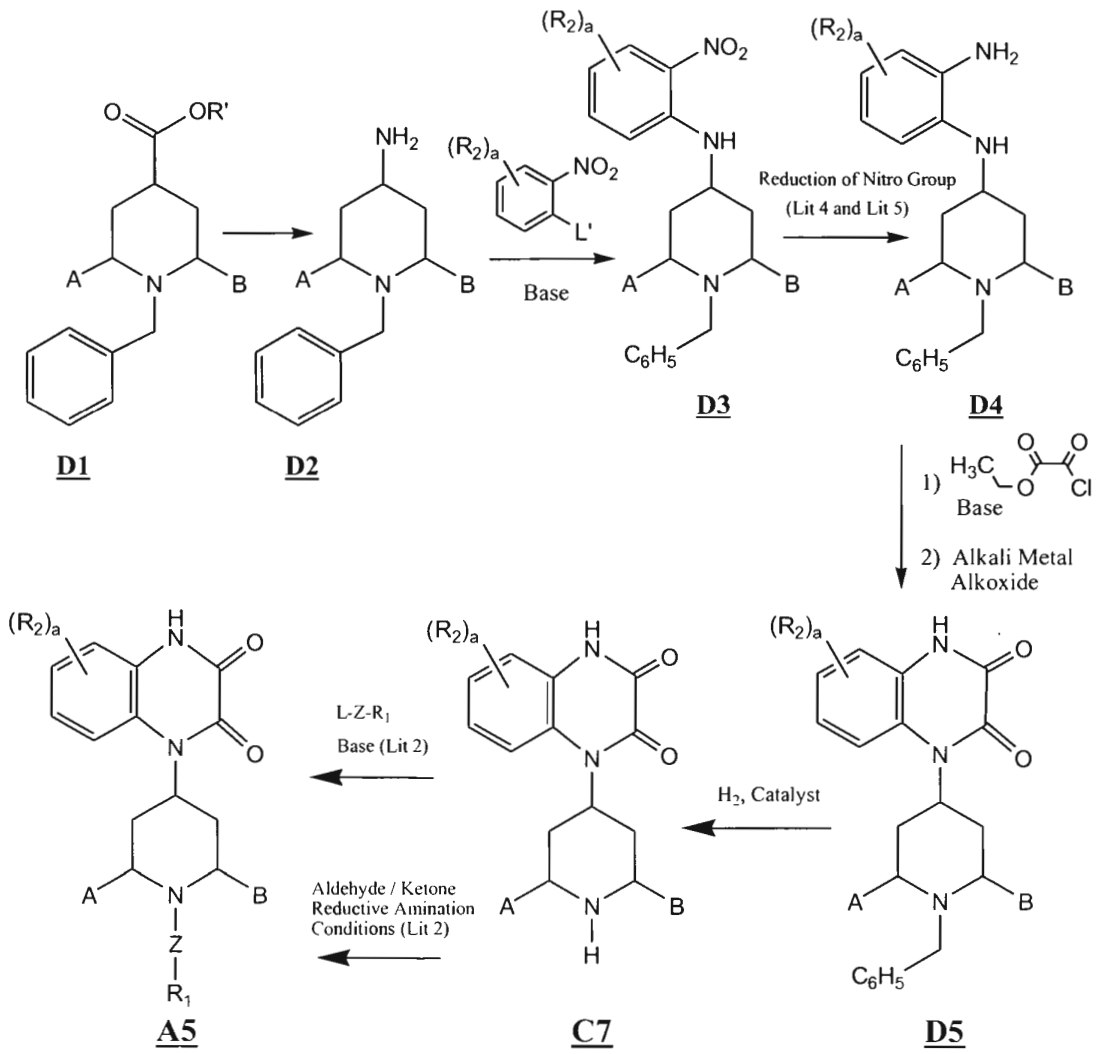


In Scheme C and the other schemes, "Lit 4" refers to the reference P.N. Rylander, *Hydrogenation Methods*, Academic Press, 104-116 (1994), which provides a review of the methods available for the reduction of nitro groups, and "Lit 5" refers to the Zinin reduction procedures described in the reference Porter, *Organic Reactions*, 20:455-481 (1973).

The compound of formula **C1** is commercially available or can be prepared by methods known to the art. Compound **C1** can be reacted with an acid chloride RCOCl, such as 2,2,2-trifluoroacetyl chloride, or anhydride $(RCO)_2O$, such as 2,2,2-trifluoroacetic anhydride, and a base such as triethylamine in a suitable solvent such as dichloromethane or tetrahydrofuran to provide compound **C2**. Compound **C2** can be converted to compound **C3** in a two step procedure by hydrolysis of the ester to the carboxylic acid using an appropriate base such as aqueous NaOH, followed by treatment with diphenyl phosphorazidate ("$(PhO)_2P(=O)N_3$") and phenylmethanol ("BnOH") under Curtius rearrangement conditions. The benzyloxycarbonyl group of compound **C3** can then be removed under hydrogenolysis conditions using a noble metal catalyst, *e.g.*, palladium on carbon, under a hydrogen

atmosphere, to provide compound **C4**. Compound **C4** can be reacted with a substituted or unsubstituted 2-halo-1-nitrobenzene (where the halo is fluoride or chloride) (similar to steps described in Scheme B) to provide compound **C5**. In the next step, compound **C5** can be converted to compound **C6** using a catalyst such as Raney nickel in a suitable solvent such as ethanol under a hydrogen atmosphere as described in reference "Lit 4." Compound **C5** can also be converted to compound **C6** by chemical means, such as with Zn, Sn(II) chloride or Fe, or using sulfides or polysulfides by the Zinin Reduction as described in reference "Lit 5." Compound **C6** can then be treated with ethyl 2-chloro-2-oxoacetate and a base such as triethylamine in a suitable solvent such as toluene, followed by treatment with an alkali metal alkoxide such as sodium ethoxide in a suitable solvent such as ethanol to provide compound **C7**. Compound **A5** can be prepared by alkylation of compound **C7** with an alkyl bromide or alkyl iodide or by reductive amination of compound **C7** with an aldehyde or ketone, each as described in Scheme A. Thereafter, compound **A5** can be converted to compound **A6** as described in Scheme A.

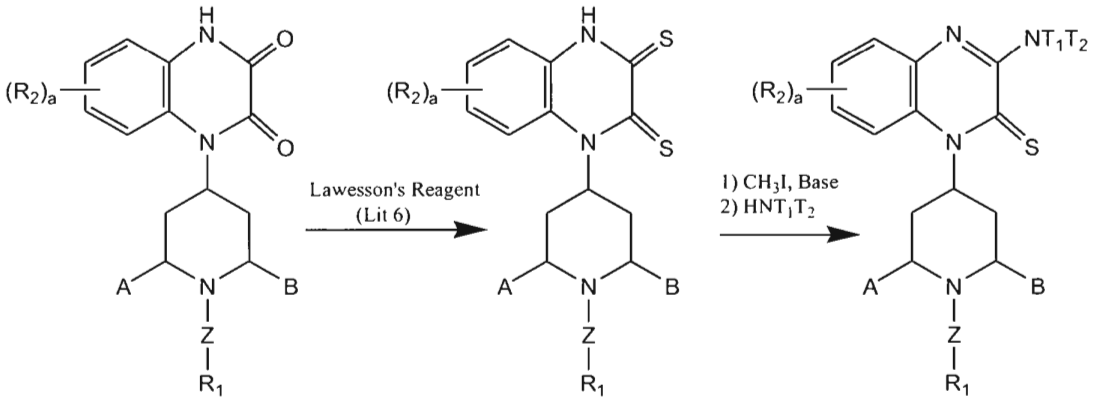
Scheme D



The compound of formula **D1** is commercially available or can be prepared from compound **C1** by methods known to the art. Compound **D2** can be prepared from compound **D1** in a similar manner to the preparation of compound **C4** from compound **C1** in Scheme C. Compound **D2** can be reacted with a substituted or unsubstituted 2-halo-1-nitrobenzene (where the halo is fluoride or chloride) (similar to steps described in Scheme B) to provide compound **D3**. In the next step (similar to steps described in Scheme B), compound **D3** can be converted to compound **D4** by treatment with a hydrogenation catalyst such as Raney nickel in a suitable solvent such as ethanol under a hydrogen atmosphere, or by chemical means using a reducing agent such as Zn, Sn(II) chloride or Fe, or using sulfide or polysulfides by the Zinin Reduction as described in Scheme C. Thereafter (similar to steps described in Scheme A), compound **D4** can be treated with ethyl 2-chloro-2-oxoacetate in the presence of a base such as triethylamine

followed by treatment with an alkali metal alkoxide such as sodium ethoxide in a suitable solvent such as ethanol to provide compound **D5**. Compound **D5** can be hydrogenolyzed using a noble metal catalyst, *e.g.*, palladium on carbon, in a suitable solvent such as methanol or ethanol under a hydrogen atmosphere to provide compound **C7**. Compound **A5** can be prepared by alkylation of compound **C7** with an alkyl bromide or alkyl iodide or by reductive amination of compound **C7** with an aldehyde or ketone (similar to steps described in Scheme A). Thereafter, compound **A5** can be converted to compound **A6** as described in Scheme A.

Scheme E

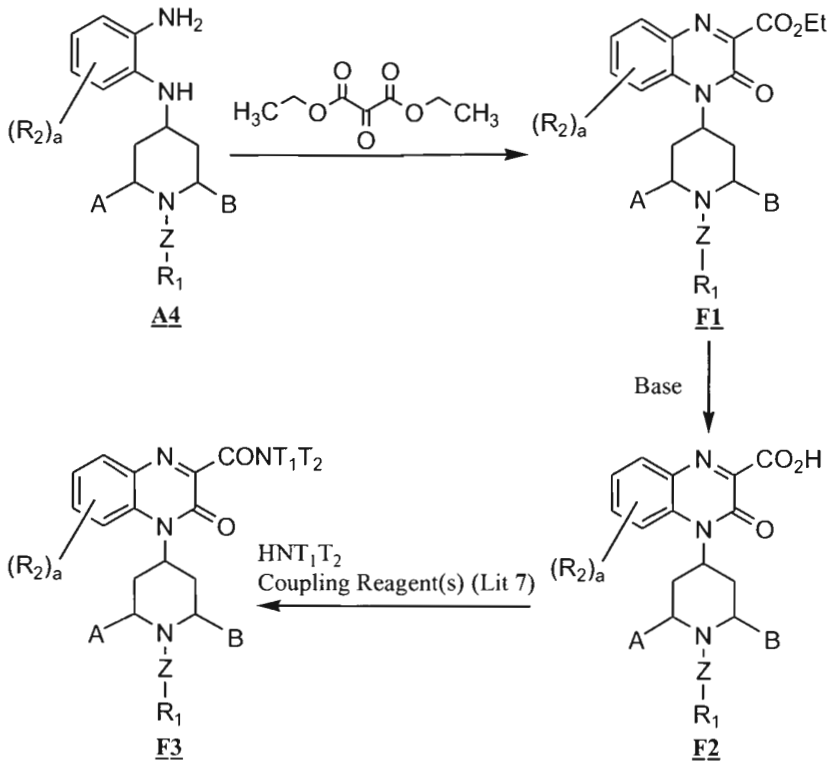


A5 **E1** **E2**

In Scheme E and the other schemes, "Lit 6" refers to the reference S.O. Lawesson *et al.*, *Bull. Soc. Chim. Belg.*, 86:679 (1977).

Compound **E1**, comprising a quinoxaline-2,3(1*H*,4*H*)-dithione, can be made by, *e.g.*, reacting Compound **A5** (*i.e.*, comprising a quinoxaline-2,3(1*H*,4*H*)-dione) with Lawesson's reagent (*i.e.*, 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide) according to the procedure described in reference "Lit 6." In one embodiment, Compound **E1** can be made by reacting Compound **A5** with Lawesson's reagent in a nonpolar solvent such as THF or toluene at a temperature of about 100°C for about 2-3 hours, as shown above. Thereafter, compound **E2** can be obtained from compound **E1** in an analogous manner as described in Scheme A for obtaining compound **A6** from compound **A5** except that methyl iodide is used in place of thionyl chloride.

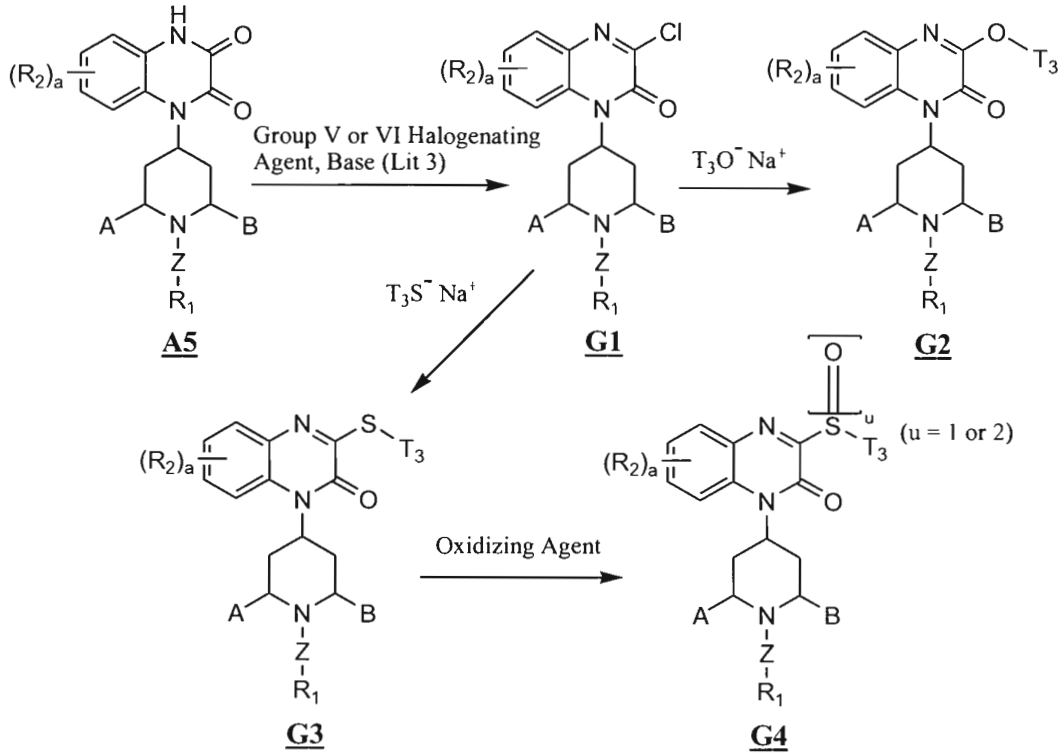
Scheme F



In Scheme F and the other schemes, "Lit 7" refers to the references *Biochem. Biophys. Res. Commun.* 63:99 (1975) and/or *Science* 211:586 (1981).

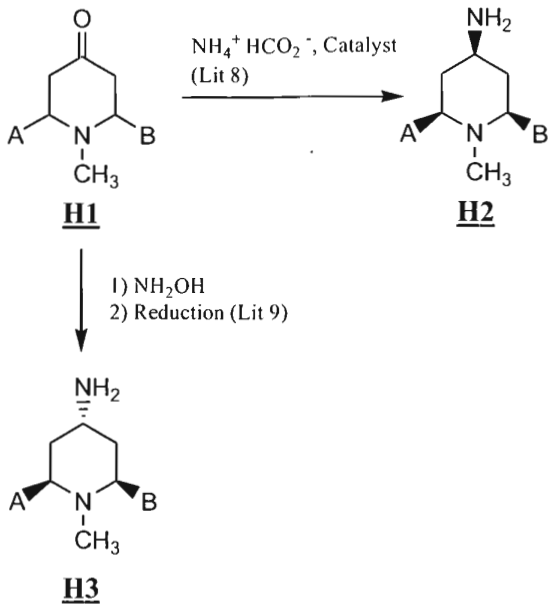
Compound **A4** and diethyl 2-oxomalonate can be dissolved in a solvent with a high boiling point, such as toluene or xylene, and heated under reflux conditions with azeotropic removal of water to provide compound **F1**. Compound **F1** can be hydrolyzed to the carboxylic acid **F2** by treatment with a base, such as aqueous NaOH, in a solvent under appropriate conditions, such as methanol or ethanol at a temperature from about 0°C to about 25°C. Upon completion of hydrolysis, the reaction mixture is neutralized, *e.g.*, with dilute HCl, to provide compound **F2**. Compound **F2** can be converted to amide derivative **F3** by treatment with a coupling agent, such as *N*-(3,3-dimethylaminopropyl)-*N'*-ethylcarbodiimide and triethylamine, and the desired amine, *e.g.*, HNT_1T_2 shown in the scheme, in a solvent, such as DMF, to provide compound **F3**, *e.g.*, according to the procedure described in reference "Lit 7."

Scheme G



Compound **G1** can be obtained by chlorinating compound **A5**, *e.g.*, by adding a chlorinating agent, such as thionyl chloride, phosphorus oxychloride or phosphorus pentachoride, to a mixture of compound **A5**, DMF, and a base such as triethylamine in a solvent with a high boiling point, such as toluene or xylene, under reflux conditions such as is described in reference "Lit 3." Compound **G1** can be converted to compound **G2** by reacting the former with the desired alkoxide, *e.g.*, a sodium alkoxide, in a solvent, such as tetrahydrofuran, DMF or an alcohol of the alkoxide, to provide compound **G2**. In a similar manner but with the desired thioalkoxide, *e.g.*, a sodium thioalkoxide, compound **G1** can be converted to compound **G3**, comprising a thioalkoxide, in a suitable solvent to provide compound **G3**. Compound **G3** can be oxidized to the sulfoxide (u=1) or sulfone (u=2) of compound **G4** by reacting compound **G3** with an oxidizing agent, such as oxone, in a suitable solvent, *e.g.*, as described in K.S. Webb, "A Mild, Inexpensive, and Practical Oxidation of Sulfides," *Tetrahedron Let.*, 35(21):3457-3460 (1994).

Scheme H

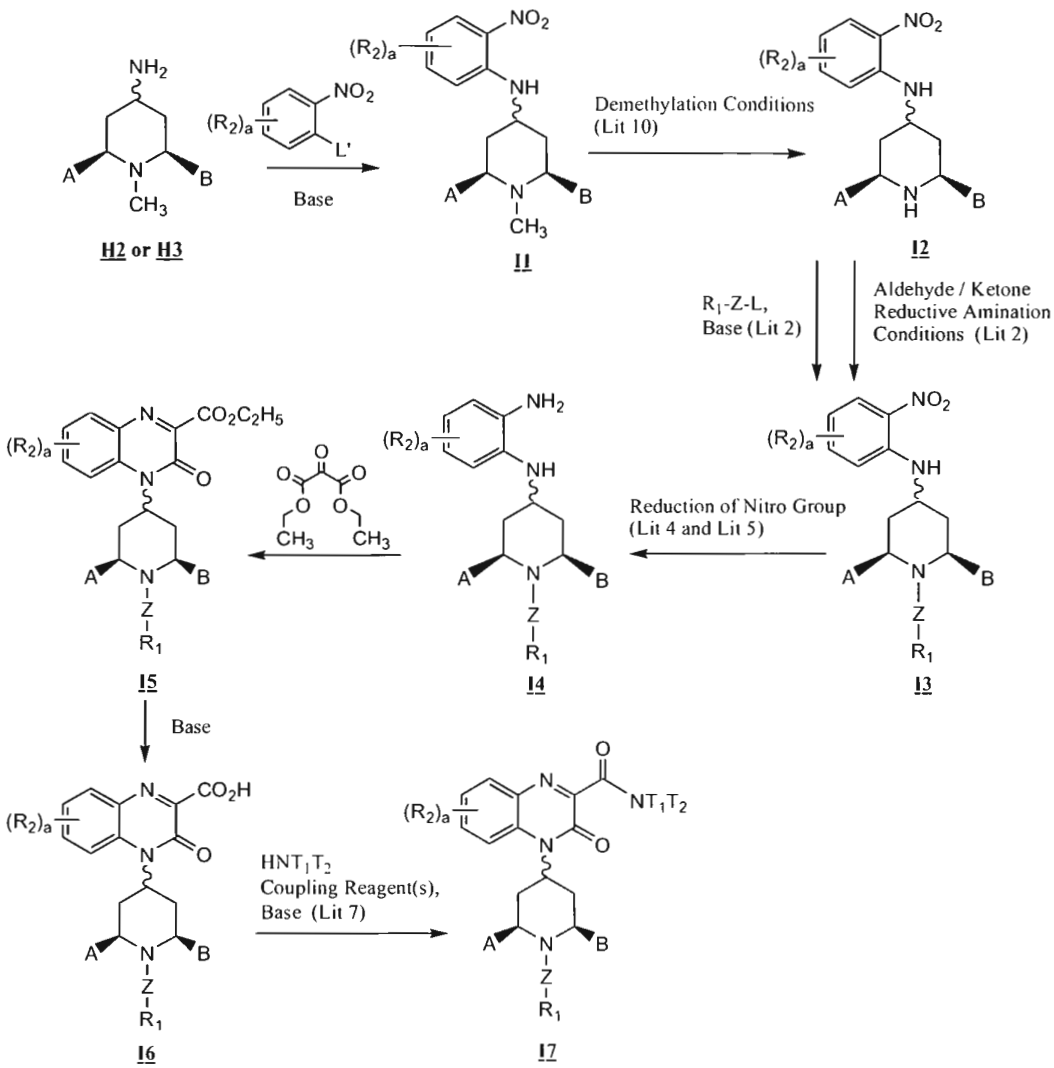


In Scheme H and the other schemes, "Lit 8" refers to "A Modified Palladium Catalyzed Reductive Amination Procedure," M. Allegretti *et al.*, *Tetrahedron Let.*, 58:5669-5674 (2002) and "Lit 9 refers to "Molecular Features Associated with Polyamine Modulation of NMDA Receptors," A.H. Lewin *et al.*, *J. Med. Chem.* 41:988-995 (1998).

The compound of formula **H1**, wherein substituent groups A and B together form a bridge, *e.g.*, a two carbon bridge, is commercially available or can be prepared by methods known to the art.

When substituent groups A and B together form a bridge, *e.g.*, a two carbon bridge, compound **H1** can be converted to compound **H2**, the "*endo*" isomer, under reductive amination conditions using, *e.g.*, ammonium formate and a noble metal catalyst, *e.g.*, palladium on carbon, in a solvent such as ethanol or methanol as described in reference "Lit 8." Similarly, where substituent groups A and B together form a bridge, *e.g.*, a two carbon bridge, compound **H1** can be reacted with aqueous hydroxylamine in a solvent such as hexanes to form an intermediate hydroxylamine, which can be converted to its oxime by dehydration in a solvent with a high boiling point such as toluene, under Dean-stark conditions. The oxime intermediate can be converted to compound **H3**, the "*exo*" isomer, by reduction using, *e.g.*, sodium in propanol as described in reference "Lit 9."

Scheme I

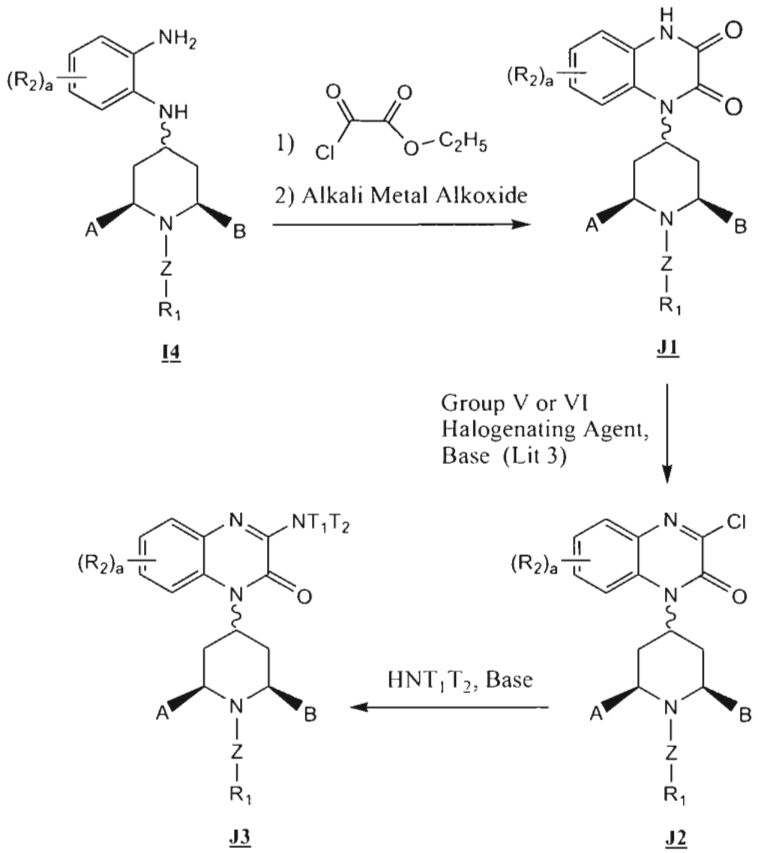


In Scheme I and the other schemes, "Lit 10" refers to the procedures described by R.A. Olofson *et al.* in *J. Org. Chem.*, 49:2081-2082 (1984) and to R.A. Olofson *et al.* in *Tetrahedron Let.*, 18:1571 (1977).

Substituted-Quinoxaline-Type Piperidine Compounds such as **I6** and **I7** where substituent groups A and B together form a bridge, *e.g.*, a two carbon bridge, can be prepared as described in Scheme I. Compound **H2** (the "*endo*" isomer) or **H3** (the "*exo*" isomer) (where substituent groups A and B together form a bridge, *e.g.*, a two carbon bridge) can be converted to compound **I1** by reaction with a substituted or unsubstituted 2-halo-1-nitrobenzene (where the halo is fluoride or chloride) and a base such as potassium carbonate, in a suitable solvent

such as DMF or acetonitrile at a temperature from about 20°C to about 100°C. Compound **I1** can be demethylated to give compound **I2** using, *e.g.*, 1-chloromethylchloroformate in a solvent such as 1,2-dichloroethane, followed by treatment with methanol as described in "Lit 10." Compound **I2** can be converted to compound **I3** (similar to steps described in reference "Lit 2" in Scheme A). Compound **I3** can be converted to compound **I4** by hydrogenation using a catalyst under a hydrogen atmosphere or by chemical means using a reducing agent (similar to steps described in references "Lit 4" and "Lit 5" in Scheme C). Compound **I4** can be converted to compound **I5** by reaction with diethyl 2-oxomalonate in a solvent with a high boiling point such as toluene or xylene under reflux conditions. Compound **I5** can be converted to the carboxylic acid derivative **I6** by hydrolysis using a base such as aqueous NaOH in a suitable solvent such as methanol or ethanol, followed by neutralization using an acid such as dilute HCl. Compound **I6** can be converted to compound **I7** by reaction with a coupling agent (similar to steps described in reference "Lit 7" in Scheme F).

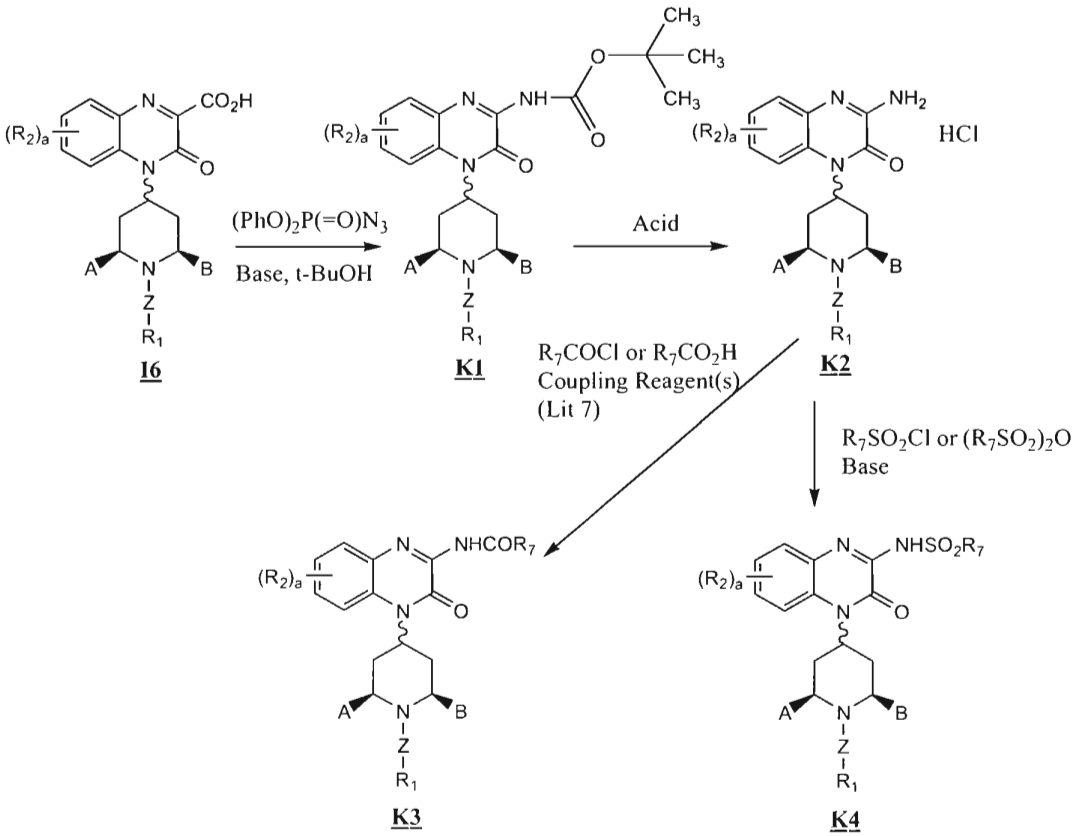
Scheme J



Substituted-Quinoxaline-Type Piperidine Compounds such as **J3** where substituent groups A

and B together form a bridge, *e.g.*, a two carbon bridge, can be prepared as described in Scheme J. Compound **I4** (where substituent groups A and B together form a bridge, *e.g.*, a two carbon bridge, and Compound **I4** may exist as either an "*endo*" isomer an "*exo*" isomer or a mixture of "*endo/exo*" isomers) can be converted to compound **J1**, as shown in Scheme J, by reaction with ethyl 2-chloro-2-oxoacetate and a base such as triethylamine in a suitable solvent such as dichloromethane, followed by reaction with an alkali metal alkoxide, using the procedures described in Scheme A. These "*endo*" and "*exo*" isomers can be conveniently separated by flash column chromatography. Compound **J1** can be converted to compound **J3**, through compound **J2** (similar to steps described previously in Scheme A).

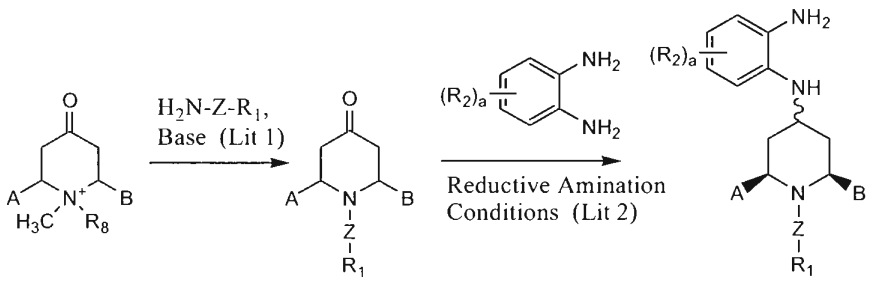
Scheme K



Substituted-Quinoxaline-Type Piperidine Compounds such as **K2**, **K3** and **K4** where substituent groups A and B together form a bridge, *e.g.*, a two carbon bridge, can be prepared as described in Scheme K. Compound **I6** (where substituent groups A and B together form a bridge, *e.g.*, a two carbon bridge, and Compound **I6** may exist as either an "*endo*" isomer an "*exo*" isomer or a mixture of "*endo/exo*" isomers) can be converted to compound **K1**, as shown in Scheme K, using diphenylphosporyl azide and t-butanol under Curtius Rearrangement

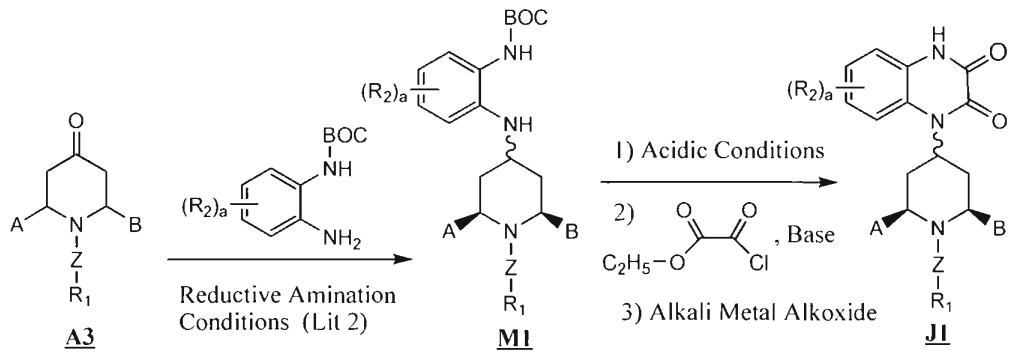
Conditions (similar to steps described in Scheme C). The *tert*-butoxycarbonyl group in compound **K1** can be removed using acid conditions such as HCl in a solvent such as dioxane or ether to give compound **K2** as the hydrochloride salt. Compound **K2** can be converted to compound **K3** using an acid chloride R_7COCl and a base such as triethylamine in a suitable solvent such as dichloromethane or DMF, or using a carboxylic acid R_7COOH, a coupling reagent such as *N*-(3,3-dimethylaminopropyl)-*N'*-ethylcarbodiimide, a base such as triethylamine in a suitable solvent such as DMF as described in the literature references in Scheme F. Compound **K2** can be converted to compound **K4** using an alkyl or aryl sulfonyl chloride such as methanesulfonyl chloride or sulfonic acid anhydride such as trifluoromethylsulfonic anhydride, a base such as triethylamine, in a suitable solvent such as dichloromethane.

Scheme L



Compound **I4** can be prepared, as shown in Scheme L, from compound **A1** (similar to steps described in Scheme A). Where substituent groups A and B of compound **I4** form a bridge, *e.g.*, a two carbon bridge, the two isomers, "*exo*" and "*endo*," can be separated by chromatography and can be separately converted to compounds such as **A5**, **A6**, **F2**, **F3**, and the like as described earlier in Schemes A, B, and F.

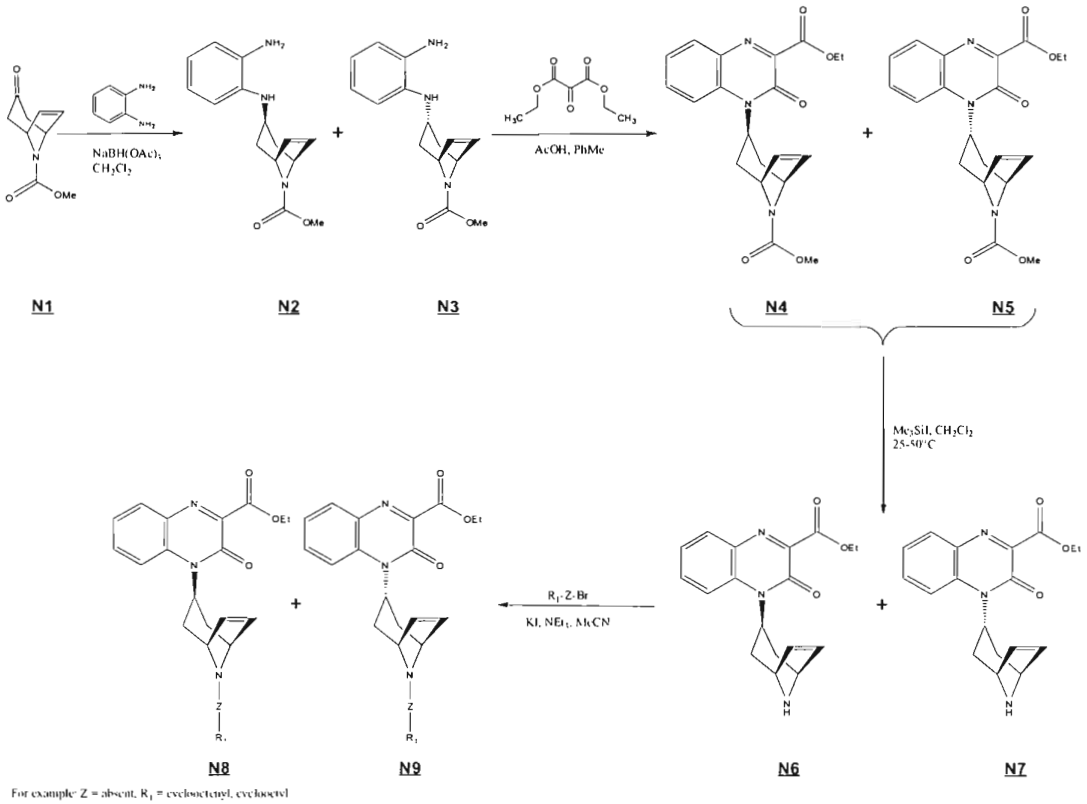
Scheme M



As shown in Scheme M, compound **A3** can be converted to compound **M1** under reductive

amination conditions using a BOC protected, substituted or unsubstituted 1,2-phenylenediamine and a reducing agent such as sodium triacetoxyborohydride or sodium cyanoborohydride in a suitable solvent such as dichloromethane or methanol respectively as described in reference "Lit 2." The BOC protecting group can be removed using acidic conditions, such as using HCl or 2,2,2-trifluoroacetic acid, to give an intermediate which can be converted to compound **J1** in a two step procedure using ethyl 2-chloro-2-oxoacetate and a base such as triethylamine, followed by reaction with an alkali metal alkoxide such as sodium ethoxide in a suitable solvent such as ethanol. Where substituent groups A and B together form a bridge, *e.g.*, a two carbon bridge, the "*exo*" and "*endo*" isomers which result can be conveniently separated using flash column chromatography.

Scheme N



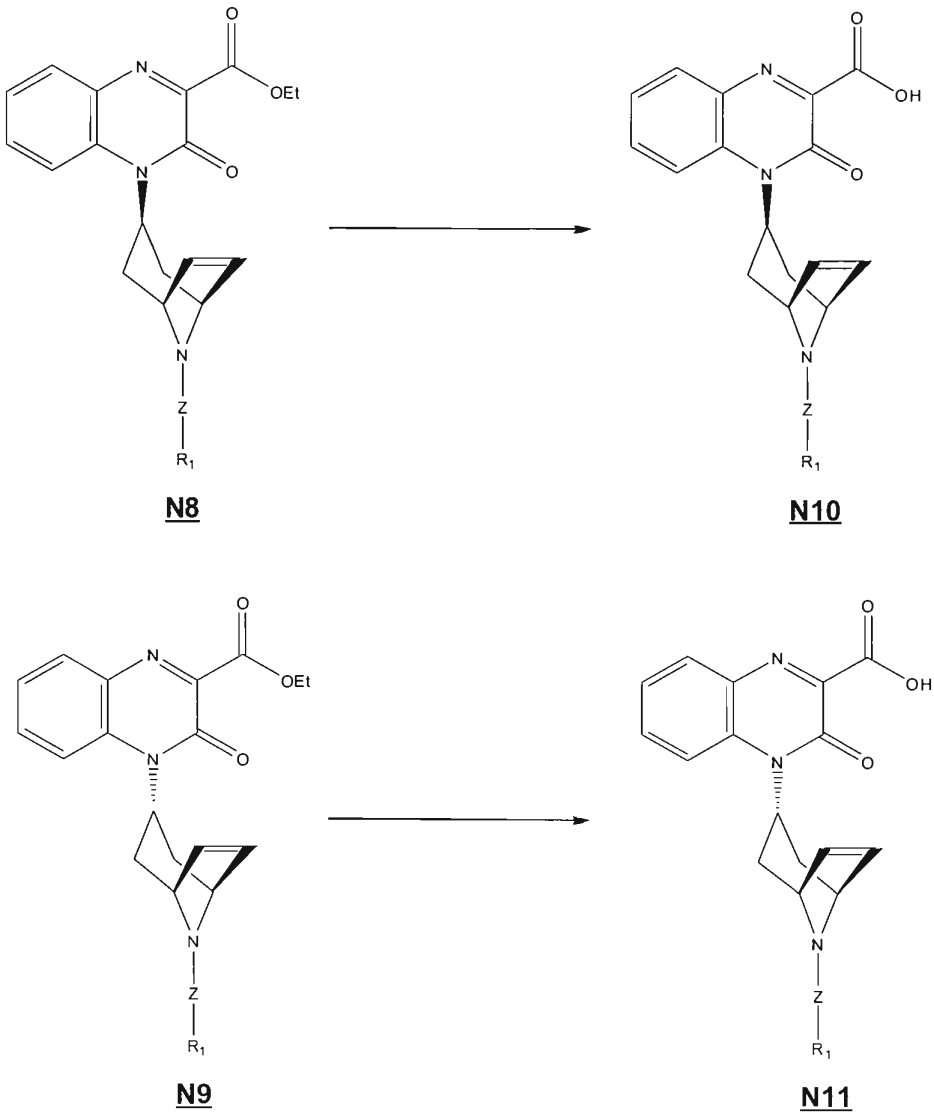
For example: Z = absent, R_1 = cyclooctanyl, cyclooctyl

Scheme N shows the conversion of the literature compound **N1** to intermediates **N8** and **N9**.

3-Oxo-8-aza-bicyclo[3.2.1]oct-6-ene-8-carboxylic acid methyl ester **N1** can be prepared according to the literature procedure discribed in N.Cramer; S.Laschat; A.Baro; W.Frey; Syn. Lett., (2003), 14, 2175-2177.

This intermediate **N1** can be reacted with 1,2-phenylene-diamine under reductive amination conditions using sodium triacetoxyborohydride in dichloromethane to give the coupled products 3-(2-amino-phenylamino)-8-aza-bicyclo[3.2.1]oct-6-ene-8-carboxylic acid methyl esters **N2** and **N3** as a mixture of endo and exo isomers which can be taken to the next step without purification. Compounds **N2** and **N3** can be dissolved in toluene and acetic acid to which diethyl ketomalonate can be added and the mixture can be heated under reflux. Purification of the reaction mixture by column chromatography gives 4-(8-methoxycarbonyl-8-aza-bicyclo[3.2.1]oct-6-en-3-yl-3-oxo-3,4-dihydro-quinoxaline-2-carboxylic acid ethyl esters **N4** and **N5** as a mixture of endo and exo esters which can be purified by chromatography. The methyl carbamate group can be removed from **N4** and **N5** using iodo trimethylsilane in dichloromethane to give 4-(8-aza-bicyclo[3.2.1]oct-6-en-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid ethyl esters **N6** and **N7** as a mixture of exo and endo isomers. Intermediates **N6** and **N7** can be alkylated with various alkyl bromides and iodides such as 3-bromo-cyclooctene and a catalytic amount of potassium iodide and triethylamine in a solvent such as acetonitrile to give isomers **N8** and **N9** which can be separated by column chromatography. Finally hydrolysis of the ester group can be achieved using sodium hydroxide in aqueous ethanol to give the carboxylic acids **N10** and **N11** as shown in Scheme O.

Scheme O



for example: Z = absent, R_1 = cyclooctenyl, cyclooctyl

4.5 Therapeutic Uses of the Substituted-Quinoxaline-Type Piperidine Compounds

In accordance with the invention, the Substituted-Quinoxaline-Type Piperidine Compounds are administered to an animal in need of treatment or prevention of a Condition.

In one embodiment, an effective amount of a Substituted-Quinoxaline-Type Piperidine Compound can be used to treat or prevent any condition treatable or preventable by inhibiting the activity of the ORL-1 receptor. Examples of Conditions that are treatable or preventable by

inhibiting the activity of the ORL-1 receptor include, but are not limited to, pain (CNS effect), memory disorders, obesity, constipation, depression, dementia, and Parkinsonism.

In another embodiment, an effective amount of a Substituted-Quinoxaline-Type Piperidine Compound can be used to treat or prevent any condition treatable or preventable by activating the ORL-1 receptor. Examples of Conditions that are treatable or preventable by activating the ORL-1 receptor include, but are not limited to, pain (PNS effect), anxiety, cough, diarrhea, blood pressure disorder (via vasodilation and via diuresis), epilepsy, anorexia/cachexia, urinary incontinence, and drug abuse.

The Substituted-Quinoxaline-Type Piperidine Compounds can be used to treat or prevent acute or chronic pain. Examples of pain that can be treated or prevented using a Substituted-Quinoxaline-Type Piperidine Compound include, but are not limited to, cancer pain, neuropathic pain, labor pain, myocardial infarction pain, pancreatic pain, colic pain, post-operative pain, headache pain, muscle pain, arthritic pain, and pain associated with a periodontal disease, including gingivitis and periodontitis.

The Substituted-Quinoxaline-Type Piperidine Compounds can also be used to treat or prevent pain associated with inflammation or with an inflammatory disease in an animal. Such pain can arise where there is an inflammation of the body tissue which can be a local inflammatory response or a systemic inflammation. For example, a Substituted-Quinoxaline-Type Piperidine Compound can be used to treat or prevent pain associated with inflammatory diseases including, but not limited to, organ transplant rejection; reoxygenation injury resulting from organ transplantation (see Grupp *et al.*, *J. Mol, Cell Cardiol.* 31:297-303 (1999)) including, but not limited to, transplantation of the heart, lung, liver, or kidney; chronic inflammatory diseases of the joints, including arthritis, rheumatoid arthritis, osteoarthritis and bone diseases associated with increased bone resorption; inflammatory bowel diseases, such as ileitis, ulcerative colitis, Barrett's syndrome, and Crohn's disease; inflammatory lung diseases, such as asthma, adult respiratory distress syndrome, and chronic obstructive airway disease; inflammatory diseases of the eye, including corneal dystrophy, trachoma, onchocerciasis, uveitis, sympathetic ophthalmitis and endophthalmitis; chronic inflammatory disease of the gum, including gingivitis and periodontitis; tuberculosis; leprosy; inflammatory diseases of the kidney, including uremic complications, glomerulonephritis and nephrosis; inflammatory disease of the skin, including sclerodermatitis, psoriasis and eczema; inflammatory diseases of the central nervous system, including chronic demyelinating diseases of the nervous system,

multiple sclerosis, AIDS-related neurodegeneration and Alzheimer 's disease, infectious meningitis, encephalomyelitis, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and viral or autoimmune encephalitis; autoimmune diseases, including Type I and Type II diabetes mellitus; diabetic complications, including, but not limited to, diabetic cataract, glaucoma, retinopathy, nephropathy (such as microaluminuria and progressive diabetic nephropathy), gangrene of the feet, atherosclerotic coronary arterial disease, peripheral arterial disease, nonketotic hyperglycemic-hyperosmolar coma, foot ulcers, joint problems, and a skin or mucous membrane complication (such as an infection, a shin spot, a candidal infection or necrobiosis lipoidica diabeticorum), immune-complex vasculitis, and systemic lupus erythematosus (SLE); inflammatory disease of the heart, such as cardiomyopathy, ischemic heart disease hypercholesterolemia, and artherosclerosis; as well as various other diseases that can have significant inflammatory components, including preeclampsia, chronic liver failure, brain and spinal cord trauma, and cancer. A Substituted-Quinoxaline-Type Piperidine Compound can also be used to treat or prevent pain associated with inflammatory disease that can, for example, be a systemic inflammation of the body, exemplified by gram-positive or gram negative shock, hemorrhagic or anaphylactic shock, or shock induced by cancer chemotherapy in response to pro-inflammatory cytokines, *e.g.*, shock associated with pro-inflammatory cytokines. Such shock can be induced, *e.g.*, by a chemotherapeutic agent that is administered as a treatment for cancer.

The Substituted-Quinoxaline-Type Piperidine Compounds can also be used to treat or prevent pain associated with nerve injury (*i.e.*, neuropathic pain). Chronic neuropathic pain is a heterogenous disease state with an unclear etiology. In chronic neuropathic pain, the pain can be mediated by multiple mechanisms. This type of pain generally arises from injury to the peripheral or central nervous tissue. The syndromes include pain associated with spinal cord injury, multiple sclerosis, post-herpetic neuralgia, trigeminal neuralgia, phantom pain, causalgia, and reflex sympathetic dystrophy and lower back pain. The chronic pain is different from acute pain in that chronic neuropathic pain patients suffer the abnormal pain sensations that can be described as spontaneous pain, continuous superficial burning and/or deep aching pain. The pain can be evoked by heat-, cold-, and mechano-hyperalgesia, or by heat-, cold-, or mechano-allodynia.

Chronic neuropathic pain can be caused by injury or infection of peripheral sensory nerves. It includes, but is not limited to, pain from peripheral nerve trauma, herpes virus

infection, diabetes mellitus, causalgia, plexus avulsion, neuroma, limb amputation, and vasculitis. Neuropathic pain can also be caused by nerve damage from chronic alcoholism, human immunodeficiency virus infection, hypothyroidism, uremia, or vitamin deficiencies. Stroke (spinal or brain) and spinal cord injury can also induce neuropathic pain. Cancer-related neuropathic pain results from tumor growth compression of adjacent nerves, brain, or spinal cord. In addition, cancer treatments, including chemotherapy and radiation therapy, can cause nerve injury. Neuropathic pain includes but is not limited to pain caused by nerve injury such as, for example, the pain from which diabetics suffer.

The Substituted-Quinoxaline-Type Piperidine Compounds can be used to treat or prevent a migraine including, but not limited to, migraine without aura ("common migraine"), migraine with aura ("classic migraine"), migraine without headache, basilar migraine, familial hemiplegic migraine, migrainous infarction, and migraine with prolonged aura.

According to the invention, some of the Substituted-Quinoxaline-Type Piperidine Compounds are agonists at the ORL-1 receptor, some of the Substituted-Quinoxaline-Type Piperidine Compounds are partial agonists at the ORL-1 receptor, and some of the Substituted-Quinoxaline-Type Piperidine Compounds are antagonists at the ORL-1 receptor. In another embodiment, a Substituted-Quinoxaline-Type Piperidine Compound is an agonist at the ORL-1 receptor and an agonist at a μ, κ and/or δ opioid receptor, particularly at a μ opioid receptor. In another embodiment, a Substituted-Quinoxaline-Type Piperidine Compound is a partial agonist at the ORL-1 receptor and an agonist at a μ, κ and/or δ opioid receptor, particularly at a μ opioid receptor. In another embodiment, a Substituted-Quinoxaline-Type Piperidine Compound is an antagonist at the ORL-1 receptor and an agonist at a μ, κ and/or δ opioid receptor, particularly at a μ opioid receptor. In another embodiment, a Substituted-Quinoxaline-Type Piperidine Compound is an agonist at the ORL-1 receptor and an antagonist at a μ, κ and/or δ opioid receptor, particularly at a μ opioid receptor. In another embodiment, a Substituted-Quinoxaline-Type Piperidine Compound is a partial agonist at the ORL-1 receptor and an antagonist at a μ, κ and/or δ opioid receptor, particularly at a μ opioid receptor. In another embodiment, a Substituted-Quinoxaline-Type Piperidine Compound is an antagonist at the ORL-1 receptor and an antagonist at a μ, κ and/or δ opioid receptor, particularly at a μ opioid receptor.

The invention also provides methods for inhibiting ORL-1 receptor function in a cell, comprising contacting a cell capable of expressing the ORL-1 receptor with an amount of a

Substituted-Quinoxaline-Type Piperidine Compound effective to inhibit ORL-1 receptor function in the cell. This method can be adapted for use *in vitro* as part of an assay to select compounds that can be useful for treating or preventing a Condition in an animal. Alternatively, this method can be adapted for use *in vivo*, (*i.e.*, in an animal such as a human) by contacting a cell in the animal with an effective amount of a Substituted-Quinoxaline-Type Piperidine Compound. In one embodiment, the method is useful for treating or preventing pain in an animal in need of such treatment or prevention. In another embodiment, the method is useful for treating or preventing a memory disorder, obesity, constipation, depression, dementia, or Parkinsonism in an animal in need of such treatment or prevention.

The invention also relates to methods for activating ORL-1 receptor function in a cell, comprising contacting a cell capable of expressing the ORL-1 receptor with an amount of a Substituted-Quinoxaline-Type Piperidine Compound effective to activate ORL-1 receptor function in the cell. This method can be adapted for use *in vitro* as part of an assay to select compounds useful for treating or preventing, pain, anxiety, cough, diarrhea, high blood pressure, epilepsy, anorexia/cachexia, urinary incontinence, or drug abuse. Alternatively, the method can be adapted for use *in vivo* (*i.e.*, in an animal such as a human), by contacting a cell in the animal with an effective amount of a Substituted-Quinoxaline-Type Piperidine Compound. In one embodiment the method is useful for treating or preventing pain in an animal in need of such treatment or prevention. In another embodiment, the method is useful for treating or preventing anxiety, cough, diarrhea, high blood pressure, epilepsy, anorexia/chachexia, urinary incontinence, or drug abuse in an animal in need of such treatment or prevention.

Examples of tissue comprising cells capable of expressing the ORL-1 receptor include but are not limited to brain, spinal cord, vas deferens, and gastrointestinal tract tissue. Methods for assaying cells that express the ORL-1 receptor are known in the art; for example, see Y. Shimohigashi *et al.*, "Sensitivity of opioid receptor-like receptor ORL1 for chemical modification on nociceptin, a naturally occurring nociceptive peptide," *J. Biol. Chem.* 271(39):23642-23645 (1996); M. Narita *et al.*, "Identification of the G-protein coupled ORL1 receptor in the mouse spinal cord by [^{35}S]-GTPγS binding and immunohistochemistry," *Brit. J. Pharmacol.* 128:1300-1306 (1999); G. Milligan, "Principles: Extending then utility of [^{35}S]GTPγS binding assays," *TIPS* 14:110-112 (2003): and S. Lazareno, "Measurement of

agonist-stimulated [^{35}S]GTPγS binding to cell membranes," *Methods in Molecular Biology* Vol. 106:231245 (1999).

4.6 Therapeutic/Prophylactic Administration and Compositions of the Invention

Due to their activity, the Substituted-Quinoxaline-Type Piperidine Compounds are advantageously useful in human and veterinary medicine. As described above, the Substituted-Quinoxaline-Type Piperidine Compounds are useful for treating or preventing a Condition in an animal in need thereof. The Substituted-Quinoxaline-Type Piperidine Compounds of the invention can be administered to any animal requiring modulation of the opioid and/or ORL-1 receptors.

When administered to an animal, a Substituted-Quinoxaline-Type Piperidine Compound can be administered as a component of a composition that comprises a pharmaceutically acceptable carrier or excipient. The invention compositions, which comprise a Substituted-Quinoxaline-Type Piperidine Compound, can be administered orally. A Substituted-Quinoxaline-Type Piperidine Compound can also be administered by any other convenient route, for example, by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral, rectal, and intestinal mucosa, etc.) and can be administered together with a second therapeutically active agent. Administration can be systemic or local. Various delivery systems are known, *e.g.*, encapsulation in liposomes, microparticles, microcapsules, multiparticulates, capsules, etc., and can be used to administer a Substituted-Quinoxaline-Type Piperidine Compound.

Methods of administration include, but are not limited to, intradermal, intramuscular, intraperitoneal, parenteral, intravenous, subcutaneous, intranasal, epidural, oral, sublingual, intracerebral, intravaginal, transdermal, rectal, by inhalation, or topical, particularly to the ears, nose, eyes, or skin. The method of administration is left to the discretion of the practitioner. In most instances, administration will result in the release of a Substituted-Quinoxaline-Type Piperidine Compound into the bloodstream.

In specific embodiments, it can be desirable to administer a Substituted-Quinoxaline-Type Piperidine Compound locally. This can be achieved, for example and not by way of limitation, by local infusion during surgery, topical application, *e.g.*, in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository

or enema, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers.

In certain embodiments, it can be desirable to introduce a Substituted-Quinoxaline-Type Piperidine Compound into the central nervous system or gastrointestinal tract by any suitable route, including intraventricular, intrathecal, and epidural injection, and enema. Intraventricular injection can be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir.

Pulmonary administration can also be employed, *e.g.*, by use of an inhaler or nebulizer, and formulation with an aerosolizing agent, or via perfusion in a fluorocarbon or synthetic pulmonary surfactant. In certain embodiments, a Substituted-Quinoxaline-Type Piperidine Compound can be formulated as a suppository, with traditional binders and excipients such as triglycerides.

When a Substituted-Quinoxaline-Type Piperidine Compound of the invention is incorporated for parenteral administration by injection (*e.g.*, continuous infusion or bolus injection), the formulation for parenteral administration can be in the form of a suspension, solution, emulsion in an oily or aqueous vehicle, and such formulations can further comprise pharmaceutically necessary additives such as one or more stabilizing agents, suspending agents, dispersing agents, and the like. A Substituted-Quinoxaline-Type Piperidine Compound of the invention can also be in the form of a powder for reconstitution as an injectable formulation.

In another embodiment, a Substituted-Quinoxaline-Type Piperidine Compound can be delivered in a vesicle, in particular a liposome (*see* Langer, *Science* 249:1527-1533 (1990); and Treat *et al.*, *Liposomes in the Therapy of Infectious Disease and Cancer* 317-327 and 353-365 (1989)).

In yet another embodiment, a Substituted-Quinoxaline-Type Piperidine Compound can be delivered in a controlled-release system or sustained-release system (*see*, *e.g.*, Goodson, "Dental Applications" (pp. 115-138) in *Medical Applications of Controlled Release, Vol. 2, Applications and Evaluation*, R.S. Langer and D.L. Wise eds., CRC Press (1984)). Other controlled- or sustained-release systems discussed in the review by Langer, *Science* 249:1527-1533 (1990) can be used. In one embodiment, a pump can be used (Langer, *Science* 249:1527-1533 (1990); Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987); Buchwald *et al.*, *Surgery*

88:507 (1980); and Saudek *et al.*, *N. Engl. J. Med.* 321:574 (1989)). In another embodiment, polymeric materials can be used (*see Medical Applications of Controlled Release* (Langer and Wise eds., 1974); *Controlled Drug Bioavailability, Drug Product Design and Performance* (Smolen and Ball eds., 1984); Ranger and Peppas, *J. Macromol. Sci. Rev. Macromol. Chem.* 23:61 (1983); Levy *et al.*, *Science* 228:190 (1985); During *et al.*, *Ann. Neurol.* 25:351 (1989); and Howard *et al.*, *J. Neurosurg.* 71:105 (1989)). In yet another embodiment, a controlled- or sustained-release system can be placed in proximity of a target of a Substituted-Quinoxaline-Type Piperidine Compound, *e.g.*, the spinal column, brain, or gastrointestinal tract, thus requiring only a fraction of the systemic dose.

The invention compositions can optionally comprise a suitable amount of a pharmaceutically acceptable excipient so as to provide the form for proper administration to the animal. Such a pharmaceutical excipient can be a diluent, suspending agent, solubilizer, binder, disintegrant, preservative, coloring agent, lubricant, and the like. The pharmaceutical excipient can be a liquid, such as water or an oil, including those of petroleum, animal, vegetable, or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil, and the like. The pharmaceutical excipient can be saline, gum acacia, gelatin, starch paste, talc, keratin, colloidal silica, urea, and the like. In addition, auxiliary, stabilizing, thickening, lubricating, and coloring agents can be used. In one embodiment, the pharmaceutically acceptable excipient is sterile when administered to an animal. Water is a particularly useful excipient when a Substituted-Quinoxaline-Type Piperidine Compound is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid excipients, particularly for injectable solutions. Suitable pharmaceutical excipients also include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene glycol, water, ethanol, and the like. The invention compositions, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. Specific examples of pharmaceutically acceptable carriers and excipients that can be used to formulate oral dosage forms are described in the *Handbook of Pharmaceutical Excipients*, American Pharmaceutical Association (1986).

The invention compositions can take the form of solutions, suspensions, emulsions, tablets, pills, pellets, capsules, capsules containing liquids, powders, sustained-release formulations, suppositories, emulsions, aerosols, sprays, suspensions, or any other form

suitable for use. In one embodiment, the composition is in the form of a capsule (*see, e.g.*, U.S. Patent No. 5,698,155). Other examples of suitable pharmaceutical excipients are described in *Remington's Pharmaceutical Sciences* 1447-1676 (Alfonso R. Gennaro ed., 19th ed. 1995), incorporated herein by reference.

In one embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds are formulated in accordance with routine procedures as a composition adapted for oral administration to human beings. A Substituted-Quinoxaline-Type Piperidine Compound to be orally delivered can be in the form of tablets, capsules, gelcaps, caplets, lozenges, aqueous or oily solutions, suspensions, granules, powders, emulsions, syrups, or elixirs, for example. When a Substituted-Quinoxaline-Type Piperidine Compound is incorporated into oral tablets, such tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, multiply compressed or multiply layered. Techniques and compositions for making solid oral dosage forms are described in *Pharmaceutical Dosage Forms: Tablets* (Lieberman, Lachman and Schwartz, eds., 2nd ed.) published by Marcel Dekker, Inc. Techniques and compositions for making tablets (compressed and molded), capsules (hard and soft gelatin) and pills are also described in *Remington's Pharmaceutical Sciences* 1553-1593 (Arthur Osol, ed., 16th ed., Mack Publishing, Easton, PA 1980).

Liquid oral dosage forms include aqueous and nonaqueous solutions, emulsions, suspensions, and solutions and/or suspensions reconstituted from non-effervescent granules, optionally containing one or more suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, coloring agents, flavoring agents, and the like. Techniques and composition for making liquid oral dosage forms are described in *Pharmaceutical Dosage Forms: Disperse Systems*, (Lieberman, Rieger and Banker, eds.) published by Marcel Dekker, Inc.

When a Substituted-Quinoxaline-Type Piperidine Compound is to be injected parenterally, it can be, *e.g.*, in the form of an isotonic sterile solution. Alternatively, when a Substituted-Quinoxaline-Type Piperidine Compound is to be inhaled, it can be formulated into a dry aerosol or can be formulated into an aqueous or partially aqueous solution.

An orally administered Substituted-Quinoxaline-Type Piperidine Compound can contain one or more agents, for example, sweetening agents such as fructose, aspartame or saccharin; flavoring agents such as peppermint, oil of wintergreen, or cherry; coloring agents; and preserving agents, to provide a pharmaceutically palatable preparation. Moreover, where

in tablet or pill form, the compositions can be coated to delay disintegration and absorption in the gastrointestinal tract thereby providing a sustained action over an extended period of time. Selectively permeable membranes surrounding an osmotically active driving compound are also suitable for orally administered compositions. In these latter platforms, fluid from the environment surrounding the capsule is imbibed by the driving compound, which swells to displace the agent or agent composition through an aperture. These delivery platforms can provide an essentially zero order delivery profile as opposed to the spiked profiles of immediate release formulations. A time-delay material such as glycerol monostearate or glycerol stearate can also be used. Oral compositions can include standard excipients such as mannitol, lactose, starch, magnesium stearate, sodium saccharin, cellulose, and magnesium carbonate. In one embodiment, the excipients are of pharmaceutical grade.

In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds can be formulated for intravenous administration. Typically, compositions for intravenous administration comprise sterile isotonic aqueous buffer. Where necessary, the compositions can also include a solubilizing agent. A Substituted-Quinoxaline-Type Piperidine Compound for intravenous administration can optionally include a local anesthetic such as benzocaine or prilocaine to lessen pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampule or sachette indicating the quantity of active agent. Where a Substituted-Quinoxaline-Type Piperidine Compound is to be administered by infusion, it can be dispensed, for example, with an infusion bottle containing sterile pharmaceutical grade water or saline. Where a Substituted-Quinoxaline-Type Piperidine Compound is administered by injection, an ampule of sterile water for injection or saline can be provided so that the ingredients can be mixed prior to administration.

A Substituted-Quinoxaline-Type Piperidine Compound can be administered by controlled-release or sustained-release means or by delivery devices that are known to those in the art. Examples include, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; and 5,733,566, each of which is incorporated herein by reference. Such dosage forms can be used to provide controlled- or sustained-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other

polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, multiparticulates, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled- or sustained-release formulations known to those in the art, including those described herein, can be readily selected for use with the active ingredients of the invention. The invention thus encompasses single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled- or sustained-release.

Controlled- or sustained-release pharmaceutical compositions can have a common goal of improving drug therapy over that achieved by their non-controlled or non-sustained-release counterparts. In one embodiment, a controlled- or sustained-release composition comprises a minimal amount of a Substituted-Quinoxaline-Type Piperidine Compound to treat or prevent the Condition or a symptom thereof in a minimum amount of time. Advantages of controlled- or sustained-release compositions include extended activity of the drug, reduced dosage frequency, and increased compliance. In addition, controlled- or sustained-release compositions can favorably affect the time of onset of action or other characteristics, such as blood levels of the Substituted-Quinoxaline-Type Piperidine Compound, and can thus reduce the occurrence of adverse side effects.

Controlled- or sustained-release compositions can initially release an amount of a Substituted-Quinoxaline-Type Piperidine Compound that promptly produces the desired therapeutic or prophylactic effect, and gradually and continually release other amounts of the Substituted-Quinoxaline-Type Piperidine Compound to maintain this level of therapeutic or prophylactic effect over an extended period of time. To maintain a constant level of the Substituted-Quinoxaline-Type Piperidine Compound in the body, the Substituted-Quinoxaline-Type Piperidine Compound can be released from the dosage form at a rate that will replace the amount of Substituted-Quinoxaline-Type Piperidine Compound being metabolized and excreted from the body. Controlled- or sustained-release of an active ingredient can be stimulated by various conditions, including but not limited to, changes in pH, changes in temperature, concentration or availability of enzymes, concentration or availability of water, or other physiological conditions or compounds.

The amount of the Substituted-Quinoxaline-Type Piperidine Compound that is effective for the treatment or prevention of a Condition can be determined by standard clinical techniques. In addition, *in vitro* and/or *in vivo* assays can optionally be employed to help

identify optimal dosage ranges. The precise dose to be employed will also depend on, *e.g.*, the route of administration and the seriousness of the Condition, and can be decided according to the judgment of a practitioner and/or each animal's circumstances. In other examples thereof, variations will necessarily occur depending upon the weight and physical condition (*e.g.*, hepatic and renal function) of the animal being treated, the affliction to be treated, the severity of the symptoms, the frequency of the dosage interval, the presence of any deleterious side-effects, and the particular compound utilized, among other things.

Suitable effective dosage amounts, however, range from about 0.01mg/kg of body weight to about 3000mg/kg of body weight of the animal per day, although they are typically from about 0.01mg/kg of body weight to about 2500mg/kg of body weight of the animal per day or from about 0.01mg/kg of body weight to about 1000mg/kg of body weight of the animal per day. In one embodiment, the effective dosage amount is about 100mg/kg of body weight of the animal per day or less. In another embodiment, the effective dosage amount ranges from about 0.01mg/kg of body weight to about 100mg/kg of body weight of the animal per day of a Substituted-Quinoxaline-Type Piperidine Compound, in another embodiment, about 0.02mg/kg of body weight to about 50mg/kg of body weight of the animal per day, and in another embodiment, about 0.025mg/kg of body weight to about 20mg/kg of body weight of the animal per day.

Administration can be as a single dose or as a divided dose. In one embodiment, an effective dosage amount is administered about every 24hr until the Condition is abated. In another embodiment, an effective dosage amount is administered about every 12hr until the Condition is abated. In another embodiment, an effective dosage amount is administered about every 8hr until the Condition is abated. In another embodiment, an effective dosage amount is administered about every 6hr until the Condition is abated. In another embodiment, an effective dosage amount is administered about every 4hr until the Condition is abated. The effective dosage amounts described herein refer to total amounts administered; that is, if more than one Substituted-Quinoxaline-Type Piperidine Compound is administered, the effective dosage amounts correspond to the total amount administered.

Where a cell capable of expressing the ORL-1 receptor, the μ-opioid receptor, the κ-opioid receptor and/or the δ-opioid receptor is contacted with a Substituted-Quinoxaline-Type Piperidine Compound *in vitro*, the amount effective for inhibiting or activating that receptor function in a cell will typically range from about 10^{-12} mol/L to about 10^{-4} mol/L, in one

embodiment, from about 10^{-12} mol/L to about 10^{-5} mol/L, in another embodiment, from about 10^{-12} mol/L to about 10^{-6} mol/L, and in another embodiment, from about 10^{-12} mol/L to about 10^{-9} mol/L of a solution or suspension of a pharmaceutically acceptable carrier or excipient. In one embodiment, the volume of solution or suspension comprising the Substituted-Quinoxaline-Type Piperidine Compound will be from about 0.01μL to about 1mL. In another embodiment, the volume of solution or suspension will be about 200μL.

The Substituted-Quinoxaline-Type Piperidine Compounds will have a binding affinity (K_i) for the human ORL-1 receptor of about 1000nM or less in one embodiment, or about 500nM or less in another embodiment, about 100nM or less in another embodiment, about 50nM or less in another embodiment, or about 20nM or less in another embodiment, or about 5nM or less in another embodiment. The binding affinity K_i can be measured in ways known to the art, *e.g.*, by an assay utilizing membranes from recombinant HEK-293 cells expressing the ORL-1 receptor.

Typically, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 300 or less for binding to ORL-1 receptors. In one embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a Ki (nM) of about 100 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a Ki (nM) of about 35 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a Ki (nM) of about 20 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a Ki (nM) of about 15 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a Ki (nM) of about 10 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a Ki (nM) of about 4 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a Ki (nM) of about 1 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a Ki (nM) of about 0.4 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a Ki (nM) of about 0.1 or less.

ORL-1 GTP EC_{50} is the concentration of a compound providing 50% of the maximal response for the compound at an ORL-1 receptor. Substituted-Quinoxaline-Type Piperidine Compounds typically will have an ORL-1 GTP EC_{50} (nM) of about 5000 or less to stimulate

ORL-1 receptor function. In one embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have an ORL-1 GTP EC_{50} (nM) of about 1000 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have an ORL-1 GTP EC_{50} (nM) of about 100 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have an ORL-1 GTP EC_{50} (nM) of about 80 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have an ORL-1 GTP EC_{50} (nM) of about 50 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have an ORL-1 GTP EC_{50} (nM) of about 35 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have an ORL-1 GTP EC_{50} (nM) of about 15 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have an ORL-1 GTP EC_{50} (nM) of about 10 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have an ORL-1 GTP EC_{50} (nM) of about 4 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have an ORL-1 GTP EC_{50} (nM) of about 1 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have an ORL-1 GTP EC_{50} (nM) of about 0.4 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have an ORL-1 GTP EC_{50} (nM) of about 0.1 or less.

ORL-1 GTP Emax (%) is the maximal effect elicited by a compound relative to the effect elicited by nociceptin, a standard ORL-1 agonist. Typically, a Substituted-Quinoxaline-Type Piperidine Compound of the invention acting as an agonist will have an ORL-1 GTP Emax (%) of about 50% or greater. In one embodiment, agonist Substituted-Quinoxaline-Type Piperidine Compounds will have an ORL-1 GTP Emax (%) of about 75% or greater. In another embodiment, agonist Substituted-Quinoxaline-Type Piperidine Compounds will have an ORL-1 GTP Emax (%) of about 85% or greater. In another embodiment, agonist Substituted-Quinoxaline-Type Piperidine Compounds will have an ORL-1 GTP Emax (%) of about 95% or greater. In another embodiment, agonist Substituted-Quinoxaline-Type Piperidine Compounds will have an ORL-1 GTP Emax (%) of about 100% or greater. Typically, a Substituted-Quinoxaline-Type Piperidine Compound of the invention acting as a partial agonist will have an ORL-1 GTP Emax (%) of less than about 10%. In one embodiment, partial agonist Substituted-Quinoxaline-Type Piperidine Compounds will have an ORL-1 GTP Emax (%) of less than about 20%. In another embodiment, partial agonist

Substituted-Quinoxaline-Type Piperidine Compounds will have an ORL-1 GTP Emax (%) of less than about 30%. In another embodiment, partial agonist Substituted-Quinoxaline-Type Piperidine Compounds will have an ORL-1 GTP Emax (%) of less than about 40%. In another embodiment, partial agonist Substituted-Quinoxaline-Type Piperidine Compounds will have an ORL-1 GTP Emax (%) of less than about 50%.

The Substituted-Quinoxaline-Type Piperidine Compounds will have a binding affinity (Ki) for the human μ-opioid receptors of about 1000nM or less in one embodiment, or about 500nM or less in another embodiment, about 100nM or less in another embodiment, about 50nM or less in another embodiment, or about 20nM or less in another embodiment, or about 5nM or less in another embodiment.

Typically, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 3000 or less for binding to μ-opioid receptors. In one embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a Ki (nM) of about 1000 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a Ki (nM) of about 650 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a Ki (nM) of about 525 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a Ki (nM) of about 250 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a Ki (nM) of about 100 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a Ki (nM) of about 10 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a Ki (nM) of about 1 or less.

μ GTP EC_{50} is the concentration of a compound providing 50% of the maximal response for the compound at a μ-opioid receptor. Substituted-Quinoxaline-Type Piperidine Compounds typically will have a μ GTP EC_{50} (nM) of about 5000 or less to stimulate μ-opioid receptor function. In one embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a μ GTP EC_{50} (nM) of about 4100 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a μ GTP EC_{50} (nM) of about 3100 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a μ GTP EC_{50} (nM) of about 2000 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine

Compounds of the invention will have a μ GTP EC_{50} (nM) of about 1000 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a μ GTP EC_{50} (nM) of about 100 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a μ GTP EC_{50} (nM) of about 10 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a μ GTP EC_{50} (nM) of about 1 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a μ GTP EC_{50} (nM) of about 0.4 or less.

μ GTP Emax (%) is the maximal effect elicited by a compound relative to the effect elicited by DAMGO, a standard μ agonist. Typically, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a μ GTP Emax (%) of about 10% or greater. In one embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a μ GTP Emax (%) of about 20% or greater. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a μ GTP Emax (%) of about 50% or greater. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a μ GTP Emax (%) of about 65% or greater. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a μ GTP Emax (%) of about 75% or greater. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a μ GTP Emax (%) of about 88% or greater.

Typically, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 20,000 or less for κ receptors. In one embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have substantially no activity. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 10,000 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 5000 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 1000 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 500 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 300 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 100 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 50 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine

Compounds will have a Ki (nM) of about 20 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 15 or less.

κ GTP EC_{50} is the concentration of a compound providing 50% of the maximal response for the compound at a κ receptor. Substituted-Quinoxaline-Type Piperidine Compounds typically will have a κ GTP EC_{50} (nM) of about 20,000 or less to stimulate κ opioid receptor function. In one embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 10,000 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 5000 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 2000 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 1500 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 800 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 500 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 300 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 100 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 50 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 25 or less.

κ GTP Emax (%) is the maximal effect elicited by a compound relative to the effect elicited by U69,593. Typically, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a κ GTP Emax (%) of about 10% or greater. In one embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a κ GTP Emax (%) of about 15% or greater. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a κ GTP Emax (%) of about 30% or greater. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a κ GTP Emax (%) of about 40% or greater. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a κ GTP Emax (%) of about 45% or greater. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a κ GTP Emax (%) of about 75% or greater. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a κ GTP Emax (%) of about 90% or greater.

Typically, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 20,000 or less for δ receptors. In one embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have substantially no activity. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 10,000 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 9000 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 7500 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 6500 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 5000 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 3000 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 2500 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 1000 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 500 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 350 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 250 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 100 or less.

δ GTP EC_{50} is the concentration of a compound providing 50% of the maximal response for the compound at a δ receptor. Substituted-Quinoxaline-Type Piperidine Compounds typically will have a δ GTP EC_{50} (nM) of about 20,000 or less to stimulate δ opioid receptor function. In one embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a δ GTP EC_{50} (nM) of about 10,000 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a δ GTP EC_{50} (nM) of about 1000 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a δ GTP EC_{50} (nM) of about 100 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a δ GTP EC_{50} (nM) of about 90 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a δ GTP EC_{50} (nM) of about 50 or less. In another embodiment, the Substituted-

Quinoxaline-Type Piperidine Compounds will have a δ GTP EC_{50} (nM) of about 25 or less or less.

δ GTP Emax (%) is the maximal effect elicited by a compound relative to the effect elicited by met-enkephalin. Typically, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a δ GTP Emax (%) of about 10% or greater. In one embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a δ GTP Emax (%) of about 30% or greater. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a δ GTP Emax (%) of about 50% or greater. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a δ GTP Emax (%) of about 75% or greater. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a δ GTP Emax (%) of about 90% or greater. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a δ GTP Emax (%) of about 100% or greater.

The Substituted-Quinoxaline-Type Piperidine Compounds can be assayed *in vitro* or *in vivo* for the desired therapeutic or prophylactic activity prior to use in humans. Animal model systems can be used to demonstrate safety and efficacy.

The methods for treating or preventing a Condition in an animal in need thereof can further comprise co-administering to the animal being administered a Substituted-Quinoxaline-Type Piperidine Compound (*i.e.*, a first therapeutic agent) a second therapeutic agent. In one embodiment, the second therapeutic agent is administered in an effective amount.

An effective amount of the second therapeutic agent will be known to those skilled the art depending on the agent. However, it is well within the skilled artisan's purview to determine the second therapeutic agent's optimal effective-amount range. A Substituted-Quinoxaline-Type Piperidine Compound and the second therapeutic agent combined can act either additively or synergistically to treat the same Condition, or they may act independently of each other such that the Substituted-Quinoxaline-Type Piperidine Compound treats or prevents a first Condition and the second therapeutic agent treats or prevents a second disorder, which can be the same as the first Condition or another disorder. In one embodiment of the invention, where a second therapeutic agent is administered to an animal for treatment of a Condition (*e.g.*, pain), the minimal effective amount of the Substituted-Quinoxaline-Type Piperidine Compound will be less than its minimal effective amount would be where the second therapeutic agent is not administered. In this embodiment, the Substituted-

Quinoxaline-Type Piperidine Compound and the second therapeutic agent can act synergistically to treat or prevent a Condition. In one embodiment, a Substituted-Quinoxaline-Type Piperidine Compound is administered concurrently with a second therapeutic agent as a single composition comprising an effective amount of a Substituted-Quinoxaline-Type Piperidine Compound and an effective amount of the second therapeutic agent. Alternatively, a composition comprising an effective amount of a Substituted-Quinoxaline-Type Piperidine Compound and a second composition comprising an effective amount of the second therapeutic agent are concurrently administered. In another embodiment, an effective amount of a Substituted-Quinoxaline-Type Piperidine Compound is administered prior or subsequent to administration of an effective amount of the second therapeutic agent. In this embodiment, the Substituted-Quinoxaline-Type Piperidine Compound is administered while the second therapeutic agent exerts its therapeutic effect, or the second therapeutic agent is administered while the Substituted-Quinoxaline-Type Piperidine Compound exerts its therapeutic effect for treating or preventing a Condition.

The second therapeutic agent can be, but is not limited to, an opioid agonist, a non-opioid analgesic, a non-steroidal anti-inflammatory agent, an antimigraine agent, a Cox-II inhibitor, a 5-lipoxygenase inhibitor, an anti-emetic, a β-adrenergic blocker, an anticonvulsant, an antidepressant, a Ca^{2+}-channel blocker, an anti-cancer agent, an agent for treating or preventing UI, an agent for treating or preventing anxiety, an agent for treating or preventing a memory disorder, an agent for treating or preventing obesity, an agent for treating or preventing constipation, an agent for treating or preventing cough, an agent for treating or preventing diarrhea, an agent for treating or preventing high blood pressure, an agent for treating or preventing epilepsy, an agent for treating or preventing anorexia/cachexia, an agent for treating or preventing drug abuse, an agent for treating or preventing an ulcer, an agent for treating or preventing IBD, an agent for treating or preventing IBS, an agent for treating or preventing addictive disorder, an agent for treating or preventing Parkinson's disease and parkinsonism, an agent for treating or preventing a stroke, an agent for treating or preventing a seizure, an agent for treating or preventing a pruritic condition, an agent for treating or preventing psychosis, an agent for treating or preventing Huntington's chorea, an agent for treating or preventing ALS, an agent for treating or preventing a cognitive disorder, an agent for treating or preventing a migraine, an agent for inhibiting vomiting, an agent for treating or preventing dyskinesia, an agent for treating or preventing depression, or any mixture thereof.

Examples of useful opioid agonists include, but are not limited to, alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, proheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tilidine, tramadol, pharmaceutically acceptable derivatives thereof, or any mixture thereof.

In certain embodiments, the opioid agonist is selected from codeine, hydromorphone, hydrocodone, oxycodone, dihydrocodeine, dihydromorphine, morphine, tramadol, oxymorphone, pharmaceutically acceptable derivatives thereof, or any mixture thereof.

Examples of useful non-opioid analgesics include, but are not limited to, non-steroidal anti-inflammatory agents, such as aspirin, ibuprofen, diclofenac, naproxen, benoxaprofen, flurbiprofen, fenoprofen, flubufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pramoprofen, muroprofen, trioxaprofen, suprofen, aminoprofen, tiaprofenic acid, fluprofen, bucloxic acid, indomethacin, sulindac, tolmetin, zomepirac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac, oxpinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid, tolfenamic acid, diflurisal, flufenisal, piroxicam, sudoxicam, isoxicam, a pharmaceutically acceptable derivative thereof, or any mixture thereof. Other suitable non-opioid analgesics include the following, non-limiting, chemical classes of analgesic, antipyretic, nonsteroidal anti-inflammatory drugs: salicylic acid derivatives, including aspirin, sodium salicylate, choline magnesium trisalicylate, salsalate, diflunisal, salicylsalicylic acid, sulfasalazine, and olsalazin; para-aminophenol derivatives including acetaminophen and phenacetin; indole and indene acetic acids, including indomethacin, sulindac, and etodolac; heteroaryl acetic acids, including tolmetin, diclofenac, and ketorolac; anthranilic acids (fenamates), including mefenamic acid and meclofenamic acid; enolic acids, including oxicams (piroxicam, tenoxicam), and pyrazolidinediones (phenylbutazone,

oxyphenthartazone); alkanones, including nabumetone; a pharmaceutically acceptable derivative thereof; or any mixture thereof. For a more detailed description of the NSAIDs, *see* Paul A. Insel, *Analgesic-Antipyretic and Anti-inflammatory Agents and Drugs Employed in the Treatment of Gout*, in *Goodman & Gilman's The Pharmacological Basis of Therapeutics* 617-57 (P.B. Molinhoff and R.W. Ruddon eds., 9th ed 1996), and G.R. Hanson, *Analgesic, Antipyretic and Anti-Inflammatory Drugs in Remington: The Science and Practice of Pharmacy Vol II* 1196-1221 (A.R. Gennaro ed. 19th ed. 1995), which are hereby incorporated by reference in their entireties.

Examples of useful Cox-II inhibitors and 5-lipoxygenase inhibitors, as well as combinations thereof, are described in U.S. Patent No. 6,136,839, which is hereby incorporated by reference in its entirety. Examples of useful Cox-II inhibitors include, but are not limited to, celecoxib, DUP-697, flosulide, meloxicam, 6-MNA, L-745337, rofecoxib, nabumetone, nimesulide, NS-398, SC-5766, T-614, L-768277, GR-253035, JTE-522, RS-57067-000, SC-58125, SC-078, PD-138387, NS-398, flosulide, D-1367, SC-5766, PD-164387, etoricoxib, valdecoxib, parecoxib, a pharmaceutically acceptable derivative thereof, or any mixture thereof.

Examples of useful antimigraine agents include, but are not limited to, alpiropride, bromocriptine, dihydroergotamine, dolasetron, ergocornine, ergocorninine, ergocryptine, ergonovine, ergot, ergotamine, flumedroxone acetate, fonazine, ketanserin, lisuride, lomerizine, methylergonovine, methysergide, metoprolol, naratriptan, oxetorone, pizotyline, propranolol, risperidone, rizatriptan, sumatriptan, timolol, trazodone, zolmitriptan, a pharmaceutically acceptable derivative thereof, or any mixture thereof.

Examples of useful anticonvulsants include, but are not limited to, acetylpheneturide, albutoin, aloxidone, aminoglutethimide, 4-amino-3-hydroxybutyric acid, atrolactamide, beclamide, buramate, calcium bromide, carbamazepine, cinromide, clomethiazole, clonazepam, decimemide, diethadione, dimethadione, doxenitroin, eterobarb, ethadione, ethosuximide, ethotoin, felbamate, fluoresone, gabapentin, 5-hydroxytryptophan, lamotrigine, magnesium bromide, magnesium sulfate, mephenytoin, mephobarbital, metharbital, methetoin, methsuximide, 5-methyl-5-(3-phenanthryl)-hydantoin, 3-methyl-5-phenylhydantoin, narcobarbital, nimetazepam, nitrazepam, oxcarbazepine, paramethadione, phenacemide, phenetharbital, pheneturide, phenobarbital, phensuximide, phenylmethylbarbituric acid, phenytoin, phethenylate sodium, potassium bromide, pregabaline, primidone, progabide,

sodium bromide, solanum, strontium bromide, suclofenide, sulthiame, tetrantoin, tiagabine, topiramate, trimethadione, valproic acid, valpromide, vigabatrin, zonisamide, a pharmaceutically acceptable derivative thereof, or any mixture thereof.

Examples of useful Ca^{2+}-channel blockers include, but are not limited to, bepridil, clentiazem, diltiazem, fendiline, gallopamil, mibefradil, prenylamine, semotiadil, terodiline, verapamil, amlodipine, aranidipine, barnidipine, benidipine, cilnidipine, efonidipine, elgodipine, felodipine, isradipine, lacidipine, lercanidipine, manidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, cinnarizine, flunarizine, lidoflazine, lomerizine, bencyclane, etafenone, fantofarone, perhexiline, a pharmaceutically acceptable derivative thereof, or any mixture thereof.

Examples of useful therapeutic agents for treating or preventing UI include, but are not limited to, propantheline, imipramine, hyoscyamine, oxybutynin, dicyclomine, a pharmaceutically acceptable derivative thereof, or any mixture thereof.

Examples of useful therapeutic agents for treating or preventing anxiety include, but are not limited to, benzodiazepines, such as alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, demoxepam, diazepam, estazolam, flumazenil, flurazepam, halazepam, lorazepam, midazolam, nitrazepam, nordazepam, oxazepam, prazepam, quazepam, temazepam, and triazolam; non-benzodiazepine agents, such as buspirone, gepirone, ipsapirone, tiospirone, zolpicone, zolpidem, and zaleplon; tranquilizers, such as barbituates, *e.g.*, amobarbital, aprobarbital, butabarbital, butalbital, mephobarbital, methohexital, pentobarbital, phenobarbital, secobarbital, and thiopental; propanediol carbamates, such as meprobamate and tybamate; a pharmaceutically acceptable derivative thereof; or any mixture thereof.

Examples of useful therapeutic agents for treating or preventing diarrhea include, but are not limited to, diphenoxylate, loperamide, a pharmaceutically acceptable derivative thereof, or any mixture thereof.

Examples of useful therapeutic agents for treating or preventing epilepsy include, but are not limited to, carbamazepine, ethosuximide, gabapentin, lamotrigine, phenobarbital, phenytoin, primidone, valproic acid, trimethadione, benzodiazepines, γ vinyl GABA, acetazolamide, felbamate, a pharmaceutically acceptable derivative thereof, or any mixture thereof.

Examples of useful therapeutic agents for treating or preventing drug abuse include, but are not limited to, methadone, desipramine, amantadine, fluoxetine, buprenorphine, an opiate agonist, 3-phenoxypyridine, levomethadyl acetate hydrochloride, serotonin antagonists, a pharmaceutically acceptable derivative thereof, or any mixture thereof.

Examples of non-steroidal anti-inflammatory agents, 5-lipoxygenase inhibitors, anti-emetics, β-adrenergic blockers, antidepressants, and anti-cancer agents are known in the art and can be selected by those skilled in the art. Examples of useful therapeutic agents for treating or preventing memory disorder, obesity, constipation, cough, high blood pressure, anorexia/cachexia, an ulcer, IBD, IBS, addictive disorder, Parkinson's disease and parkinsonism, a stroke, a seizure, a pruritic condition, psychosis, Huntington's chorea, ALS, a cognitive disorder, a migraine, dyskinesia, depression, and/or treating, preventing or inhibiting vomiting include those that are known in the art and can be selected by those skilled in the art.

A composition of the invention is prepared by a method comprising admixing a Substituted-Quinoxaline-Type Piperidine Compound or a pharmaceutically acceptable derivative thereof with a pharmaceutically acceptable carrier or excipient. Admixing can be accomplished using methods known for admixing a compound (or derivative) and a pharmaceutically acceptable carrier or excipient. In one embodiment, the Substituted-Quinoxaline-Type Piperidine Compound is present in the composition in an effective amount.

4.7 Kits

The invention further provides kits that can simplify the handling and administration of a Substituted-Quinoxaline-Type Piperidine Compound to an animal.

A typical kit of the invention comprises a unit dosage form of a Substituted-Quinoxaline-Type Piperidine Compound. In one embodiment, the unit dosage form comprises a first container, which can be sterile, containing an effective amount of a Substituted-Quinoxaline-Type Piperidine Compound and a pharmaceutically acceptable carrier or excipient. The kit can further comprise a label or printed instructions instructing the use of the Substituted-Quinoxaline-Type Piperidine Compound to treat or prevent a Condition. The kit can further comprise a unit dosage form of a second therapeutic agent, for example, a second container containing an effective amount of the second therapeutic agent and a pharmaceutically acceptable carrier or excipient. In another embodiment, the kit comprises a container containing an effective amount of a Substituted-Quinoxaline-Type Piperidine

Compound, an effective amount of a second therapeutic agent and a pharmaceutically acceptable carrier or excipient. Examples of second therapeutic agents include, but are not limited to, those listed above.

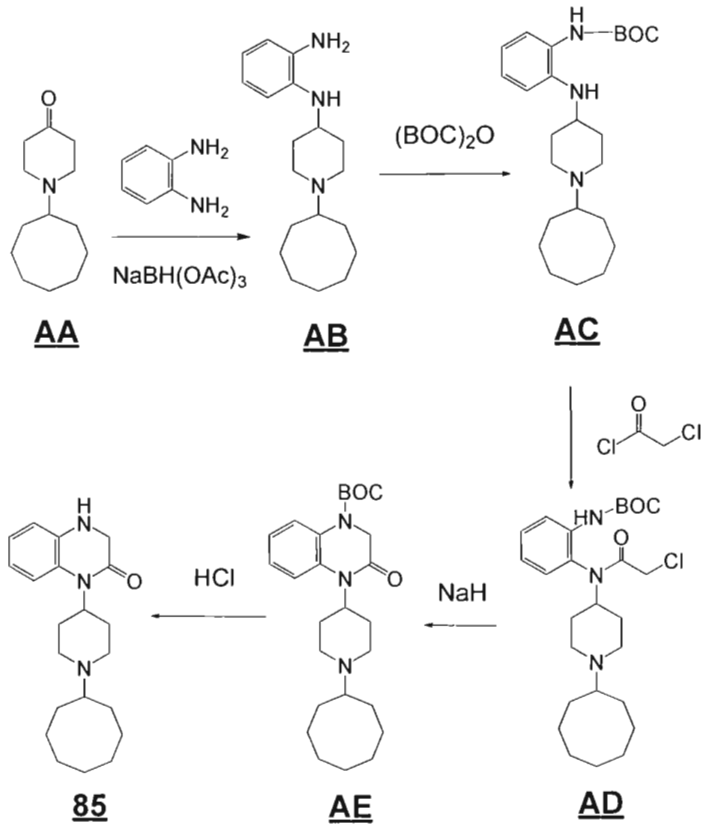
Kits of the invention can further comprise a device that is useful for administering the unit dosage forms. Examples of such a device include, but are not limited to, a syringe, a drip bag, a patch, an inhaler, and an enema bag.

The following examples are set forth to assist in understanding the invention and should not be construed as specifically limiting the invention described and claimed herein. Such variations of the invention, including the substitution of all equivalents now known or later developed, that would be within the purview of those skilled in the art, and changes in formulation or changes in experimental design, are to be considered to fall within the scope of the invention incorporated herein.

5. EXAMPLES

The following examples illustrate various aspects of the invention, and are not to be construed to limit the claims in any manner whatsoever.

5.1 Example 1



1-Cyclooctylpiperidin-4-one (compound of formula **AA**) was purchased from Vasudha Pharma Chem LTD (Hyderabad, Andhra Pradesh, India).

The compound of formula **AA** (10.00g, 48.0mmol) and 1,2-phenylenediamine (10.38g, 96.0mmol, Sigma-Aldrich, St. Louis, MO) were suspended in 200mL of CH_2Cl_2. To this mixture, sodium triacetoxyborohydride ($NaBH(OAc)_3$, 30.42g, 144.0mmol, Acros Organics, Geel, Belgium) and acetic acid (10mL) were added. The reaction mixture was stirred at a temperature of about 25°C for 24hrs after which the reaction mixture was extracted 10 times with about 200mL of water each time. The organic portion was dried ($MgSO_4$), filtered, and concentrated to dryness under reduced pressure to provide 9.48g of a compound of formula **AB** as a light orange oil (yield 65.6%).

The identity of the compound of formula **AB**, N^1-(1-cyclooctylpiperidin-4-yl)benzene-1,2-diamine, was confirmed using liquid chromatography/mass spectrometry (LC/MS).

Compound **AB**: LC/MS (95%, t_r=1.832min): m/z=301.1 $[M+H]^+$ (Calc: 302.2).

To a suspension of 199mg (0.66mmol) of the compound of formula **AB** and excess $NaHCO_3$ in 10mL of DCM at 0°C was added di-*tert*-butyl dicarbonate ($(BOC)_2O$, 144mg, 0.66mmol, Sigma-Aldrich). After the addition, the reaction mixture was warmed to a temperature of about 25°C and stirred for 2hrs. The reaction mixture was then poured onto a silica gel column and eluted with 5%:95% MeOH:DCM to provide 247mg of the compound of formula **AC** as light yellow solid (yield 93%).

The identity of the compound of formula **AC**, *tert*-butyl 2-(1-cyclooctylpiperidin-4-ylamino)phenylcarbamate, was confirmed using ^1H NMR.

Compound **AC**: ^1H NMR: δ_H (400MHz, $CDCl_3$): 7.24 (bs, 1H), 6.98 (dt, 1H, J=1.5, 8Hz), 6.67 (m, 2H), 6.12 (bs, 1H), 3.53 (bs, 1H), 3.13 (m, 1H), 2.71 (m, 2H), 2.56 (m, 1H), 2.27 (t, 2H, J=10Hz), 1.95 (m, 2H), 1.70-1.35 (m, 15H), 1.43 (s, 9H).

To a suspension of 230mg of the compound of formula **AC** and excess of $NaHCO_3$ in DCM at 0°C was added dropwise via a syringe 2-chloroacetyl chloride (0.047mL, 0.57mmol, Sigma-Aldrich). After addition, the reaction mixture was warmed to a temperature of about 25°C and stirred for 30min more. Thereafter, the reaction mixture was evaporated to dryness under reduced pressure to provide 273mg of the compound of formula **AD** (yield >98%).

The identity of the compound of formula **AD**, *tert*-butyl 2-(2-chloro-*N*-(1-cyclooctylpiperidin-4-yl)acetamido)phenylcarbamate, was confirmed using mass spectrometry (MS).

Compound **AD**: MS: *m/z*=478 (M+1) (Calc: 477).

50mg of the compound of formula **AD** was added to 3mL of DMF at 0°C. To this mixture was added excess of NaH (3 equivalents, Sigma-Adrich). Thereafter, the reaction mixture was warmed to a temperature of about 25°C and stirred for 10min. After cooling to 0°C, the reaction mixture was quenched by the addition of ice water. The reaction mixture was diluted with EtOAc then washed twice with brine. The brine was extracted with EtOAc. The organic portions were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to provide a residue. The residue was chromatographed with a silica gel column eluted with EtOAc to provide the compound of formula **AE** (yield >98%).

The identity of the compound of formula **AE**, *tert*-butyl 4-(1-cyclooctylpiperidin-4-yl)-3-oxo-3,4-dihydroquinoxaline-1(2*H*)-carboxylate, was confirmed using ^1H NMR.

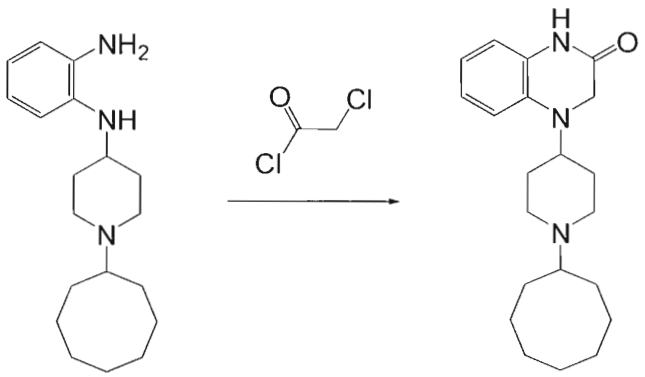
Compound **AE**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.63 (bs, 1H), 7.34 (dd, 1H, J=1.5, 8Hz), 7.13 (dt, 1H, J=1.5, 8Hz), 7.08 (dt, 1H, J=1.5, 8Hz), 4.29 (s, 2H), 4.29 (m, 1H), 2.92 (bd, 2H, J=10Hz), 2.66 (m, 1H), 2.54 (m, 2H), 2.36 (t, 2H, J=10Hz), 1.80-1.43 (m, 16H), 1.54 (s, 9H).

The compound of formula **AE** was added to 4N HCl in 1,4-dioxane at a temperature of about 25°C for 30min then concentrated under reduced pressure to provide a residue. The residue was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ solution. The organic portion was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to provide a residue. The residue was then chromatographed by preparative TLC (eluted with 15%:85% MeOH:DCM) to provide 31mg of the Substituted-Quinoxaline-Type Piperidine Compound of formula **85** (yield 98%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **85**, 1-(1-cyclooctylpiperidin-4-yl)-3,4-dihydroquinoxalin-2(1*H*)-one, was confirmed using ^{1}H NMR and MS.

Substituted-Quinoxaline-Type Piperidine Compound **85**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 12.21 (bs, 0.5H), 7.78 (m, 1H), 6.99 (m, 1H), 6.87 (t, 1H, J=8Hz), 6.66 (d, 1H, J=8Hz), 5.03 (bs, 1H), 3.79 (s, 2H), 3.71 (s, 1H), 3.34 (m, 4H), 2.95 (m, 1H), 2.19 (m, 1H), 1.8-1.3 (m, 18H); MS: *m/z*=342 (M+1) (Calc: 341).

5.2 Example 2



AB **86**

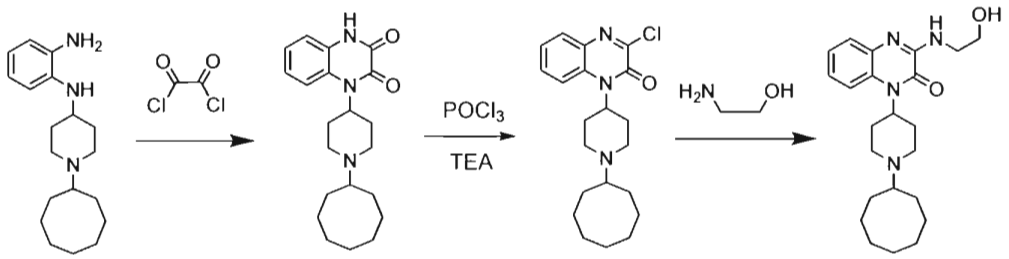
190mg (0.63mmol) of the compound of formula **AB** was mixed with 7mL of DCM. $NaHCO_3$ (158mg, 1.89mmol) was added and the resulting suspension was stirred at 0°C. To the suspension was then added dropwise via a syringe 2-chloroacetyl chloride (0.051mL,

0.63mmol). After addition, the reaction mixture was warmed to a temperature of about 25°C and stirred for 10min. The reaction mixture was then evaporated to dryness under reduced pressure, acetonitrile was added, and the resulting suspension was heated at 80°C for 48hr. The suspension was poured onto a silica gel column and eluted with 5%:95% MeOH:DCM to provide 168mg of Substituted-Quinoxaline-Type Piperidine Compound **86** as light yellow solid (yield 78%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **86**, 4-(1-cyclooctylpiperidin-4-yl)-3,4-dihydroquinoxalin-2(1*H*)-one, was confirmed using ^{1}H NMR and MS.

Substituted-Quinoxaline-Type Piperidine Compound **86**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.53 (bs, 1H), 6.93 (dt, 1H, J=1.5, 8Hz), 6.69 (m, 2H), 3.71 (s, 2H), 3.43 (m, 1H), 2.88 (m, 2H), 2.61 (m, 1H), 2.31 (m, 2H), 1.80-1.38 (m, 18H); MS: *m/z*=342 (M+1) (Calc: 341).

5.3 Example 3



AB **BA** **404** **3**

The compound of formula **AB** (14.40g, 47.84mmol) was added to 100mL of dry DCE. This mixture was added dropwise to a solution of oxalyl dichloride (8.37g, 66.44mmol, Sigma-Aldrich) in 200mL of dry DCE. Under an argon atmosphere, the resulting mixture was magnetically stirred at a temperature of about 25°C for 1hr. The mixture was then warmed to 60°C for 10hrs. The mixture was then cooled to a temperature of about 25°C and the solvent was removed under reduced pressure. The remaining material was added to 300mL of MeOH and adsorbed onto silica gel to provide residues that were chromatographed with a silica gel column eluted with a gradient of from 100%:0% EtOAc:MeOH to 0%:100% EtOAc:MeOH. The product fractions were combined and concentrated to dryness under reduced pressure to provide 10.0g of the compound of formula **BA** as a light orange solid (yield 58%).

The identity of the compound of formula **BA**, 1-(1-cyclooctylpiperidin-4-yl)quinoxaline-2,3(1*H*,4*H*)-dione, was confirmed using ^{1}H NMR and LC/MS.

Compound **BA**: ^{1}H NMR: δ_H (400MHz, CD_3OD): 7.81 (1H, m), 7.31 (3H, m), 3.57 (3H, m), 3.43 (2H, m), 3.22 (2H, m), 2.17 (4H, m), 1.99 (4H, m), 1.78-1.46 (14H, m); LC/MS (100%, t_r=5.011min): *m/z*=356.3 $[M+H]^+$ (Calc: 355.5).

TEA (2mmol) and $POCl_3$ (5mmol, Sigma-Aldrich) were added to a suspension of the compound of formula **BA** (784mg, 2mmol) in toluene (15mL) and DMF (2mL) at 25°C. The reaction mixture was warmed to 100°C with stirring. A pale yellow solid formed after 30min. Thereafter, the mixture was cooled to a temperature of about 25°C, filtered, washed twice with 1:5 EtOAc:Et_2O (10mL for each wash), and dried under reduced pressure at 60°C for 12hr to provide 712mg of Substituted-Quinoxaline-Type Piperidine Compound **404** as a colorless solid (yield 87%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **404**, 3-chloro-1-(1-cyclooctylpiperidin-4-yl)quinoxalin-2(1*H*)-one, was confirmed using ^{1}H NMR.

Substituted-Quinoxaline-Type Piperidine Compound **404**: ^{1}H NMR: δ_H (300MHz, DMSO): 8.11 (1H, br), 7.79 (1H, d, J=8Hz), 7.67 (1H, m), 7.44 (1H, t, J=8Hz), 5.11 (1H, br), 3.45-3.30 (4H, m), 3.11 (2H, m), 1.96 (2H, m), 1.73 (2H, d, J=8Hz), 1.76-1.42 (13H, m).

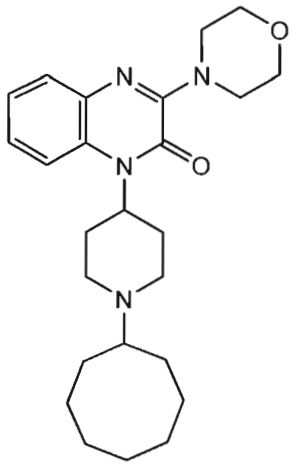
TEA (0.38mmol) and 2-aminoethanol (0.57mmol, Sigma-Aldrich) were added to a suspension of Substituted-Quinoxaline-Type Piperidine Compound **404** (80mg, 0.19mmol) in acetonitrile (3mL) at 25°C. The resulting reaction mixture was stirred at 80°C for 90min. After cooling to about 25°C and quenching with water (3mL), a white precipitate formed. The precipitate was filtered, washed with water, and dried under reduced pressure at 60°C for 12hr to provide 55mg of Substituted-Quinoxaline-Type Piperidine Compound **3** as light yellow solid (yield 73%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **3**, 1-(1-cyclooctylpiperidin-4-yl)-3-(2-hydroxyethylamino)quinoxalin-2(1*H*)-one, was confirmed using ^{1}H NMR and MS.

Substituted-Quinoxaline-Type Piperidine Compound **3**: ^{1}H NMR: δ_H (300MHz, DMSO): 7.66 (1H, m), 7.44-7.32 (2H, m), 7.18 (2H, m), 4.82 (1H, t, J=5.4Hz), 4.67 (1H, br), 3.58 (2H, q, J=5.7Hz), 3.47 (2H, q, J=5.7Hz), 2.86-2.68 (5H, m), 2.43-2.36 (2H, m), 1.72-1.41 (16H, m); MS: *m/z*=436.9 $[M+H]^+$ (Calc: 435.4).

5.4 Example 4

In a manner similar to Example 3, the following Substituted-Quinoxaline-Type Piperidine Compounds were prepared from Substituted-Quinoxaline-Type Piperidine Compound **404**.

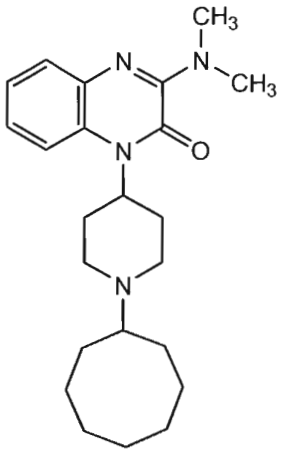


1

Substituted-Quinoxaline-Type Piperidine Compound **1** was prepared by using morpholine (Sigma-Aldrich) in place of 2-aminoethanol (yield 96%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **1**, 1-1-ycloоctylpiperidin-4-yl)-3-morpholinoquinoxalin-2(1*H*)-one, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **1**: ^{1}H NMR: δ_H (400MHz, DMSO): 7.67 (1H, d, J=8Hz), 7.45 (1H, d, J=8Hz), 7.28 (2H, t, J=8Hz), 7.21 (2H, t, J=8Hz), 4.64 (1H, br), 3.77 (4H, m), 3.71 (4H, m), 2.84 (2H, m), 2.69-2.61 (3H, m), 2.39 (2H, m), 1.72-1.41 (17H, m); LC/MS: *m/z*=425.1 $[M+H]^+$ (Calc: 424.6).

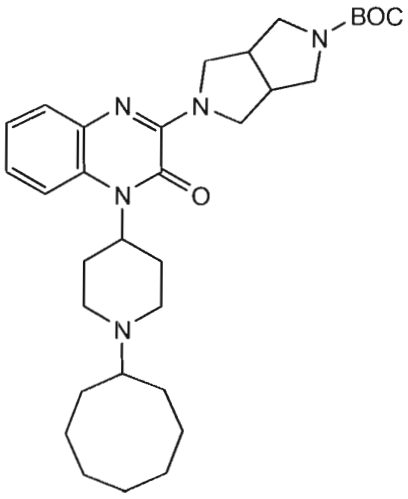


2

Substituted-Quinoxaline-Type Piperidine Compound **2** was prepared by using dimethylamine (Sigma-Aldrich) in place of 2-aminoethanol (yield 92%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **2**, 1-(1-cyclooctylpiperidin-4-yl)-3-(dimethylamino)quinoxalin-2(1*H*)-one, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **2**: ^{1}H NMR: δ_H (400MHz, DMSO): 7.60 (1H, d, J=8Hz), 7.40 (1H, d, J=8Hz), 7.20 (2H, m), 4.60 (1H, br), 3.22 (6H, s), 2.84 (2H, m), 2.69-2.62 (3H, m), 2.40 (2H, m), 1.72-1.41 (17H, m); LC/MS: *m/z*=383.1 $[M+H]^+$ (Calc: 382.5).

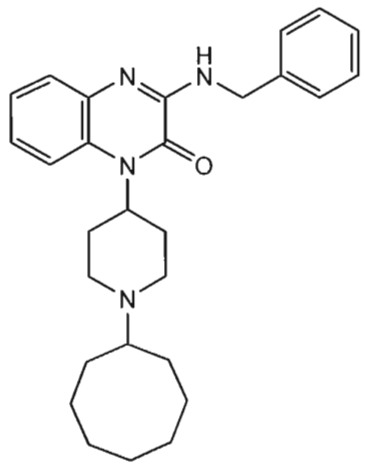


4

Substituted-Quinoxaline-Type Piperidine Compound **4** was prepared by using *tert*-butyl hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (Chembasics Pty. Ltd., Perth, Australia) in place of 2-aminoethanol (yield >98%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **4**, *tert*-butyl 5-(4-(1-cyclooctylpiperidin-4-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **4**: ^{1}H NMR: δ_H (400MHz, DMSO): 7.61 (1H, d, J=4Hz), 7.34 (1H, m), 7.22-7.18 (2H, m), 4.65 (1H, br), 4.01 (2H, m), 3.71 (1H, m), 3.44 (2H, m), 3.15 (3H, m), 2.92 (5H, m), 2.72 (3H, m), 1.78-1.40 (17H, m), 1.39 (9H, s); LC/MS: *m/z*=550.2 $[M+H]^+$ (Calc: 549.8).

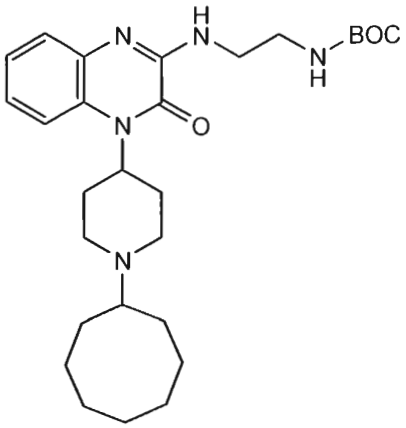


6

Substituted-Quinoxaline-Type Piperidine Compound **6** was prepared by using phenylmethanamine (Sigma-Aldrich) in place of 2-aminoethanol (yield >98%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **6**, 3-(benzylamino)-1-(1-cyclooctylpiperidin-4-yl)quinoxalin-2(1*H*)-one, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **6**: ^{1}H NMR: δ_H (300MHz, DMSO): 8.08 (1H, m), 7.40-7.19 (9H, m), 4.60 (2H, d, J=6Hz), 3.41 (5H, m), 3.15 (2H, m), 2.10-1.47 (17H, m); LC/MS: *m/z*=445.1 $[M+H]^+$ (Calc: 444.6).

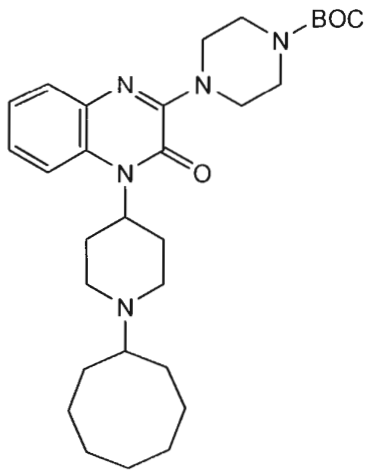


7

Substituted-Quinoxaline-Type Piperidine Compound 7 was prepared by using *tert*-butyl 2-aminoethylcarbamate (Sigma-Aldrich) in place of 2-aminoethanol (yield 90%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound 7, *tert*-butyl 2-(4-(1-cyclooctylpiperidin-4-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)ethylcarbamate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound 7: ^{1}H NMR: δ_H (400MHz, DMSO): 8.00-7.5 (2H, br), 7.43 (1H, m), 7.22 (2H, m), 6.98 (1H, m), 4.98 (1H, br), 3.45 (7H, m), 3.21-3.09 (5H, m), 2.04-1.45 (15H, m), 1.37 (9H, s); LC/MS: *m/z*=498.1 $[M+H]^+$ (Calc: 497.7).

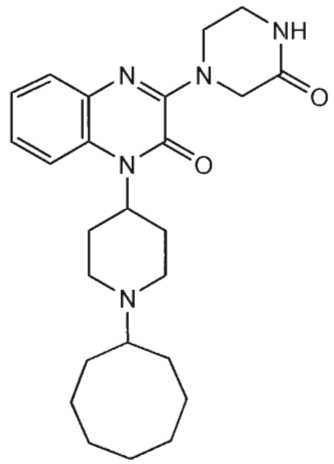


8

Substituted-Quinoxaline-Type Piperidine Compound 8 was prepared by using *tert*-butyl piperazine-1-carboxylate (Sigma-Aldrich) in place of 2-aminoethanol (yield 86%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **8**, *tert*-butyl 4-(4-(1-cyclooctylpiperidin-4-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)piperazine-1-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **8**: ^{1}H NMR: δ_H (400MHz, DMSO): 7.67 (1H, d, J=8Hz), 7.45 (1H, d, J=8Hz), 7.29 (1H, d, J=8Hz), 7.21 (1H, d, J=8Hz), 4.63 (1H, br), 3.75 (4H, s), 3.45 (4H, s), 2.84 (2H, m), 2.69-2.61 (3H, m), 2.39 (2H, t, J=8Hz), 1.71-1.42 (17H, m), 1.42 (9H, s); LC/MS: *m/z*=524.1 $[M+H]^+$ (Calc: 523.7).

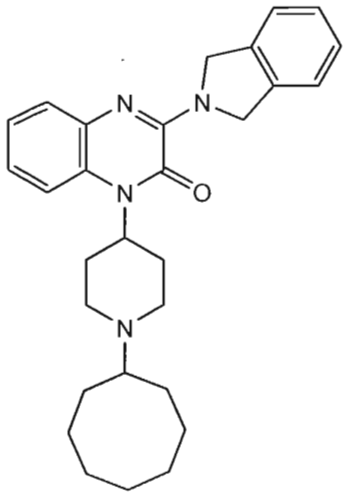


18

Substituted-Quinoxaline-Type Piperidine Compound **18** was prepared by using piperazin-2-one (Sigma-Aldrich) in place of 2-aminoethanol to provide a colorless solid (yield 86%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **18**, 1-(1-cyclooctylpiperidin-4-yl)-3-(3-oxopiperazin-1-yl)quinoxalin-2(1*H*)-one, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **18**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 8.01 (1H, s), 7.83 (1H, m), 7.49 (1H, d, J=7.6Hz), 7.28 (2H, m), 4.94 (1H, br), 4.31 (2H, s), 4.02 (2H, t, J=5.2Hz), 3.41-3.58 (8H, m), 2.01-1.47 (17H, m); LC/MS: *m/z*=438 $[M+H]^+$ (Calc: 437.6).

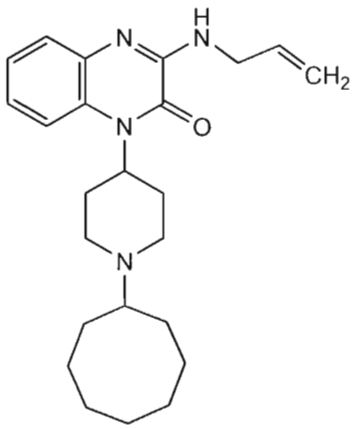


19

Substituted-Quinoxaline-Type Piperidine Compound **19** was prepared by using isoindoline (Sigma-Aldrich) in place of 2-aminoethanol to provide a colorless solid (yield 75%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **19**, 1-(1-cyclooctylpiperidin-4-yl)-3-(isoindolin-2-yl)quinoxalin-2(1*H*)-one, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **19**: ^{1}H NMR: δ_H (300MHz, DMSO): 7.62 (1H, s), 7.41 (3H, s), 7.31 (2H, s), 7.19 (2H, m), 5.23 (4H, br), 4.69 (1H, br), 2.87-2.28 (7H, m), 1.78-1.44 (16H, m); LC/MS: *m/z*=457 $[M+H]^+$ (Calc: 456.6).

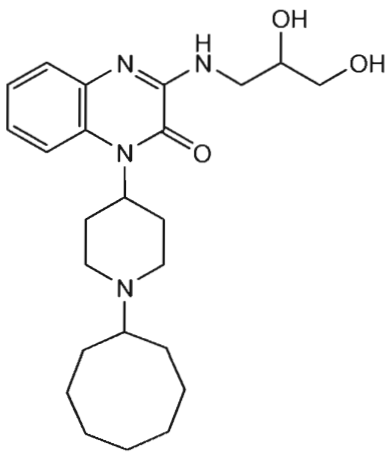


24

Substituted-Quinoxaline-Type Piperidine Compound **24** was prepared by using prop-2-en-1-amine (Sigma-Aldrich) in place of 2-aminoethanol to provide a colorless solid (yield 90%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **24**, 3-(allylamino)-1-(1-cyclooctylpiperidin-4-yl)quinoxalin-2(1*H*)-one, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **24**: ^{1}H NMR: δ_H (300MHz, DMSO): 7.65 (2H, m), 7.37 (1H, m), 7.18 (2H, m), 5.94 (1H, m), 5.14 (2H, m), 4.62 (1H, br), 4.01 (2H, t, J=5.4Hz), 2.85-2.31 (7H, m), 1.73-1.42 (16H, m); LC/MS: *m/z*=395 $[M+H]^+$ (Calc: 394.6).

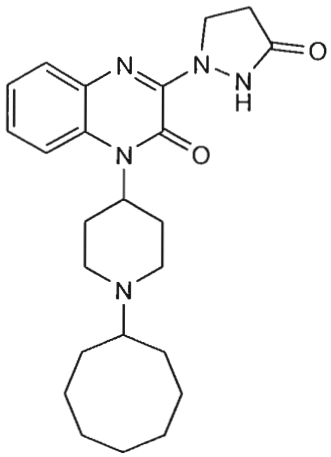


25

Substituted-Quinoxaline-Type Piperidine Compound **25** was prepared by using 3-aminopropane-1,2-diol (Sigma-Aldrich) in place of 2-aminoethanol to provide a colorless solid (yield 77%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **25**, 1-(1-cyclooctylpiperidin-4-yl)-3-(2,3-dihydroxypropylamino)quinoxalin-2(1*H*)-one, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **25**: ^{1}H NMR: δ_H (300MHz, DMSO): 7.70 (1H, m), 7.38 (1H, m), 7.31 (1H, m), 7.20 (2H, m), 5.02 (1H, d, J=5.1Hz), 4.73 (1H, t, J=5.7Hz), 4.72 (1H, br), 3.71 (1H, m), 3.57 (1H, m), 3.44-3.33 (3H, m), 3.00-2.36 (6H, m), 1.78-1.44 (17H, m); LC/MS: *m/z*=429 $[M+H]^+$ (Calc: 428.6).



119

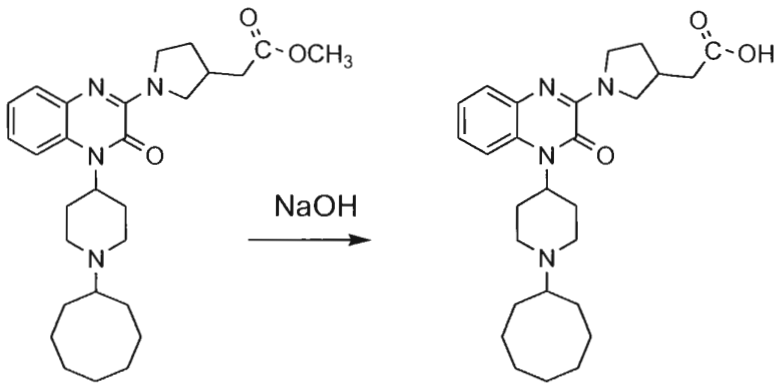
Substituted-Quinoxaline-Type Piperidine Compound **119** was prepared by using pyrazolidin-3-one hydrochloride (Sigma-Aldrich) in place of 2-aminoethanol to provide a white amorphous solid (yield 59%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **119**, 1-(1-cyclooctylpiperidin-4-yl)-3-(3-oxopyrazolidin-1-yl)quinoxalin-2(1*H*)-one, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **119**: ^{1}H NMR: δ_H (300MHz, $CDCl_3$): 7.64 (1H, br), 7.51 (1H, d, J=4Hz), 7.25 (2H, m), 4.90 (1H, m), 4.44 (2H, d, J=8Hz), 2.98 (2H, m), 2.80 (2H, d, J=8Hz), 2.80 (1H, m), 2.70 (2H, m), 2.43 (2H, m), 1.75-1.40 (16H, m); LC/MS (100%, t_r=1.19min): *m/z*=424.2 $[M+H]^+$ (Calc: 423.3).

5.5 Example 5

In a manner similar to Example 3, the following Substituted-Quinoxaline-Type Piperidine Compound was prepared from Substituted-Quinoxaline-Type Piperidine Compound **404**.



138 **111**

Substituted-Quinoxaline-Type Piperidine Compound **138** was prepared by using methyl 2-(pyrrolidin-3-yl)acetate in place of 2-aminoethanol (yield 98%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **138**, methyl 2-(1-(4-(1-cyclooctylpiperidin-4-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)pyrrolidin-3-yl)acetate, was confirmed using ^{1}H NMR and LC/MS.

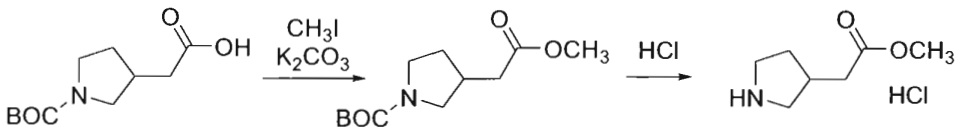
Substituted-Quinoxaline-Type Piperidine Compound **138**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.53 (1H, br), 7.45 (1H, d, J=8Hz), 7.13 (2H, m), 4.90 (1H, br), 4.12 (1H, br), 4.10 (1H, br), 3.85 (1H, br), 3.71 (3H, s), 3.55 (1H, br), 2.95 (2H, d, J=12Hz), 2.79 (2H, m), 2.65 (2H, m), 2.55-2.36 (3H, m), 2.18 (1H, m), 1.90-1.40 (18H, m); LC/MS (99%, t_r=1.42min): *m/z*=481.2 $[M+H]^+$ (Calc: 480.3).

To convert the ester to the acid, to a mixture of Substituted-Quinoxaline-Type Piperidine Compound **138** (115mg, 0.239mmol) and MeOH (4mL) at a temperature of about 25°C was added 2N aqueous NaOH (0.14mL, 0.958mmol). The resulting reaction mixture was warmed to a temperature of 50°C and stirred for 2h. After concentration under reduced pressure, the reaction mixture was diluted with water (5mL) and extracted with EtOAc (5mL). The aqueous portion was neutralized by adding 2N aqueous HCl at a temperature of 0°C. Thereafter, the mixture was extracted twice with EtOAc (10mL for each extraction). The organic portions were combined, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide 107mg of Substituted-Quinoxaline-Type Piperidine Compound **111** as a white solid (yield 96%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **111**, 2-(1-(4-(1-cyclooctylpiperidin-4-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)pyrrolidin-3-yl)acetic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **111**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.61 (1H, m), 7.34 (1H, d, J=8Hz), 7.14 (2H, m), 4.70 (1H, br), 4.40-3.40 (4H, m), 3.00 (2H, m), 2.80 (4H, m), 2.65 (2H, m), 2.40 (2H, m), 2.10 (1H, m), 1.85-1.40 (18H, m); LC/MS (100%, t_r=1.32min): *m/z*=467.2 $[M+H]^+$ (Calc: 466.3).

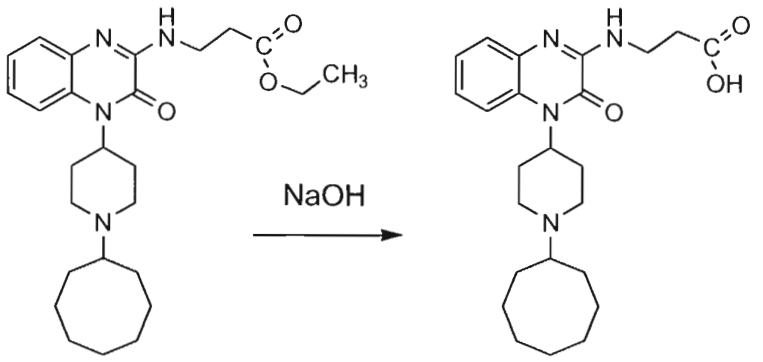
Methyl 2-(pyrrolidin-3-yl)acetate was prepared as follows:



To a suspension of 2-(1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)acetic acid (500mg, 2.18mmol, Astatec Pharmaceutical Technology Co.) in DMF (10mL) was added methyl iodide (163μL, 2.62mmol, Sigma-Aldrich) and K_2CO_3 (904mg, 6.53mmol). These ingredients were stirred at a temperature of about 25°C for 1h after which the reaction mixture was quenched with water (20mL), extracted three times with EtOAc (20mL for each extraction), washed twice with water (20mL for each wash), washed with saturated aqueous NaCl (10mL), dried ($MgSO_4$), and concentrated under reduced pressure to provide *tert*-butyl 3-(2-methoxy-2-oxoethyl)pyrrolidine-1-carboxylate as an oil. To a mixture of *tert*-butyl 3-(2-methoxy-2-oxoethyl)pyrrolidine-1-carboxylate (2.18mmol) in dioxane (10mL) at a temperature of about 25°C was added 4N HCl in dioxane (10.8mmol). Then the reaction mixture was stirred at 50°C for 2h. Thereafter, the mixture was concentrated under reduced pressure to provide 380mg of the hydrochloride of methyl 2-(pyrrolidin-3-yl)acetate as a colorless oil (yield 96% for two steps), the identity of which was confirmed using ^{1}H NMR and LC/MS.

Methyl 2-(pyrrolidin-3-yl)acetate: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 9.70 (2H, br), 3.70 (3H, s), 3.62 (1H, m), 3.47 (1H, m), 3.30 (1H, m), 3.00 (1H, m), 2.74 (1H, m), 2.54 (2H, d, J=8Hz), 2.26 (1H, m), 1.73 (1H, m); LC/MS (100%, t_r=0.34min): *m/z*=144.0 $[M+H]^+$ (Calc: 143.1).

In a manner similar to Example 3, the following Substituted-Quinoxaline-Type Piperidine Compounds were prepared from Substituted-Quinoxaline-Type Piperidine Compound **404** then converted from the ester to the acid in a manner similar to that described above.



139 **113**

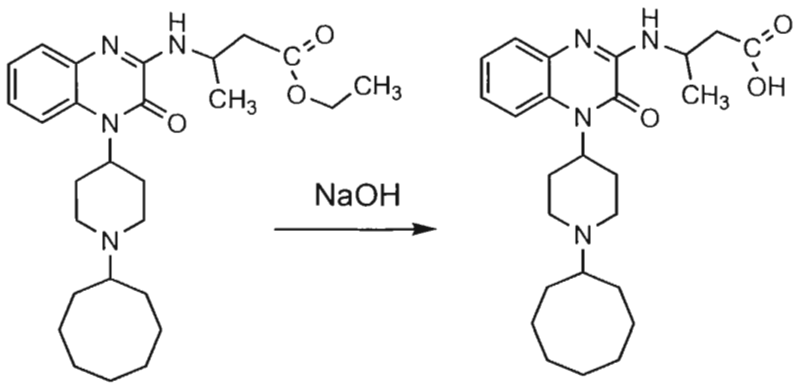
Substituted-Quinoxaline-Type Piperidine Compound **139** was prepared by using ethyl 3-aminopropanoate (Sigma-Aldrich) in place of 2-aminoethanol (yield >98%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **139**, ethyl 3-(4-(1-cyclooctylpiperidin-4-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)propanoate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **139**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.60 (1H, br), 7.52 (1H, m), 7.19 (2H, m), 6.69 (1H, m), 5.00 (1H, br), 4.17 (2H, q, J=8Hz), 3.82 (2H, q, J=8Hz), 2.96 (2H, m), 2.80 (2H, m), 2.71 (2H, t, J=8Hz), 2.50-2.35 (3H, m), 2.01 (2H, m), 1.80-1.40 (14H, m); LC/MS (95%, t_r=1.47min): *m/z*=455.1 $[M+H]^+$ (Calc: 454.3).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **113**, 3-(4-(1-cyclooctylpiperidin-4-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)propanoic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **113**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.68 (1H, m), 7.47 (1H, m), 7.41 (1H, m), 7.19 (1H, m), 5.00-4.30 (2H, m), 3.59 (2H, q, J=8Hz), 3.50-3.10 (2H, m), 2.91 (2H, m), 2.71 (2H, m), 2.60 (2H, t, J=8Hz), 2.50 (2H, m), 1.80-1.40 (16H, m); LC/MS (98%, t_r=1.34min): *m/z*=427.2 $[M+H]^+$ (Calc: 426.3).



140 **116**

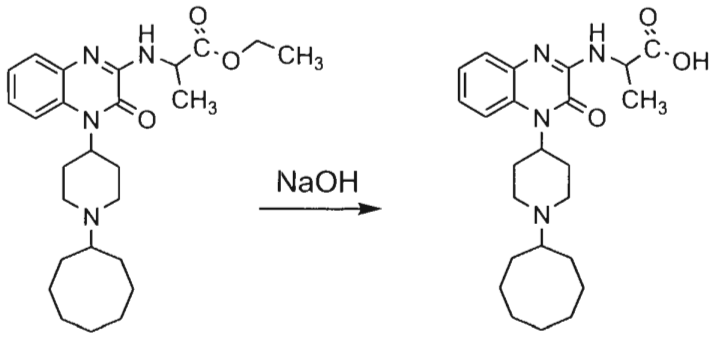
Substituted-Quinoxaline-Type Piperidine Compound **140** was prepared by using ethyl 3-aminobutanoate hydrochloride (Sigma-Aldrich) in place of 2-aminoethanol (yield 89%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **140**, ethyl 3-(4-(1-cyclooctylpiperidin-4-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)butanoate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **140**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.60 (1H, br), 7.52 (1H, m), 7.19 (2H, m), 6.57 (1H, d, J=8Hz), 5.00 (1H, br), 4.60 (1H, m), 4.14 (2H, q, J=8Hz), 3.20-2.30 (9H, m), 2.00-1.40 (16H, m), 1.37 (3H, d, J=8Hz), 1.26 (3H, t, J=8Hz); LC/MS (100%, t_r=1.52min): *m/z*=469.2 $[M+H]^+$ (Calc: 468.3).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **116**, 3-(4-(1-cyclooctylpiperidin-4-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)butanoic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **116**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.60 (1H, m), 7.40 (1H, m), 7.06 (2H, m), 5.70-5.00 (2H, m), 4.55 (1H, m), 3.40-3.20 (3H, m), 3.02 (2H, m), 2.80-2.60 (4H, m), 1.96 (2H, m), 1.80-1.38 (14H, m), 1.41 (3H, d, J=8Hz); LC/MS (100%, t_r=1.47min): *m/z*=441.2 $[M+H]^+$ (Calc: 440.3).



141 **118**

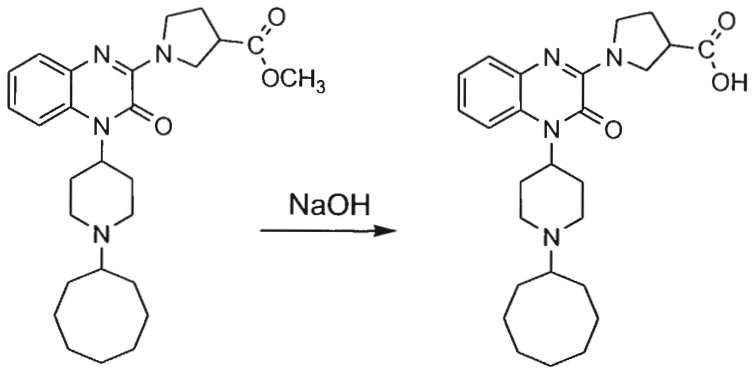
Substituted-Quinoxaline-Type Piperidine Compound **141** was prepared by using ethyl 2-aminopropanoate hydrochloride (Sigma-Aldrich) in place of 2-aminoethanol (yield 92%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **141**, ethyl 2-(4-(1-cyclooctylpiperidin-4-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)propanoate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **141**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.60 (1H, br), 7.50 (1H, m), 7.19 (2H, m), 6.73 (1H, d, J=8Hz), 4.75 (1H, m), 4.23 (2H, q, J=8Hz), 2.97 (2H, m), 2.80 (2H, m), 2.67 (1H, m), 2.43 (2H, m), 1.85-1.40 (16H, m), 1.56 (3H, d, J=4Hz), 1.29 (3H, t, J=8Hz); LC/MS (100%, t_r=1.55min): *m/z*=455.2 $[M+H]^+$ (Calc: 454.3).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **118**, 2-(4-(1-cyclooctylpiperidin-4-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)propanoic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **118**: ^{1}H NMR: δ_H (400MHz, DMSO): 7.77 (1H, m), 7.50 (1H, d, J=8Hz), 7.39 (1H, m), 7.19 (2H, m), 4.80 (1H, br), 4.39 (1H, m), 3.20-2.85 (7H, m), 2.00-1.40 (16H, m), 1.44 (3H, d, J=8Hz); LC/MS (100%, t_r=1.54min): *m/z*=427.2 $[M+H]^+$ (Calc: 426.3).



142 **109**

Substituted-Quinoxaline-Type Piperidine Compound **142** was prepared by using methyl pyrrolidine-3-carboxylate hydrochloride (Sigma-Aldrich) in place of 2-aminoethanol (yield 71%).

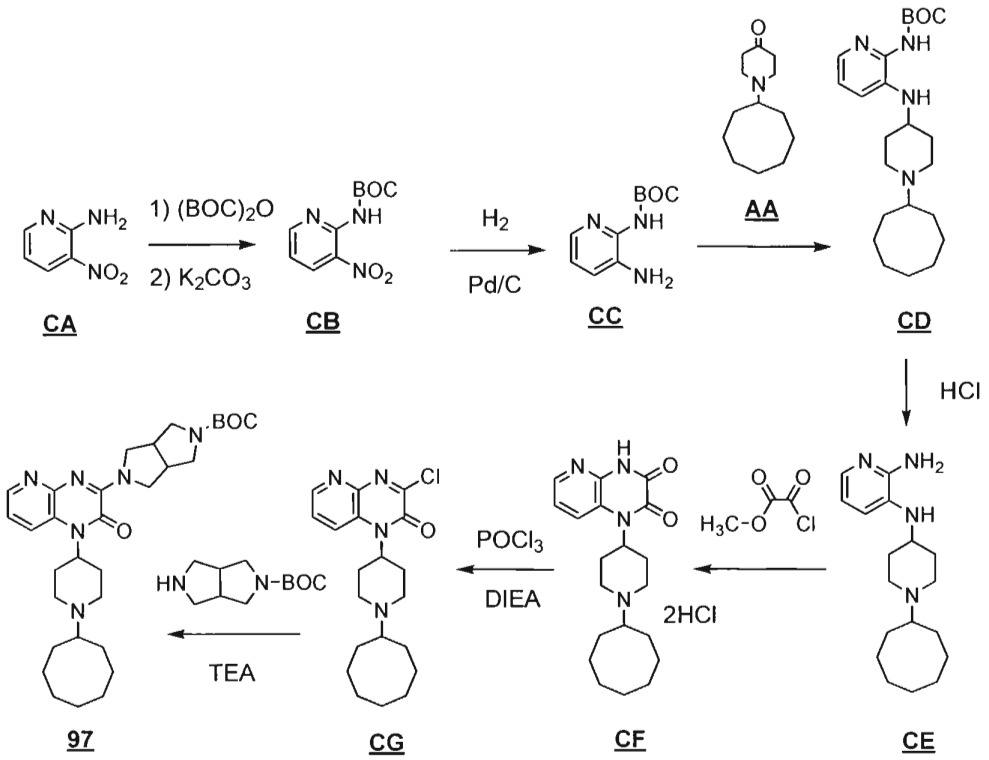
The identity of Substituted-Quinoxaline-Type Piperidine Compound **142**, methyl 1-(4-(1-cyclooctylpiperidin-4-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)pyrrolidine-3-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **142**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.55 (1H, br), 7.50 (1H, d, J=8Hz), 7.14 (2H, m), 4.90 (1H, br), 4.30-3.90 (4H, m), 3.72 (3H, s), 3.13 (1H, m), 2.95 (2H, m), 2.79 (2H, m), 2.67 (1H, m), 2.42 (2H, m), 2.23 (2H, m), 1.90-1.40 (18H, m); LC/MS (98%, t_r=1.46min): *m/z*=467.1 $[M+H]^+$ (Calc: 466.3).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **109**, 1-(4-(1-cyclooctylpiperidin-4-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)pyrrolidine-3-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **109**: ^{1}H NMR: δ_H (400MHz, DMSO): 7.76 (1H, br), 7.36 (1H, m), 7.16 (2H, m), 4.90 (1H, br), 4.20-3.70 (4H, m), 3.60-2.90 (8H, m), 2.20-1.90 (4H, m), 1.80-1.40 (14H, m); LC/MS (100%, t_r=1.38min): *m/z*=453.3 $[M+H]^+$ (Calc: 452.3).

5.6 Example 6



A mixture of the compound of formula **CA** (3-nitropyridin-2-amine, 1.39g, 10mmol, Sigma-Aldrich), $(BOC)_2O$ (20mmol), and DMAP (catalytic amount, Sigma-Aldrich) in THF (28mL) was stirred at 90°C for 1hr. After cooling to a temperature of about 25°C and quenching with water (10mL), the mixture was extracted three times with EtOAc, dried ($MgSO_4$), and concentrated under reduced pressure. At a temperature of about 25°C, the resulting yellow oil was mixed with MeOH (33mL) then added to K_2CO_3 (30mmol). The reaction mixture was stirred at 60°C for 1hr. After cooling to a temperature of about 25°C, 2N aqueous HCl (10mL) was added and the pH was adjusted to be within the range of from about 7 to about 8. Thereafter, the mixture was extracted three times with EtOAc, dried ($MgSO_4$), and concentrated under reduced pressure. The resulting oil was chromatographed with a silica gel column eluted with a gradient of from 10%:90% EtOAc:n-hexane to 50%:50% EtOAc:n-hexane to provide the compound of formula **CB** as a yellow solid (yield 91%).

The identity of the compound of formula **CB**, *tert*-butyl 3-nitropyridin-2-ylcarbamate, was confirmed using ^1H NMR.

Compound **CB**: ^1H NMR: δ_H (300MHz, $CDCl_3$): 9.59 (1H, s), 8.72 (1H, dd, J=4.5, 1.5Hz), 8.5 (1H, dd, J=8.4, 1.5Hz), 7.14 (1H, dd, J=8.4, 4.8Hz), 1.56 (9H, s).

Under a hydrogen atmosphere, a mixture of the compound of formula **CB** (2.11g, 9.07mmol), 10% palladium on carbon (210mg, Sigma-Aldrich), and MeOH (35mL) was stirred at a temperature of about 25°C for 16hr. After the Pd/C was filtered off, the mixture was washed with EtOAc and MeOH, and the filtrate was concentrated under reduced pressure. The resulting solid was suspended with 3:2 n-hexane:diethyl ether which was filtered and washed with n-hexane to provide the compound of formula **CC** as a pale yellow solid (yield 87%).

The identity of the compound of formula **CC**, *tert*-butyl 3-aminopyridin-2-ylcarbamate, was confirmed using ^{1}H NMR.

Compound **CC**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.76 (1H, d, J=1.5Hz), 7.10 (1H, dd, J=8.4, 1.5Hz), 6.99 (1H, dd, J=8.4, 4.8Hz), 1.52 (9H, s).

A mixture of the compound of formula **CC** (710mg, 3.4mmol), the compound of formula **AA** (5.1mmol), $NaBH(OAc)_3$ (10.2mmol) and AcOH (5.1mmol) in $CHCl_3$ (18mL) was stirred at a temperature of about 25°C for 16hr. After quenching with saturated $NaHCO_3$ solution, the mixture was extracted with $CHCl_3$, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed with an amino-silica gel column (Yamazen Corp. W091-01) eluted with a gradient of from 5%:95% EtOAc:n-hexane to 20%:80% EtOAc:n-hexane to 50%:50% EtOAc:n-hexane to provide the compound of formula **CD** as a colorless solid (yield 63%).

The identity of the compound of formula **CD**, *tert*-butyl 3-(1-cyclooctylpiperidin-4-ylamino)pyridin-2-ylcarbamate, was confirmed using ^{1}H NMR.

Compound **CD**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 8.59 (1H, s), 7.60 (1H, t, J=4Hz), 7.01 (2H, d), 4.67 (1H, d, J=8Hz), 3.25 (1H, m), 2.67 (2H, m), 2.35-2.30 (2H, m), 1.88-1.85 (2H, m), 1.69-1.60 (2H, m), 1.56-1.32 (25H, m).

To a suspension of the compound of formula **CD** (317mg, 0.79mmol) in EtOAc (5mL) at a temperature of about 25°C was added 4N HCl in EtOAc (7.9mmol) which was stirred at about 25°C for 1hr and then for 3hr more at 50°C. After neutralization with 28% aqueous ammonia, the pH was adjusted to be within the range of from about 13 to about 14. Thereafter, the mixture was extracted three times with EtOAc, the organic portions were combined, dried ($MgSO_4$), and concentrated under reduced pressure to provide 237mg of the compound of formula **CE** as a brown solid (yield >98%).

The identity of the compound of formula **CE**, N^3-(1-cyclooctylpiperidin-4-yl)pyridine-2,3-diamine, was confirmed using ^{1}H NMR.

Compound **CE**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.80 (1H, d, J=4Hz), 7.66 (1H, s), 6.39 (1H, d, J=4Hz), 4.12 (1H, m), 2.79 (1H, m), 2.68-2.61 (6H, m), 2.43 (2H, m), 1.92-1.48 (24H, m).

To a mixture of the compound of formula **CE** (168mg, 0.79mmol) in CH_2Cl_2 (10mL) at 0°C was added dropwise over 10min methyl 2-chloro-2-oxoacetate (0.79mmol, Sigma-Aldrich) in CH_2Cl_2 (3mL). The resulting reaction mixture was stirred at 0°C for 30min. After quenching with saturated $NaHCO_3$ solution, the mixture was extracted three times with $CHCl_3$. Thereafter, the organic portions were combined, dried ($MgSO_4$), and concentrated under reduced pressure. At a temperature of about 25°C, the resulting oil was mixed with ethanol (4mL) and the mixture was then added to sodium methoxide (1.09mmol, Sigma-Aldrich). The reaction mixture was stirred at 70°C for 1hr. After concentration under reduced pressure, to the resulting oil was added water (0.5mL) and 2N HCl (1mL). The resulting precipitate was filtered, washed with 90%:10% water:MeOH, and dried under reduced pressure at 60°C for 12hr to provide the dihydrochloride of the compound of formula **CF** as a colorless solid.

The identity of the compound of formula **CF**, 1-(1-cyclooctylpiperidin-4-yl)pyrido[3,2-*b*]pyrazine-2,3(1*H*,4*H*)-dione, was confirmed using ^{1}H NMR and LC/MS.

Compound **CF**: ^{1}H NMR: δ_H (300MHz, DMSO-d_6): 12.39 (1H, s), 9.8 (1H, br), 8.27 (1H, m), 8.14 (1H, d, J=4.5Hz), 7.21 (1H, dd, J=4.5, 8.1Hz), 4.91 (1H, m), 3.45-3.3 (6H, m), 2.99 (2H, m), 2.02 (2H, m), 1.99 (2H, m), 1.58-1.46 (11H, m); LC/MS: *m/z*=357 $[M+H]^+$ (Calc: 356.5).

Phosphoryl chloride (1.85mmol, Sigma-Aldrich) was added to a suspension of the compound of formula **CF** (220mg, 0.62mmol) and DIEA (1.85mmol, Sigma-Aldrich) in toluene (6mL) and DMF (1mL) at 25°C. The resulting reaction mixture was stirred at 100°C for 45min. After cooling to a temperature of about 25°C and quenching with water, the mixture was extracted three times with $CHCl_3$/water, dried (Na_2SO_4), and concentrated under reduced pressure to provide 187mg of the compound of formula **CG** as a brown solid (yield 81%).

The identity of the compound of formula **CG**, 3-chloro-1-(1-cyclooctylpiperidin-4-yl)pyrido[3,2-*b*]pyrazin-2(1*H*)-one, was confirmed using LC/MS.

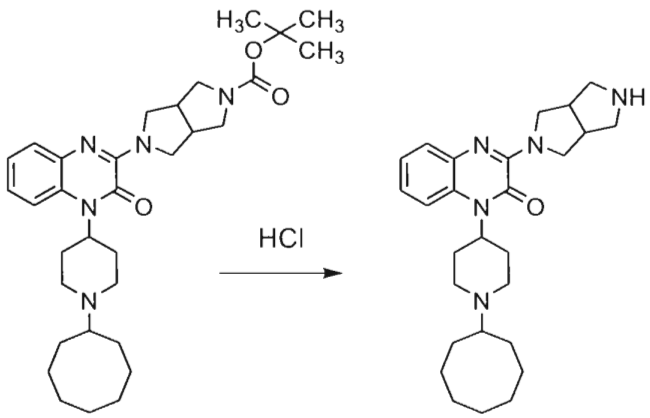
Compound **CG**: LC/MS: *m/z*=375 $[M+H]^+$ (Calc: 374.2).

TEA (0.21mmol) and *tert*-butyl hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (0.21mmol) were added to a suspension of the compound of formula **CG** (80mg, 0.21mmol) in acetonitrile (3mL) at 25°C. The resulting reaction mixture was stirred at 80°C for 2hr. After cooling to a temperature of about 25°C and quenching with water (3mL), the mixture was extracted three times with $CHCl_3$/water, dried (Na_2SO_4), and concentrated under reduced pressure to provide a yellow oil. The oil was chromatographed with a silica gel column eluted with a gradient of from 97%:3% $CHCl_3$:MeOH to 90%:10% $CHCl_3$:MeOH to provide 68mg of Substituted-Quinoxaline-Type Piperidine Compound **97** as a yellow amorphous solid (yield 62%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **97**, *tert*-butyl 5-(1-(1-cyclooctylpiperidin-4-yl)-2-oxo-1,2-dihydropyrido[3,2-*b*]pyrazin-3-yl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate, was confirmed using ^{1}H NMR.

Substituted-Quinoxaline-Type Piperidine Compound **97**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 8.33 (1H, d, J=4.8Hz), 7.87 (1H, m), 7.04 (1H, m), 4.46 (1H, m), 4.20 (1H, m), 4.00 (1H, m), 3.82 (1H, m), 3.62 (2H, m), 3.30 (2H, m), 2.96 (4H, m), 2.66 (2H, m), 2.41 (2H, m), 1.75-1.44 (26H, m).

5.7 Example 7



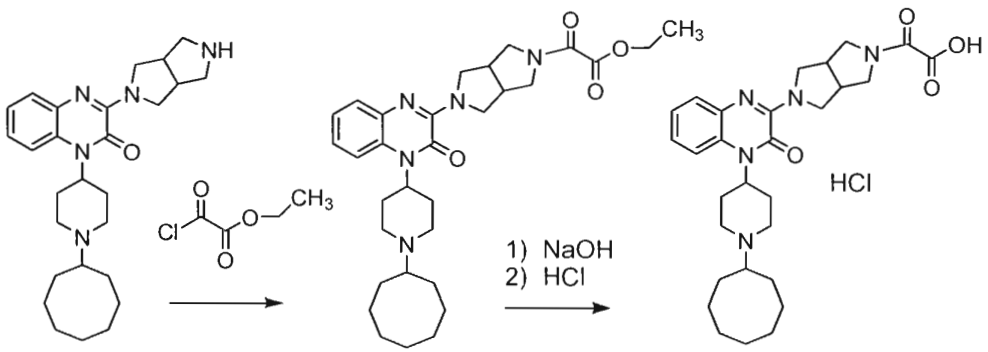
4 **5**

To a suspension of Substituted-Quinoxaline-Type Piperidine Compound **4** (120mg, 0.22mmol) in 1,4-dioxane (4mL) and MeOH (1mL) was added 4N HCl in 1,4-dioxane (2mL)

at a temperature of about 25°C. The reaction mixture was stirred at 25°C for 1hr. The resulting precipitate was filtered, washed with diethyl ether (3mL), and dried under reduced pressure at 70°C to provide 123mg of Substituted-Quinoxaline-Type Piperidine Compound **5** as a colorless solid (yield >98%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **5**, 1-(1-cyclooctylpiperidin-4-yl)-3-(hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)quinoxalin-2(1*H*)-one, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **5**: ^{1}H NMR: δ_H (400MHz, DMSO): 9.67-9.54 (3H, br), 7.91 (1H, br), 7.53 (1H, s), 7.22 (2H, m), 5.03 (1H, br), 4.50-3.90 (12H, m), 3.41-3.00 (6H, m), 2.07 (2H, m), 1.89-1.43 (13H, m); LC/MS: *m/z*=450.1 $[M+H]^+$ (Calc: 449.6).



5 **173** **174**

To a mixture of Substituted-Quinoxaline-Type Piperidine Compound **5** (180mg, 0.328mmol) and CH_2Cl_2 (4mL) at 0°C was added pyridine (93μL, 1.148mmol) and ethyl 2-chloro-2-oxoacetate (92μL, 0.820mmol, Sigma-Aldrich). After heating to a temperature of about 25°C the reaction mixture was stirred for 2h. The reaction mixture was diluted with water (5mL) then extracted three times with $CHCl_3$ (10mL for each extraction). The organic portions were combined, washed with saturated aqueous NaCl (10mL), dried ($MgSO_4$), filtrated, and concentrated under reduced pressure. The residue was chromatographed with an amino-silica gel column (Yamazen Corp. W091-01) eluted with a gradient of from 10%:90% EtOAc:n-hexane to 50%:50% EtOAc:n-hexane to provide 89mg of Substituted-Quinoxaline-Type Piperidine Compound **173** as a white amorphous solid (yield 47%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **173**, ethyl 2-(5-(4-(1-cyclooctylpiperidin-4-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)-2-oxoacetate, was confirmed using ^{1}H NMR and MS.

Substituted-Quinoxaline-Type Piperidine Compound **173**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.46 (1H, m), 7.32 (1H, m), 7.18 (2H, m), 5.20 (1H, br), 4.31 (2H, q, J=8.0Hz), 4.20 (2H, m), 3.95-3.85 (4H, m), 3.70-3.50 (4H, m), 3.00 (2H, m), 2.40-1.90 (5H, m), 1.90-1.45 (18H, m), 1.39 (3H, t, J=8.0Hz); MS: *m/z*=576 $[M+H]^+$ (Calc: 575.3).

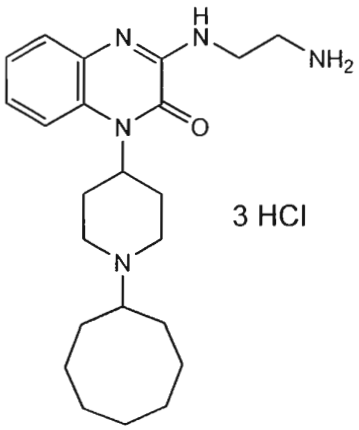
To a mixture of Substituted-Quinoxaline-Type Piperidine Compound **173** (85mg, 0.148mmol) in MeOH (4mL) at a temperature of about 25°C was added 2N aqueous NaOH (0.15mL, 0.295mmol). The reaction mixture was stirred for 2h at a temperature of about 25°C. After concentration under reduced pressure, the mixture was diluted with water (5mL) then extracted with EtOAc (5mL). The aqueous portion was neutralized by adding a first treatment of 2N aqueous HCl at a temperature of 0°C. Thereafter, the mixture was extracted twice with $CHCl_3$ (10mL for each extraction). The organic portions portions were combined, dried ($MgSO_4$), filtrated, and concentrated under reduced pressure to provide a white solid. To the solid was added water (2mL) then a second treatment of 2N aqueous HCl (1mL). Thereafter, the mixture was concentrated under reduced pressure to provide 77mg of the hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **174** (yield 89%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **174**, 2-(5-(4-(1-cyclooctylpiperidin-4-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1*H*)-yl)-2-oxoacetic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **174**: ^{1}H NMR: δ_H (400MHz, DMSO): 10.62 (0.9H, m), 9.84 (0.1H, m), 7.83 (0.9H, m), 7.72 (0.1H, m), 7.60 (1H, m), 7.28 (2H, m), 5.86 (1H, m), 4.40-4.00 (6H, m), 3.90-3.35 (4H, m), 3.10 (2H, m), 2.97 (1H, m), 2.60 (2H, m), 2.40-1.30 (20H, m); LC/MS (100%, t_r=1.45min): *m/z*=548 $[M+H]^+$ (Calc: 547.3).

5.8 Example 8

In a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **5** in Example 7, the following Substituted-Quinoxaline-Type Piperidine Compounds were prepared.

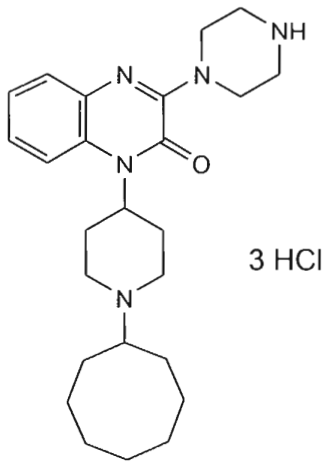


9

The trihydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **9** was prepared by using Substituted-Quinoxaline-Type Piperidine Compound **7** in place of Substituted-Quinoxaline-Type Piperidine Compound **4** (yield 90%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **9**, 3-(2-aminoethylamino)-1-(1-cyclooctylpiperidin-4-yl)quinoxalin-2(1*H*)-one, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **9**: ^{1}H NMR: δ_H (400MHz, DMSO): 8.10-7.80 (4H, br), 7.50 (1H, s), 7.25 (2H, m), 5.00 (1H, br), 3.68 (2H, d, J=4Hz), 3.43-3.39 (5H, m), 3.19-3.08 (4H, m), 2.06 (2H, s), 1.99-1.19 (15H, m); LC/MS: *m/z*=398.1 $[M+H]^+$ (Calc: 397.6).

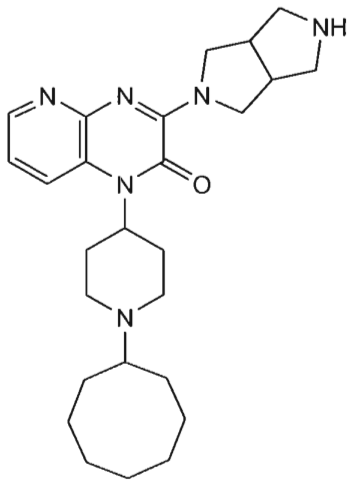


10

The trihydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **10** was prepared by using Substituted-Quinoxaline-Type Piperidine Compound **8** in place of Substituted-Quinoxaline-Type Piperidine Compound **4** (yield 98%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **10**, 1-(1-cyclooctylpiperidin-4-yl)-3-(piperazin-1-yl)quinoxalin-2(1*H*)-one, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **10**: ^{1}H NMR: δ_H (400MHz, DMSO): 9.53 (1H, s), 7.53 (1H, d, J=4Hz), 7.33-7.26 (2H, m), 5.39 (1H, br), 4.04 (4H, s), 3.42-3.35 (5H, m), 3.20 (4H, s), 1.99 (2H, s), 1.73-1.43 (15H, m); LC/MS: *m/z*=424.1 $[M+H]^+$ (Calc: 423.6).

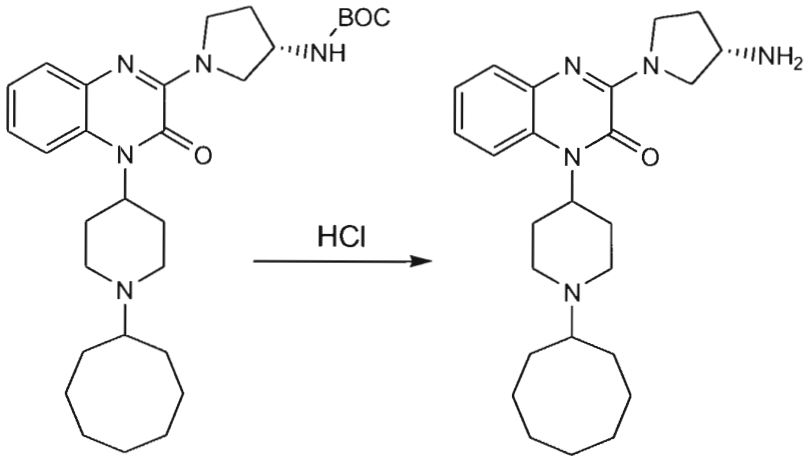


87

Substituted-Quinoxaline-Type Piperidine Compound **87** was prepared by using Substituted-Quinoxaline-Type Piperidine Compound **97** in place of Substituted-Quinoxaline-Type Piperidine Compound **4** (yield 82%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **87**, 1-(1-cyclooctylpiperidin-4-yl)-3-(hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)pyrido[3,2-*b*]pyrazin-2(1*H*)-one, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **87**: ^{1}H NMR: δ_H (400MHz, DMSO): 10.0 (1H, m), 9.58 (1H, m), 8.89 (1H, br), 8.26 (1H, d, J=5.2Hz), 7.44 (1H, m), 5.15 (1H, br), 4.42-4.36 (3H, m), 3.95-3.88 (3H, m), 3.56-3.02 (11H, m), 2.08-1.44 (16H, m); LC/MS: *m/z*=451 $[M+H]^+$ (Calc: 450.6).



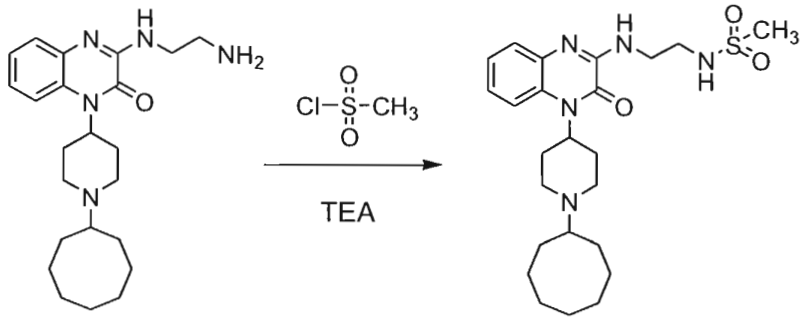
161 **162**

In a manner similar to Example 3, the hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **161**, (*S*)-*tert*-butyl 1-(4-(1-cyclooctylpiperidin-4-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)pyrrolidin-3-ylcarbamate, was prepared from Substituted-Quinoxaline-Type Piperidine Compound **404** by using (*S*)-*tert*-butyl pyrrolidin-3-ylcarbamate (Sigma-Aldrich) in place of 2-aminoethanol. Thereafter, in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **5** in Example 7, Substituted-Quinoxaline-Type Piperidine Compound **162** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **161** (yield 98% for two steps).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **162**, (*S*)-3-(3-aminopyrrolidin-1-yl)-1-(1-cyclooctylpiperidin-4-yl)quinoxalin-2(1*H*)-one, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **162**: ^{1}H NMR: δ_H (400MHz, CD_3OD): 7.64 (1H, br), 7.41 (1H, br), 7.14 (2H, m), 4.08 (2H, m), 3.93 (1H, m), 3.72 (1H, m), 3.57 (1H, m), 3.02 (2H, d, J=12Hz), 2.91 (2H, m), 2.77 (1H, m), 2.54 (2H, m), 2.14 (1H, m), 1.90-1.45 (18H, m); LC/MS (99%, t_r=0.58min): *m/z*=424.3 $[M+H]^+$ (Calc: 423.3).

5.9 Example 9



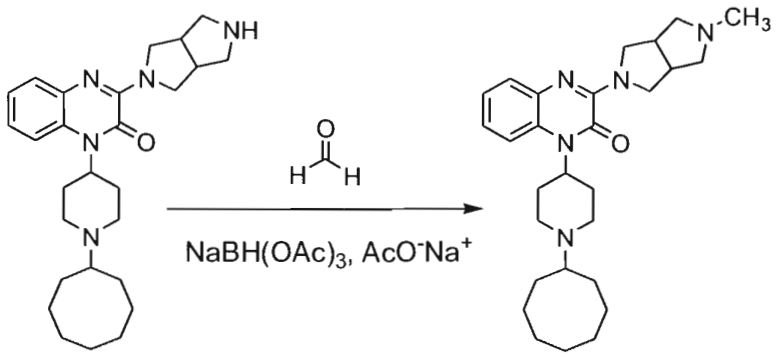
9 **11**

TEA (0.316mmol) and methansulfonyl chloride (0.087mmol, Sigma-Aldrich) were added to a mixture of Substituted-Quinoxaline-Type Piperidine Compound **9** (40mg, 0.079mmol) in CH_2Cl_2 at 0°C and the resulting reaction mixture was stirred for 3hr. Thereafter, an additional portion of methansulfonyl chloride (0.174mmol) was added and the reaction mixture was stirred at 50°C for 7hr. After cooling to a temperature of about 25°C, the mixture was extracted three times with $CHCl_3$/water, dried ($MgSO_4$), and concentrated under reduced pressure to provide a colorless oil. The oil was chromatographed with a silica gel column eluted with a gradient of from 95%:5% $CHCl_3$:MeOH to 90%:10% $CHCl_3$:MeOH to provide 27mg of Substituted-Quinoxaline-Type Piperidine Compound **11** as a colorless solid (yield 73%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **11**, *N*-(2-(4-(1-cyclooctylpiperidin-4-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)ethyl)methanesulfonamide, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **11**: ^{1}H NMR: δ_H (400MHz, DMSO): 7.68 (1H, m), 7.57 (1H, m), 7.25-7.15 (2H, m), 3.53 (2H, t), 3.23 (2H, m), 2.93 (3H, s), 2.85-2.55 (4H, m), 2.45-2.30 (5H, m), 1.80-1.40 (14H, m); LC/MS (100%): *m/z*=476.7 $[M+H]^+$ (Calc: 476.1).

5.10 Example 10



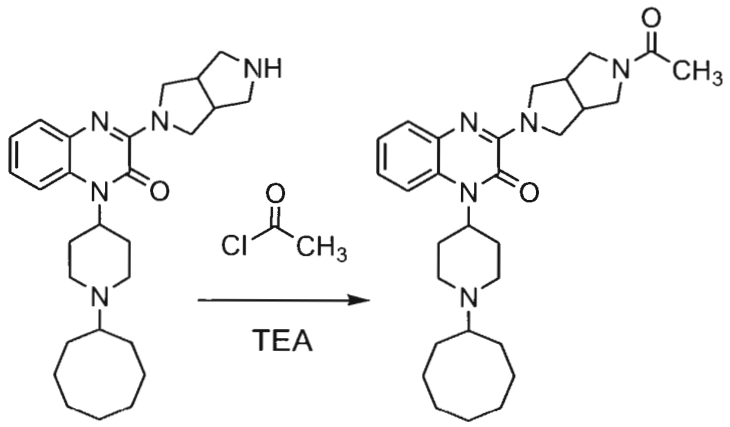
5 **12**

Substituted-Quinoxaline-Type Piperidine Compound **5** (100mg, 0.18mmmol), 39% formaldehyde (0.27mmol, Sigma-Aldrich), $NaBH(OAc)_3$ (0.54mmol), and sodium acetate (0.54mmol, Sigma-Aldrich) were added to $CHCl_3$ (5mL) and the resulting reaction mixture was stirred at 25°C for 16hr. After quenching with saturated $NaHCO_3$ solution, the mixture was extracted with $CHCl_3$/water. Thereafter, the organic portion was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed with an amino-silica gel column (Yamazen Corp. W091-01) eluted with a gradient of from 30%:70% EtOAc:n-hexane to 70%:30% EtOAc:n-hexane to provide Substituted-Quinoxaline-Type Piperidine Compound **12** as a colorless solid (yield 75%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **12**, 1-(1-cyclooctylpiperidin-4-yl)-3-(5-methylhexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)quinoxalin-2(1*H*)-one, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **12**: ^{1}H NMR: δ_H (400MHz, DMSO): 7.61 (1H, d, J=8Hz), 7.36 (1H, t, J=4Hz), 7.19-7.13 (2H, m), 4.66 (1H, br), 3.96 (3H, s), 3.78 (3H, m), 2.95-2.54 (10H, m), 2.22 (3H, s), 1.74-1.43 (17H, m); LC/MS: *m/z*=464.1 $[M+H]^+$ (Calc: 463.7).

5.11 Example 11



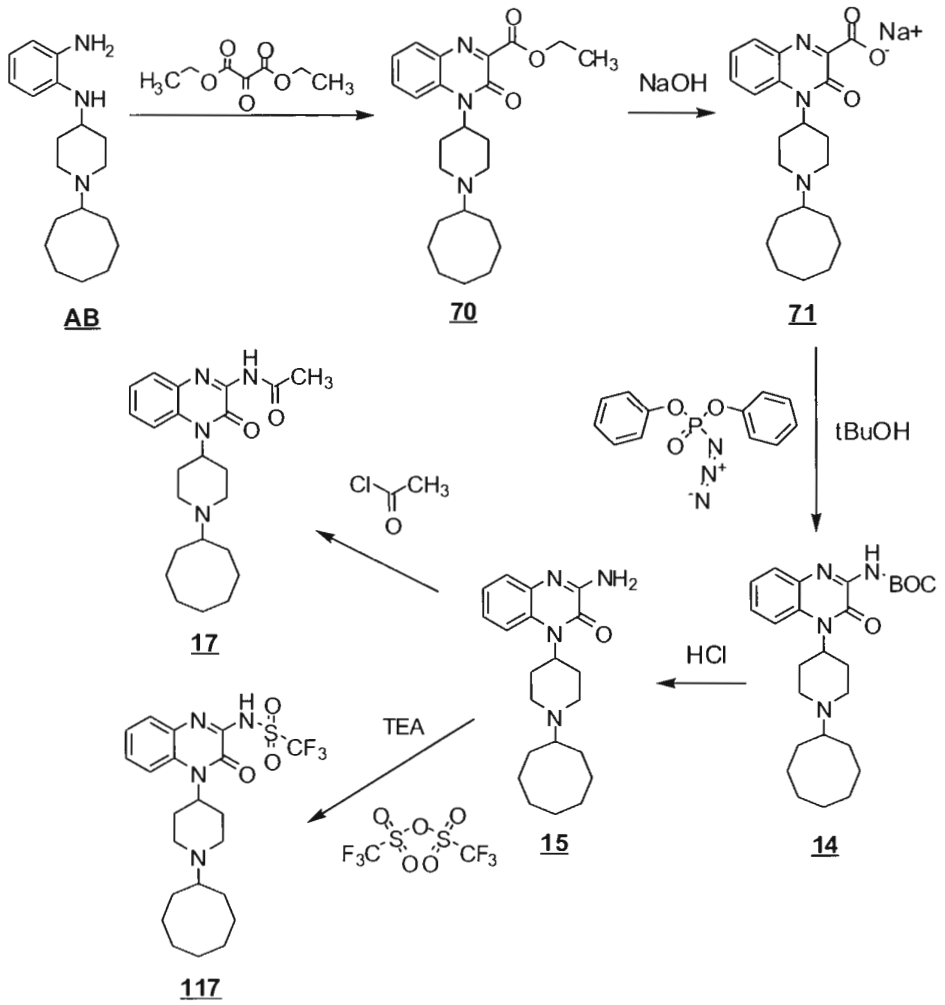
5 **13**

TEA (0.9mmol) and acetyl chloride (0.27mmol, Sigma-Aldrich) were added to a mixture of Substituted-Quinoxaline-Type Piperidine Compound **5** (100mg, 0.18mmol) in CH_2Cl_2 at 0°C. The resulting reaction mixture was stirred at 0°C for 1hr. After heating to a temperature of about 25°C, the mixture was extracted three times with $CHCl_3$/water, dried ($MgSO_4$), and concentrated under reduced pressure to provide a colorless oil. The oil was chromatographed with a silica gel column eluted with a gradient of from 97%:3% $CHCl_3$:MeOH to 90%:10% $CHCl_3$:MeOH to 85%:15% $CHCl_3$:MeOH to provide 64mg of Substituted-Quinoxaline-Type Piperidine Compound **13** as a colorless solid (yield 73%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **13**, 3-(5-acetylhexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)-1-(1-cyclooctylpiperidin-4-yl)quinoxalin-2(1*H*)-one, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **13**: ^{1}H NMR: δ_H (400MHz, DMSO): 7.58 (1H, d, J=8Hz), 7.35 (1H, t, J=4Hz), 7.18-7.13 (2H, m), 4.61 (1H, br), 4.03 (1H, br), 3.68 (2H, dd, J=4Hz), 3.54 (1H, dd, J=4Hz), 3.40 (1H, m), 3.24 (1H, m), 2.99-2.40 (7H, m), 2.38 (2H, t, J=12Hz), 1.93-1.43 (17H, m); LC/MS: *m/z*=492.1 $[M+H]^+$ (Calc: 491.7).

5.12 Example 12



Diethyl 2-oxomalonate (5mmol, Sigma-Aldrich) was added dropwise to a suspension of the compound of formula **AB** (1507mg, 5mmol) in toluene (15mL) at 25°C. The resulting reaction mixture was stirred at 130°C for 4hr. After cooling to a temperature of about 25°C and concentrating under reduced pressure, a red oil was obtained. The oil was chromatographed with a silica gel column eluted with a gradient of from 99%:1% $CHCl_3$:MeOH to 95%:5% $CHCl_3$:MeOH to provide a red amorphous solid. The solid was chromatographed with a silica gel column eluted with a gradient of from 95%:5% EtOAc:MeOH to 90%:10% EtOAc:MeOH to provide 1100mg of Substituted-Quinoxaline-Type Piperidine Compound **70** as a colorless solid (yield 53%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **70**, ethyl 4-(1-cyclooctylpiperidin-4-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **70**: ^{1}H NMR: δ_H (300MHz, DMSO): 7.95 (1H, d, J=8.7Hz), 7.87 (1H, dd, J=7.8, 1.8Hz), 7.31 (1H, t, J=7.2Hz), 7.44 (1H, t, J=6.9Hz), 4.78 (1H, br), 4.37 (2H, d, J=7.2Hz), 2.85 (2H, m), 2.60-2.34 (5H, m), 1.70-1.42 (16H, m), 1.32 (3H, t, J=7.2Hz); LC/MS: *m/z*=412 $[M+H]^+$ (Calc: 411.5).

2N NaOH (0.25mmol) was added to a mixture of Substituted-Quinoxaline-Type Piperidine Compound **70** (104mg, 0.25mmol) in ethanol at 25°C. The resulting reaction mixture was stirred at 50°C for 90min. After concentration under reduced pressure, the resulting yellow solid was dried under reduced pressure at 80°C for 12hr to provide 100mg of the sodium salt of Substituted-Quinoxaline-Type Piperidine Compound **71** as a yellow solid (yield >98%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **71**, 4-(1-cyclooctylpiperidin-4-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **71**: ^{1}H NMR: δ_H (300MHz, DMSO): 7.76 (1H, d, J=8.4Hz), 7.64 (1H, dd, J=7.8, 1.5Hz), 7.48 (1H, t, J=8.4Hz), 7.28 (1H, t, J=7.5Hz), 4.67 (1H, br), 2.87-2.34 (7H, m), 1.71-1.42 (16H, m); LC/MS: *m/z*=384 $[M+H]^+$ (Calc: 383.5).

Diphenylphosphoryl azide ("DPPA", 1.2mmol, Sigma-Aldrich) was added to a mixture of the sodium salt of Substituted-Quinoxaline-Type Piperidine Compound **71** (120mg, 0.3mmol) in *tert*-BuOH (*i.e.*, 2-methylpropan-2-ol) at 25°C. Thereafter, the reaction mixture was warmed to a temperature of 100°C and stirred for 3.5h. After cooling to about 25°C and quenching with saturated $NaHCO_3$ solution, the mixture was extracted three times with EtOAc/water, dried ($MgSO_4$), and concentrated under reduced pressure to provide an orange oil. The oil was chromatographed with a silica gel column eluted with a gradient of from 99%:1% $CHCl_3$:MeOH to 95%:5% $CHCl_3$:MeOH to provide 124mg of Substituted-Quinoxaline-Type Piperidine Compound **14** as a pale yellow amorphous solid (yield 91%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **14**, *tert*-butyl 4-(1-cyclooctylpiperidin-4-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylcarbamate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **14**: ^{1}H NMR: δ_H (300MHz, DMSO): 8.84 (1H, s), 7.83 (1H, d, J=8.7Hz), 7.60 (1H, d, J=7.8Hz), 7.47 (1H, t, J=7.9Hz), 7.34 (1H, t, J=7.2Hz), 4.69 (1H, br), 2.83-2.42 (8H, m), 1.71-1.43 (24H, m); LC/MS: *m/z*=455.1 $[M+H]^+$ (Calc: 454.6).

Substituted-Quinoxaline-Type Piperidine Compound **15** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **14** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **5** in Example 7 (yield 84%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **15**, 3-amino-1-(1-cyclooctylpiperidin-4-yl)quinoxalin-2(1*H*)-one, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **15**: ^{1}H NMR: δ_H (400MHz, DMSO): 7.65 (1H, d, J=8Hz), 7.33 (1H, m), 7.19 (2H, m), 7.01 (2H, br), 4.72 (1H, br), 4.04 (4H, s), 2.85 (2H, d, J=12Hz), 2.69-2.50 (3H, m), 2.40 (2H, m), 1.71-1.43 (16H, m); LC/MS: *m/z*=355.1 $[M+H]^+$ (Calc: 354.5).

Substituted-Quinoxaline-Type Piperidine Compound **17** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **15** in a manner similar to Example 11 (yield 78%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **17**, *N*-(4-(1-cyclooctylpiperidin-4-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)acetamide, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **17**: ^{1}H NMR: δ_H (300MHz, DMSO): 9.65 (1H, s), 7.90 (1H, br), 7.63 (1H, d, J=6.3Hz), 7.49 (1H, t, J=8.4Hz), 7.35 (1H, t, J=7.5Hz), 4.78 (1H, br), 3.25-2.52 (6H, m), 2.37 (3H, s), 1.90-1.42 (17H, m); LC/MS: *m/z*=397 $[M+H]^+$ (Calc: 396.5).

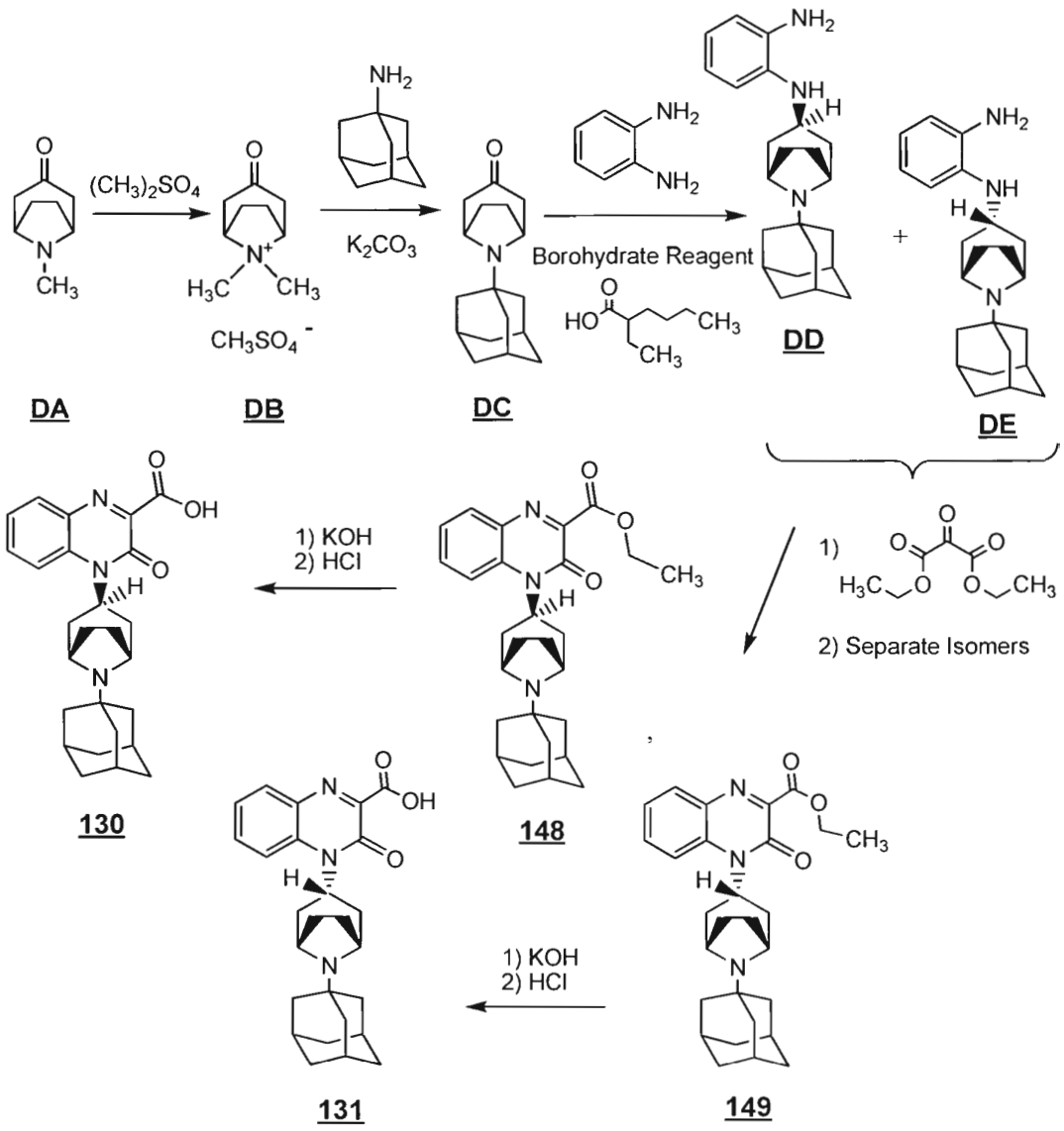
At a temperature of 0°C, trifluoromethanesulfonic anhydride (41.4μL, 0.246mmol, Sigma-Aldrich) and TEA (86.2μL, 0.615mmol) were added to a mixture of Substituted-Quinoxaline-Type Piperidine Compound **15** (80mg, 0.205mmol) in CH_2Cl_2 (3mL). After warming it to a temperature of about 25°C, the reaction mixture was stirred for 5.5h. After

cooling to 0°C, the mixture was quenched with saturated aqueous $NaHCO_3$ (5mL) and extracted three times with $CHCl_3$ (5mL for each extraction). The organic portions were combined, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide a residue. The residue was triturated with MeOH, filtered, rinsed with MeOH, and collected to provide 36mg of Substituted-Quinoxaline-Type Piperidine Compound **117** as a white solid (yield 36%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **117**, *N*-(4-(1-cyclooctylpiperidin-4-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)-1,1,1-trifluoromethanesulfonamide, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **117**: ^{1}H NMR: δ_H (400MHz, DMSO): 9.10 (1H, br), 7.68 (1H, d, J=8Hz), 7.35 (1H, d, J=8Hz), 7.24 (1H, t, J=8Hz), 7.17 (1H, t, J=8Hz), 4.90 (1H, m), 3.50-3.30 (3H, m), 3.10 (2H, m), 2.00-1.40 (18H, m); LC/MS: (100%, t_r=1.91min): *m/z*=487.1 $[M+H]^+$ (Calc: 486.2).

5.13 Example 13



A mixture of the compound of formula **DA** (tropinone, 200g, 1.438mol, Sigma-Aldrich) and acetone (1L) was cooled to 0°C. Dimethyl sulfate (143mL, 1.5098 mol, Sigma-Aldrich) was added dropwise over 30min and the resulting reaction mixture was stirred for 3h, then filtered. The filter cake was dried under reduced pressure for 18h to provide 380g of a compound of formula **DB** as a white solid (yield >98%).

The identity of the compound of formula **DB**, tropinone dimethylsulfate salt, was confirmed using ^{1}H NMR.

Compound **DB**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 4.14 (2H, m), 3.40 (3H, s), 3.38 (3H, s), 3.32 (1H, m), 3.12 (1H, m), 2.55-2.40 (4H, m), 1.96 (2H, m).

A mixture of the compound of formula **DB** (40g, 150.8mmol) and water (70mL) was added dropwise to a boiling mixture of 1-adamantylamine (22.8g, 150.8mmol, Sigma-Aldrich) in ethanol (250mL) containing K_2CO_3 (2.1g, 15mmol). The reaction mixture was refluxed an additional 3h then evaporated to dryness under reduced pressure to provide a residue. The residue was partitioned between EtOAc (500mL) and 1M K_2CO_3 solution (500mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (500mL). The organic portions were combined, dried ($MgSO_4$), and evaporated to dryness under reduced pressure to provide a brown oil. Flash chromatography of the oil with a silica gel column eluting with 3:10 hexanes:EtOAc provided 5.0g of a compound of formula **DC** as a pale yellow solid (yield 13%).

The identity of the compound of formula **DC**, 8-adamantan-1-yl-8-aza-bicyclo[3.2.1]octan-3-one, was confirmed using ^{1}H NMR.

Compound **DC**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 3.96 (2H, m), 2.50 (2H, dd, J=16.0, 4.5Hz), 2.27 (2H, dd, J=16, 1.7Hz), 2.07 (2H, m), 1.78 (2H, m), 1.71-1.56 (15H, m).

Sodium tetrahydroborate (9.46g, 250mmol, Sigma-Aldrich) was suspended in dry CH_2Cl_2 (500mL). 2-Ethylhexanoic acid (126.2g, 875mmol, Sigma-Aldrich) was added and the mixture stirred at a temperature of about 25°C for 16h. The resulting borohydrate reagent, believed to comprise sodium tris(2-ethylhexanoyloxy)hydroborate and assumed to have a molarity of 0.5M, was held for later use.

To a mixture of the compound of formula **DC** (5.2g, 20.05mmol), 1,2-phenylenediamine (4.34g, 40.1mmol), and CH_2Cl_2 (50mL) was added 2-ethylhexanoic acid (5.2mL, 20.05mmol). Under a nitrogen atmosphere, the resulting mixture was cooled to 0°C with stirring. The borohydride reagent (0.5M, 120.3mL, 60.15mmol), previously prepared as described above, was added and the reaction mixture was stirred for 18h. The mixture was partitioned between EtOAc (400mL) and 2M sodium carbonate (400mL). The organic phase was separated, dried ($MgSO_4$), and evaporated to dryness under reduced pressure to provide a residue. Flash chromatography of the residue with a silica gel column eluting with 1:1 EtOAc:hexanes followed by eluting with 100:100:10:1 EtOAc:hexanes:MeOH:ammonia

provided 5g of the compounds of formula **DD** and **DE** as an approximately 2:1 mixture of *endo*:*exo* (**DD**:**DE**) isomers (yield 71%).

The identity of the compound of formula **DD**:**DE** isomeric mixture, *N*-(8-adamantan-1-yl-8-aza-bicyclo[3.2.1]oct-3-yl)-benzene-1,2-diamine, was confirmed using ^{1}H NMR.

Compounds **DD**:**DE**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 6.82-6.50 (4H[isomer 1+2], m), 3.90-3.60 (3H[isomer 1+2], m), 2.55-1.96 (11H[isomer 1+2], m), 1.87-1.52 (15H[isomer 1+2], m).

The above **DD**:**DE** mixture (5.0g, 14.22mmol) and diethyl 2-oxomalonate (3.25mL, 21.3mmol, Sigma-Aldrich) were dissolved in dry toluene (100mL). Powdered 4Å molecular sieves (5g) were added and the reaction mixture was refluxed for 7h. The mixture was cooled then evaporated to dryness under reduced pressure to provide a residue. Flash chromatography of the residue with a silica gel column eluting with 3:1 hexanes:EtOAc provided two fractions - less polar fraction 1 and more polar fraction 2. Less polar fraction 1 was triturated with diethyl ether (25mL) to provide 930mg of a yellow solid. LC/MS showed this material to be a mixture of Substituted-Quinoxaline-Type Piperidine Compound **148**, the *endo* isomer, and Substituted-Quinoxaline-Type Piperidine Compound **149**, the *exo* isomer. More polar fraction 2 was also triturated with diethyl ether (50mL) to provide 1.4g of Substituted-Quinoxaline-Type Piperidine Compound **149** as a white solid.

The identity of Substituted-Quinoxaline-Type Piperidine Compound **149**, *exo*-4-(8-adamantan-1-yl-8-aza-bicyclo[3.2.1]oct-3-yl)-3-oxo-3,4-dihydro-quinoxaline-2-carboxylic acid ethyl ester, was confirmed by nuclear Overhauser enhancement spectroscopy ("NOESY") NMR experiments and MS.

Substituted-Quinoxaline-Type Piperidine Compound **149**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 8.37 (1H, bm), 7.91 (1H, dd, J=8.10, 1.56Hz), 7.59 (1H, dt, 7.24, 1.59Hz), 7.34 (1H, dt, J=8.04, 0.84Hz), 5.91 (1H, m), 4.51 (2H, q, J=7.1Hz), 3.94 (2H, m), 2.61(2H, dt, J=11.49, 8.30Hz), 2.09 (3H, m), 1.85-1.55 (19H, m), 1.44 (3H, t, J=7.13Hz); MS: *m/z*=462.3 $[M+1]^+$ (Calc.: 462.3).

Re-chromatography of Fraction 1 with a silica gel column eluting with 300:30:1:0.1 hexanes:EtOAc:MeOH:ammonia provided 440mg of Substituted-Quinoxaline-Type Piperidine Compound **148** as a pale yellow solid.

The identity of Substituted-Quinoxaline-Type Piperidine Compound **148**, *endo*-4-(8-adamantan-1-yl-8-aza-bicyclo[3.2.1]oct-3-yl)-3-oxo-3,4-dihydro-quinoxaline-2-carboxylic acid ethyl ester, was confirmed by NOESY NMR and MS.

Substituted-Quinoxaline-Type Piperidine Compound **148**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.92 (1H, dd, J=8.02, 1.49Hz), 7.61 (1H, t, J=8.15Hz), 7.52 (1H, d, J=8.15Hz), 7.34 91H, dt, J=8.15, 1.49Hz), 4.51 (2H, q, J=4.0Hz), 3.87 (1H, m), 2.22 (2H, m), 2.05 (4H, m), 1.83 (4H, m), 1.72-1.53 (15H, m), 1.44 (3H, t, J=4.0Hz); MS: *m/z*=462.3 $[M+1]^+$ (Calc.: 462.3).

To a mixture of Substituted-Quinoxaline-Type Piperidine Compound **148** (440mg, 0.95mmol) and tetrahydrofuran (10mL) was added potassium hydroxide (220mg, 3.8mmol) in water (1mL) and the reaction mixture was stirred at a temperature of about 25°C for 3h. TLC showed that the reaction was incomplete after this time so additional MeOH (5mL) was added to form a homogeneous solution and the reaction mixture was stirred at about 25°C for an additional 2h. The reaction mixture was evaporated to dryness under reduced pressure to provide a residue. The residue was suspended in water (50mL) and, using a pH meter, slowly acidified to pH 5.5 with 1M HCl. The mixture was filtered. The filter cake was washed with acetone (50mL) and dried under reduced pressure at 70°C for 18h to provide 315mg of a white solid (yield 78%). This solid (200mg) was suspended in diethyl ether (5mL) and 1M HCl (1mL) was added. The resulting mixture was stirred at a temperature of about 25°C for 1h then filtered. The filter cake was dried under reduced pressure at 70°C for 18h to provide 208mg of Substituted-Quinoxaline-Type Piperidine Compound **130** as a pale yellow solid.

The identity of Substituted-Quinoxaline-Type Piperidine Compound **130**, *endo*-4-(8-adamantan-1-yl-8-aza-bicyclo[3.2.1]oct-3-yl)-3-oxo-3,4-dihydro-quinoxaline-2-carboxylic acid hydrochloride was confirmed using ^{1}H NMR and MS.

Substituted-Quinoxaline-Type Piperidine Compound **130**: ^{1}H NMR: δ_H (500MHz, CD_3OD+DCl): 8.16 (1H, d, J=8.61Hz), 7.99 (1H, dd, J=6.87, 1.16Hz), 7.82 (1H, dt, J=8.61, 1.16Hz), 7.53 (1H, t, J=7.76Hz), 6.15 (1H, m), 4.54 (2H, m), 2.96 (2H, m), 2.55 (2H, m), 2.37-2.25 (13H, m), 1.81-1.74 (6H, m); MS: *m/z*=434.5 $[M+1]^+$ (Calc.: 434.2).

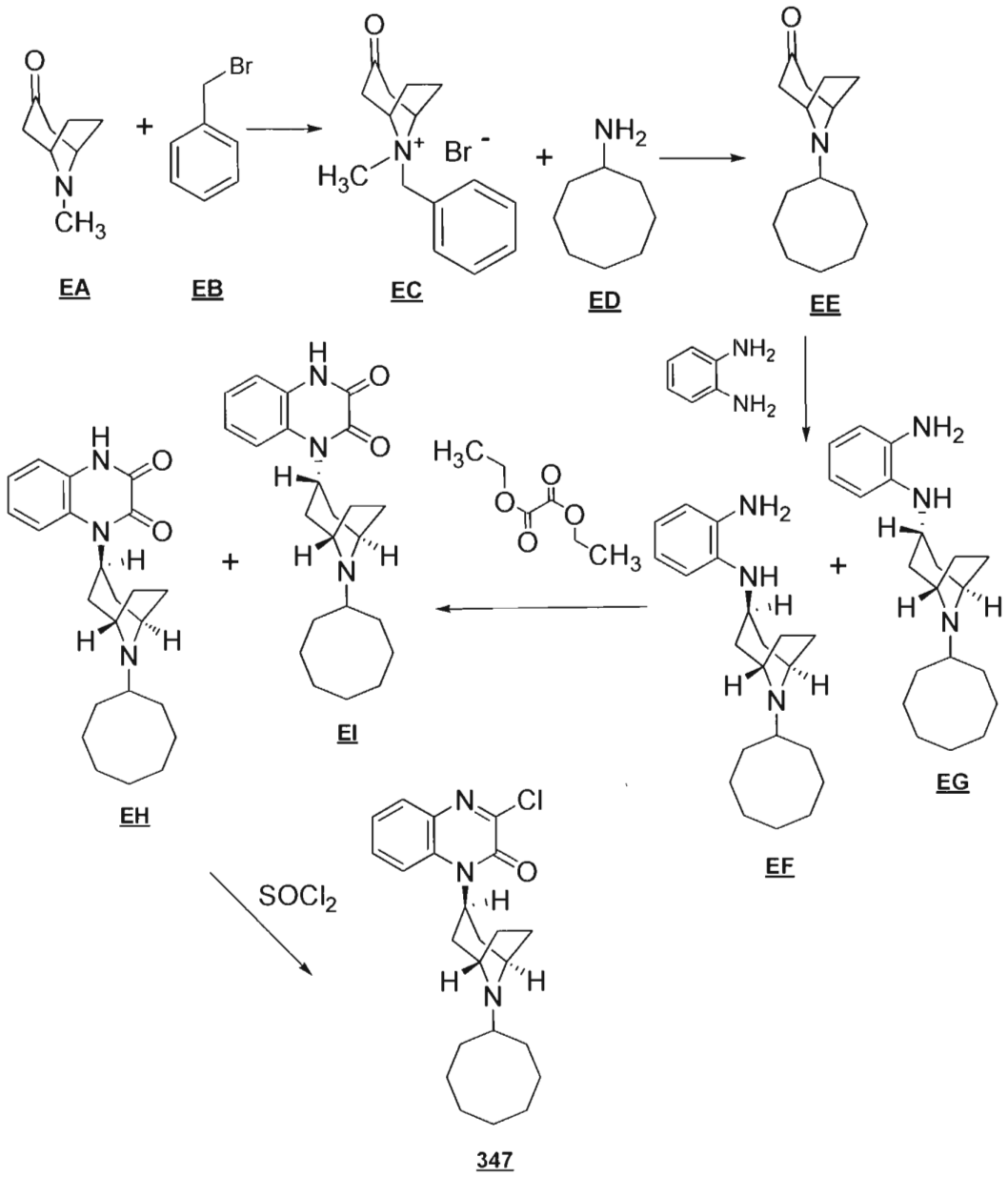
Substituted-Quinoxaline-Type Piperidine Compound **149** (400mg, 0.867mmol) was dissolved in MeOH (10mL) with minimal heating then the solution was quickly cooled to a temperature of about 25°C. Potassium hydroxide (300mg, 5.35mmol) in water (2mL) was

added and the reaction mixture was stirred at a temperature of about 25°C for 18h. The reaction mixture was evaporated to dryness under reduced pressure to provide a residue. The residue was suspended in water (30mL) and, using a pH meter, slowly acidified to pH 5.5 with 1M HCl. The mixture was filtered. The filter cake was dried under reduced pressure at 50°C for 18h to provide 165mg of a white solid. The solid was suspended in dry diethyl ether (5mL) and 2M HCl in diethyl ether (1mL) was added. The resulting mixture was stirred at a temperature of about 25°C for 1h then filtered. The filter cake was dried under reduced pressure at 50°C for 18h to provide 160mg of Substituted-Quinoxaline-Type Piperidine Compound **131** as a pale yellow solid.

The identity of Substituted-Quinoxaline-Type Piperidine Compound **131**, *exo*-4-(8-adamantan-1-yl-8-aza-bicyclo[3.2.1]oct-3-yl)-3-oxo-3,4-dihydro-quinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and MS.

Substituted-Quinoxaline-Type Piperidine Compound **131**: ^{1}H NMR: δ_H (400MHz, $(CD_3)_2SO$): 14.07 (1H, bs), 8.17 (1H, m), 7.85 (1H, dd, J=7.6, 1.28Hz), 7.69 (1H, t, J=8.28Hz), 7.44 (1H, t, J=7.6Hz), 5.29 (1H, bs), 4.54 (2H, s), 3.11 (2H, t, J=12.93Hz), 2.28-2.04 (13H, m), 1.94 (2H, d, J=11.67Hz), 1.62 (6H, s); MS: m/z=434.5 $[M+1]^+$ (Calc.: 434.5).

5.14 Example 14



The compound of formula **EB**, (bromomethyl)benzene (6.5g, 38mmol, Sigma-Aldrich), was added to a mixture of the compound of formula **EA**, 8-methyl-8-azabicyclo[3.2.1]octan-3-one (5g, 36mmol, Sigma-Aldrich), in acetone (100mL) over 30 min at a temperature of about 25°C. The resulting reaction mixture was stirred at a temperature of about 25°C for 1h then at 38°C for 2h. Thereafter, the mixture was cooled to a temperature of

about 25°C, filtered, and washed twice with hexanes (10mL for each wash) to provide 10g of the compound of formula **EC** as white solid (yield 85%).

The compound of formula **EC**, 8-benzyl-8-methyl-3-oxo-8-azoniabicyclo[3.2.1]octane bromide (5g, 16.1mmol), was mixed with 40mL of ethanol and 20mL of water. Over 30min, this mixture was added to a mixture of the compound of formula **ED** (cyclooctanamine, 2.0g, 16mmol, Sigma-Aldrich) and K_2CO_3 (0.2g, 1.4mmol) in ethanol (150mL) at 70°C. After 3h at 70°C, the reaction mixture was cooled to a temperature of about 25°C and concentrated under reduced pressure. The residue was treated with water (50mL) and extracted three times with $CHCl_3$ (100mL for each extraction). The combined organic portions were washed with brine (50mL) and concentrated under reduced pressure to provide 3.5g of the compound of formula **EE** (yield 92%).

Sodium triacetoxyborohydride (50mmol) was added to a mixture of the compound of formula **EE**, 8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-one (3g, 12.8mmol), and 1,2-phenylenediamine (3g, 27.8mmol) in 100mL of CH_2Cl_2 at a temperature of about 25°C. Thereafter, 3mL of acetic acid was added. The resulting reaction mixture was stirred at a temperature of about 25°C for about 16h. Thereafter, MeOH (2mL) and water (25mL) were added and the mixture was neutralized with 28% aqueous ammonia to adjust the pH to about 8. The organic portion was separated, washed with brine (10mL), concentrated under reduced pressure, and chromatographed with a silica gel column eluted with 10:1:1 EtOAc:MeOH:TEA to provide 2.8g of a mixture of **EF** and **EG** as brown oil (yield 68%).

The identity of the compound of formula **EF**, N^1-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)benzene-1,2-diamine, was confirmed using TLC.

Compound **EF**: TLC (SiO_2) 100:7:1 EtOAc:MeOH:NH_4OH: Rf=0.6 with UV detection, Dragendorff's reagent.

The identity of the compound of formula **EG**, N^1-((*exo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)benzene-1,2-diamine, was confirmed using TLC.

Compound **EG**: TLC (SiO_2) 100:7:1 EtOAc:MeOH:NH_4OH: Rf=0.4 with UV detection, Dragendorff's reagent.

A mixture of the above brown oil (0.3g, of the compounds of formula **EF** and **EG**) in 20mL of diethyl oxalate (Sigma-Aldrich) was heated at 140°C for 16h. After cooling to a temperature of about 25°C, the reaction mixture was diluted with EtOAc, washed with 2N

aqueous NaOH (30mL), washed with brine (20mL), concentrated under reduced pressure, and chromatographed with a silica gel column eluted with 5:5:0.5:0.5 EtOAc:hexane:MeOH:TEA to provide 60mg and 20mg of the two compounds of formula **EH** and **EI**, respectively, each as a white solid (yield 18% and 6%, respectively).

The identity of the compound of formula **EH**, 1-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)quinoxaline-2,3(1*H*,4*H*)-dione (*i.e.*, the *endo* isomer), was confirmed using ^{1}H NMR, LC/MS and TLC.

Compound **EH:** ^{1}H NMR: δ_H (400MHz, (CD_3OD+$CDCl_3$)): 7.51 (1H, d, J=7.9Hz), 7.11-7.21 (m, 3H), 5.16-5.24 (m, 1H), 4.08 (br, 2H), 2.9 (br, 1H), 2.56-2.64 (m, 2H), 2.06-2.26 (m, 6H), 1.72-1.96 (m, 6H), 1.32-1.62 (m, 8H); LC/MS (100%, t_r=4.988min): *m/z*=382.4 $[M+H]^+$ (Calc: 381.5); TLC (SiO_2) 100:7:1 EtOAc:MeOH:NH_4OH: Rf=0.5 with UV detection, Dragendorff's reagent.

The identity of the compound of formula **EI**, 1-((*exo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)quinoxaline-2,3(1*H*,4*H*)-dione (*i.e.*, the *exo* isomer), was confirmed using ^{1}H NMR, LC/MS and TLC.

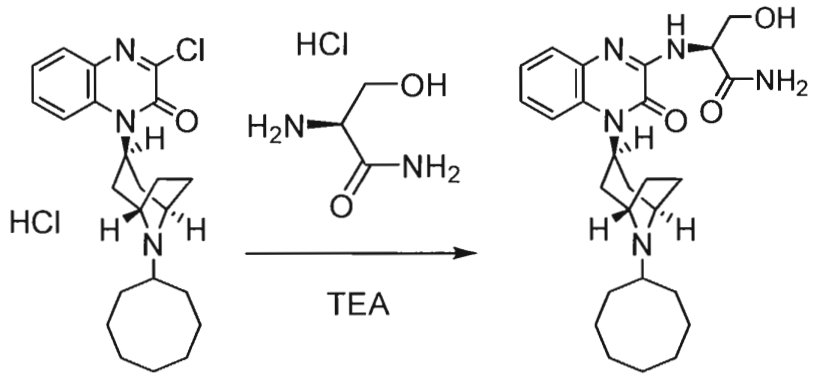
Compound **EI:** ^{1}H NMR: δ_H (400MHz, (CD_3OD+$CDCl_3$)): 7.62 (br, 1H), 7.21-7.24 (m, 3H), 4.95 (br, 1H), 3.75 (br, 2H), 3.36 (br, 1H), 2.91-2.98 (m, 2H), 2.06-2.16 (m, 2H), 1.42-1.96 (m, 18H); LC/MS (100%, t_r=4.718min): *m/z*=382.2 $[M+H]^+$ (Calc: 381.5); TLC (SiO_2) 100:7:1 EtOAc:MeOH:NH_4OH: Rf=0.45 with UV detection, Dragendorff's reagent.

The compound of formula **EH** (191mg, 0.500mmol) was suspended in thionyl chloride (0.8mL, Sigma-Aldrich). A catalytic amount of DMF was added and the reaction mixture was refluxed for 30min. Thereafter, the reaction mixture was cooled to 0°C and diethyl ether (5mL) was added. A precipitate formed. The precipitate was filtered and washed with diethyl ether to provide 196mg of the hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **347** as a pale yellow solid (yield 90%). Thereafter, this hydrochloride was suspended in saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$ to provide the free Substituted-Quinoxaline-Type Piperidine Compound **347**, *i.e.*, the *endo* isomer.

The identity of Substituted-Quinoxaline-Type Piperidine Compound **347**, 3-chloro-1-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)quinoxalin-2(1*H*)-one, was confirmed using ^{1}H NMR.

Substituted-Quinoxaline-Type Piperidine Compound **347**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.80 (1H, d, J=8.1Hz), 7.60-7.54 (2H, m), 7.37-7.33 (1H, m), 5.17 (1H, br s), 3.67 (2H, br s), 2.34-2.22 (5H, m), 2.04-1.98 (2H, m), 1.89-1.36 (16H, m).

5.15 Example 15



347 **98**

TEA (1.2mmol) and serine amide hydrochloride (*i.e.*, (*S*)-2-amino-3-hydroxypropanamide hydrochloride, 0.45mmol, Sigma-Aldrich) were added to a mixture of the hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **347** (130mg, 0.3mmol) in *N*-methyl pyrrolidine (3mL) at 25°C. The resulting reaction mixture was stirred at 80°C for 3hr. After cooling to a temperature of about 25°C and quenching with water (3mL), the mixture was extracted three times with EtOAc/water (50mL for each extraction), washed three times with water (50mL for each wash), dried (Na_2SO_4), and concentrated under reduced pressure to provide a yellow oil. The oil was chromatographed with a silica gel column eluted with a gradient of from 95:5:0.5 $CHCl_3$:MeOH:aqueous ammonia to 9:1:0.1 $CHCl_3$:MeOH:aqueous ammonia to provide 42mg of Substituted-Quinoxaline-Type Piperidine Compound **98** as a pale yellow amorphous solid (yield 30%).

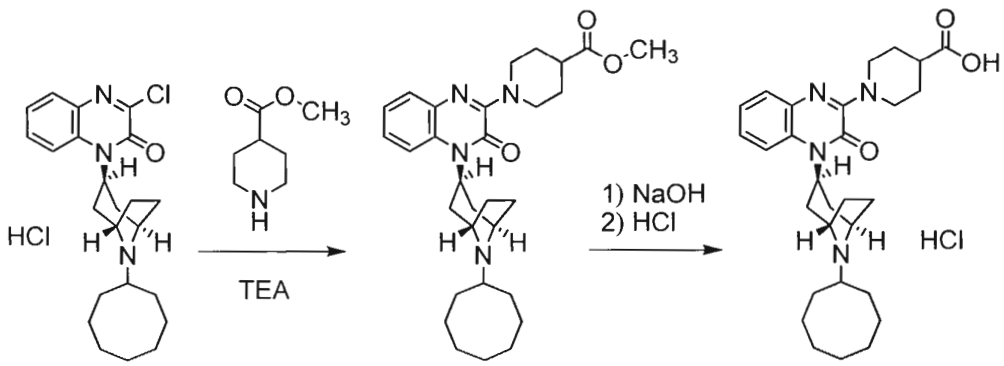
The identity of Substituted-Quinoxaline-Type Piperidine Compound **98**, (2*S*)-2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)-3-hydroxypropanamide, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **98**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 7.46-7.41 (3H, m), 7.28-7.15 (4H, m), 5.05 (1H, t, J=5.83Hz), 4.45-4.41 (1H, m),

3.85-3.64 (4H, m), 2.38-1.41 (23H, m); LC/MS (98%, t_r=1.24min): *m/z*=468.2 $[M+H]^+$ (Calc: 467.6).

5.16 Example 16

In a manner similar to Example 15, the following Substituted-Quinoxaline-Type Piperidine Compounds were prepared from Substituted-Quinoxaline-Type Piperidine Compound **347**.



347 **143** **99**

Substituted-Quinoxaline-Type Piperidine Compound **143** was prepared by using methyl piperidine-4-carboxylate (Sigma-Aldrich) in place of serine amide hydrochloride (yield 73%).

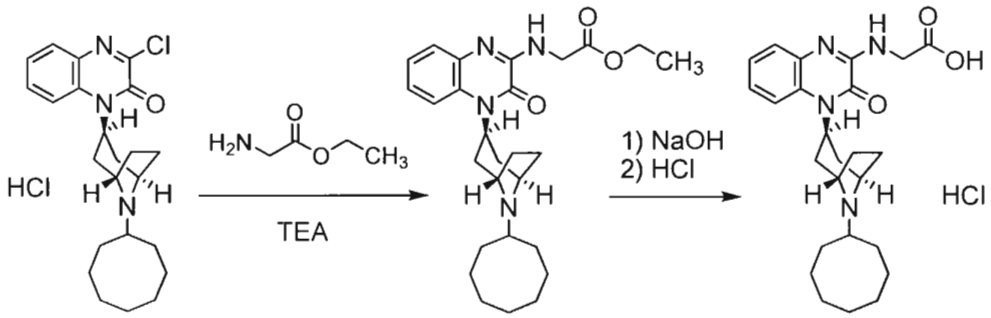
The identity of Substituted-Quinoxaline-Type Piperidine Compound **143**, methyl 1-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)piperidine-4-carboxylate, was confirmed using ^{1}H NMR.

Substituted-Quinoxaline-Type Piperidine Compound **143**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 7.45-7.18 (4H, m), 5.19 (1H, s), 4.57 (2H, d, J=13.18Hz), 3.62 (5H, s), 3.04 (2H, t, J=11.15Hz), 2.64 (1H, d, J=11.15Hz), 2.36 (1H, s), 2.19 (2H, s), 2.02-1.40 (24H, m).

The hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **99** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **143** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **174** in Example 7 (yield 70%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **99**, 1-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)piperidine-4-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **99**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 10.50 (1H, s), 7.84 (1H, d, J=8.11Hz), 7.50 (1H, dd, J=7.60, 1.52Hz), 7.26 (2H, ddd, J=20.78, 12.67, 5.32Hz), 5.83 (1H, t, J=9.38Hz), 4.61 (2H, d, J=13.18Hz), 4.21 (3H, s), 3.10 (2H, t, J=11.41Hz), 2.93 (1H, s), 2.67-2.54 (3H, m), 1.88 (22H, m); LC/MS (100%, t_r=1.79min): *m/z*=493.3 $[M+H]^+$ (Calc: 492.7).



347 **144** **106**

Substituted-Quinoxaline-Type Piperidine Compound **144** was prepared by using glycine ethyl ester (*i.e.*, ethyl 2-aminoacetate, Sigma-Aldrich) in place of serine amide hydrochloride (yield 67%).

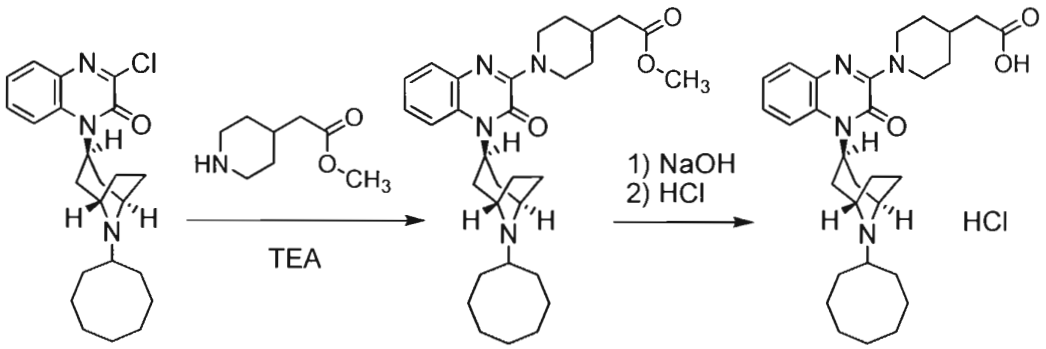
The identity of Substituted-Quinoxaline-Type Piperidine Compound **144**, ethyl 2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)acetate, was confirmed using MS.

Substituted-Quinoxaline-Type Piperidine Compound **144**: MS: *m/z*=467.3 $[M+H]^+$ (Calc: 466.6).

The hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **106** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **144** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **174** in Example 7 (yield 88%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **106**, 2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)acetic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **106**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 10.25 (0.9H, s), 9.43 (0.1H, s), 7.85-7.77 (2H, m), 7.41 (1H, dd, J=7.10, 2.03Hz), 7.25 (2H, ddd, J=16.86, 9.25, 2.91Hz), 5.81 (0.9H, t, J=9.38Hz), 5.15 (0.1H, s), 4.21 (2H, s), 4.06 (2H, d, J=6.08Hz), 2.93 (1H, s), 2.65 (2H, dt, J=17.07, 6.72Hz), 2.40-1.39 (22H, m); LC/MS (100%, t_r=1.46min): *m/z*=439.2 $[M+H]^+$ (Calc: 438.6).



347 **175** **176**

Substituted-Quinoxaline-Type Piperidine Compound **175** was prepared by using methyl 2-(piperidin-4-yl)acetate (Sigma-Aldrich) in place of serine amide hydrochloride (yield 89%).

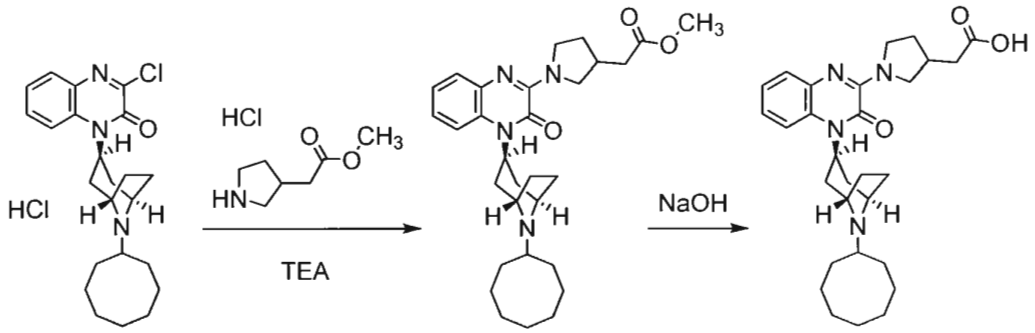
The identity of Substituted-Quinoxaline-Type Piperidine Compound **175**, methyl 2-(1-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)piperidin-4-yl)acetate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **175**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.52 (1H, d, J=8.0Hz), 7.37 (1H, d, J=8.0Hz), 7.20 (2H, m), 5.20 (1H, br), 4.71 (2H, d, J=12.0Hz), 3.69 (3H, s), 3.65 (2H, m), 2.90 (2H, t, J=12.0Hz), 2.40-1.90 (7H, m), 1.90-1.35 (22H, m); LC/MS: *m/z*=521 $[M+H]^+$ (Calc: 520.3).

The hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **176** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **175** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **174** in Example 7 (yield 76%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **176**, 2-(1-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)piperidin-4-yl)acetic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **176**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 12.1 (1H, m), 10.4 (0.9H, m), 9.52 (0.1H, m), 7.80 (1H, m), 7.43 (1H, m), 7.21 (2H, m), 5.80 (1H, m), 4.70 (2H, d, J=12.0Hz), 4.20 (2H, m), 2.92 (2H, t, J=12.0Hz), 2.60 (2H, m), 2.40-1.23 (27H, m); LC/MS (100%, t_r=1.84min): *m/z*=507 $[M+H]^+$ (Calc: 506.3).



Substituted-Quinoxaline-Type Piperidine Compound **145** was prepared by using the hydrochloride of methyl 2-(pyrrolidin-3-yl)acetate in place of serine amide hydrochloride (yield 90%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **145**, methyl 2-(1-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)pyrrolidin-3-yl)acetate, was confirmed using ^{1}H NMR.

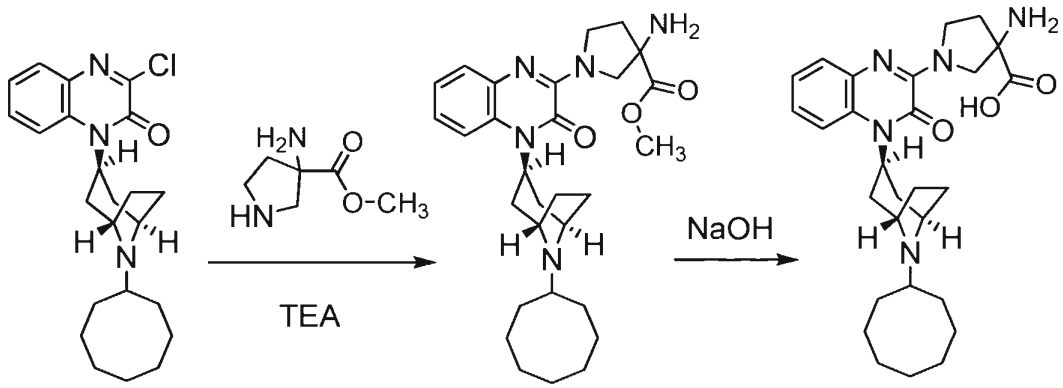
Substituted-Quinoxaline-Type Piperidine Compound **145**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 7.31 (2H, dt, J=16.90, 6.84Hz), 7.19-7.11 (2H, m), 5.12 (1H, br), 3.80 (6H, m), 3.62 (3H, s), 2.35 (1H, s), 2.22-1.38 (23H, m).

Substituted-Quinoxaline-Type Piperidine Compound **114** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **145** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **111** in Example 5 (yield 71%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **114**, 2-(1-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)pyrrolidin-3-yl)acetic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **114**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 7.32 (2H, td, J=10.01, 3.72Hz), 7.19-7.10 (2H, m), 5.17 (1H, br), 4.22-3.03 (6H,

br), 2.41 (4H, m), 2.25-1.37 (24 H, m); LC/MS (99%, t_r=1.39min): *m/z*=493.3 $[M+H]^+$ (Calc: 492.7).



347 **177** **178**

Substituted-Quinoxaline-Type Piperidine Compound **177** was prepared by using methyl 3-aminopyrrolidine-3-carboxylate (Sigma-Aldrich) in place of serine amide hydrochloride (yield 88%).

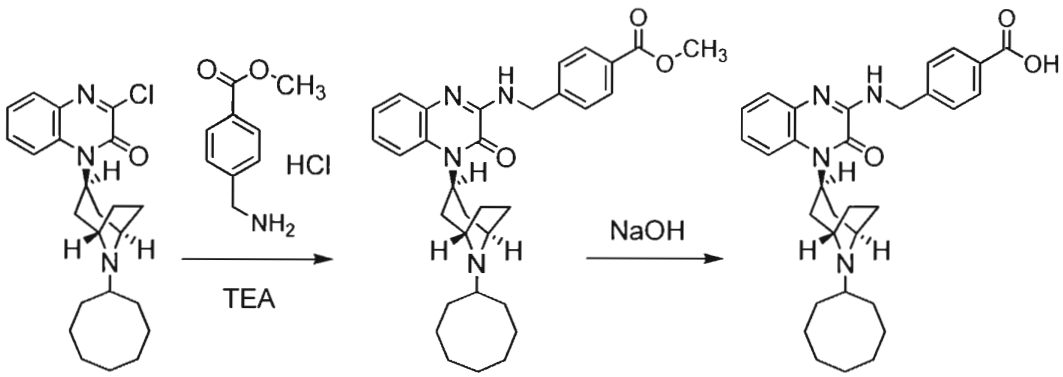
The identity of Substituted-Quinoxaline-Type Piperidine Compound **177**, methyl 3-amino-1-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)pyrrolidine-3-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **177**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.45 (1H, m), 7.30 (1H, m), 7.13 (2H, m), 5.20 (1H, br), 4.30-4.00 (4H, m), 3.77 (3H, s), 3.65 (2H, m), 2.50-2.00 (9H, m), 1.90-1.36 (16H, m); LC/MS: *m/z*=508 $[M+H]^+$ (Calc: 507.3).

Substituted-Quinoxaline-Type Piperidine Compound **178** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **177** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **111** in Example 5 (yield 72%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **178**, 3-amino-1-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)pyrrolidine-3-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **178**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 7.90 (2H, br), 7.36 (2H, m), 7.17 (2H, m), 5.20 (1H, m), 4.40-3.50 (6H, m), 2.50-1.30 (25H, m); LC/MS (100%, t_r=1.12min): *m/z*=494 $[M+H]^+$ (Calc: 493.3).



347 **179** **180**

Substituted-Quinoxaline-Type Piperidine Compound **179** was prepared by using methyl 4-(aminomethyl)benzoate hydrochloride (Sigma-Aldrich) in place of serine amide hydrochloride (yield 36%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **179**, methyl 4-((4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)methyl)benzoate, was confirmed using LC/MS.

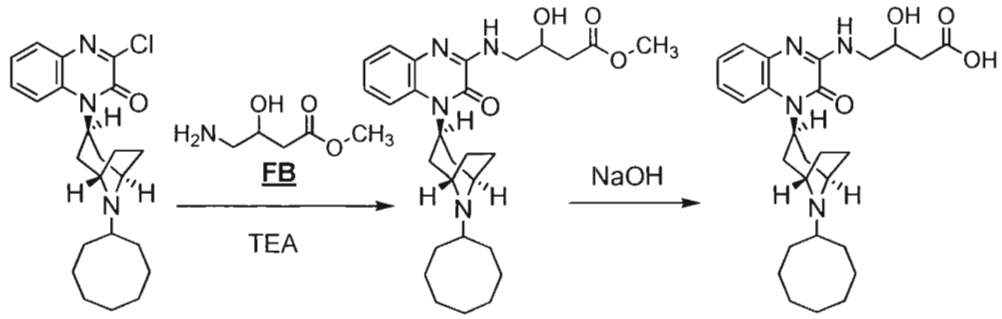
Substituted-Quinoxaline-Type Piperidine Compound **179**: LC/MS: *m/z*=529 $[M+H]^+$ (Calc: 528).

Substituted-Quinoxaline-Type Piperidine Compound **180** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **179** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **111** in Example 5 (yield 28%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **180**, 4-((4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)methyl)benzoic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **180** ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 10.24 (br, 1H), 8.67 (br, 1H), 7.88 (d, 2H, J=8.1Hz), 7.78-7.79 (m, 1H), 7.49 (d, 2H, J=8.1Hz), 7.39-7.45 (m, 1H), 7.20-7.27 (m, 2H), 5.76-5.80 (m, 1H), 4.71 (m, 2H), 4.18-

4.26 (m, 2H), 2.95 (m, 1H), 2.60-2.67 (m, 2H), 1.39-2.38 (m, 20H); LC/MS: *m/z*=515 $[M+H]^+$ (Calc: 514).



347 **181** **182**

Substituted-Quinoxaline-Type Piperidine Compound **181** was prepared by using methyl 4-amino-3-hydroxybutanoate (**FB**) in place of serine amide hydrochloride (yield 28%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **181**, methyl 4-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)-3-hydroxybutanoate, was confirmed using LC/MS.

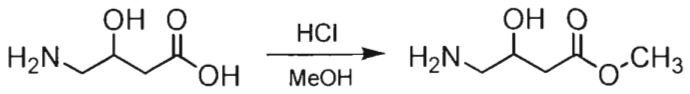
Substituted-Quinoxaline-Type Piperidine Compound **181**: LC/MS: *m/z*=497 $[M+H]^+$ (Calc: 496).

Substituted-Quinoxaline-Type Piperidine Compound **182** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **181** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **111** in Example 5 (yield 46%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **182**, 4-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)-3-hydroxybutanoic acid, was confirmed using ^{1}H NMR and LC/MS.

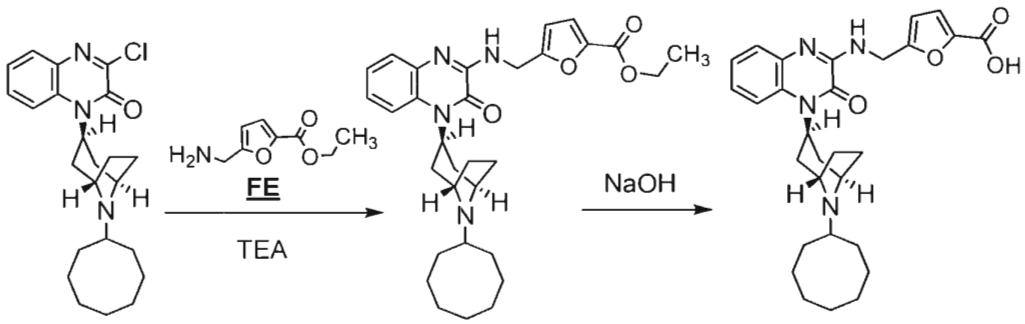
Substituted-Quinoxaline-Type Piperidine Compound **182**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 7.31-7.40 (m, 2H), 7.16-7.24 (m, 2H), 4.01 (m, 1H), 3.63 (m, 2H), 3.29-3.41 (m, 2H), 1.39-2.37 (m, 25H); LC/MS: *m/z*=483 $[M+H]^+$ (Calc: 482).

The compound of formula **FB** was prepared as follows:



FA **FB**

A mixture of 4-amino-3-hydroxybutanoic acid (**FA**, 1.00g, 8.40mmol, Sigma-Aldrich) and concentrated HCl (1mL) in MeOH (20mL) was refluxed for 19hr. The mixture was concentrated under reduced pressure to provide 1.43g of the compound of formula **FB** as a colorless oil (yield >98%).



347 **183** **184**

Substituted-Quinoxaline-Type Piperidine Compound **183** was prepared by using ethyl 5-(aminomethyl)furan-2-carboxylate (**FE**) in place of serine amide hydrochloride (yield 27%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **183**, ethyl 5-((4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)methyl)furan-2-carboxylate, was confirmed using LC/MS.

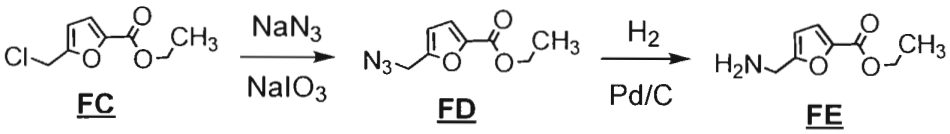
Substituted-Quinoxaline-Type Piperidine Compound **183**: LC/MS: *m/z*=533 $[M+H]^+$ (Calc: 532).

Substituted-Quinoxaline-Type Piperidine Compound **184** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **183** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **111** in Example 5 (yield 37%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **184**, 5-((4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)methyl)furan-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **184**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 10.65 (br, 1H), 8.55 (br, 1H), 7.89-7.90 (m, 1H), 7.52-7.53 (m, 1H), 7.24-7.27 (m, 2H), 7.14-7.24 (m, 1H), 6.56 (s, 1H), 5.93-5.97 (m, 2H), 4.69 (m, 2H), 4.15-4.23 (m, 2H), 2.92 (m, 1H), 2.62-2.67 (m, 2H), 2.18-2.34 (m, 6H), 1.27-1.96 (m, 14H); LC/MS: *m/z*=505 $[M+H]^+$ (Calc: 504).

The compound of formula **FE** was prepared as follows:



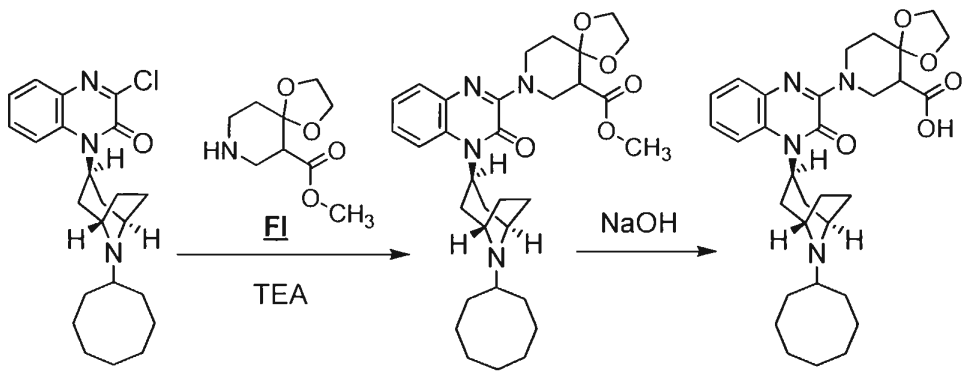
FC **FD** **FE**

A mixture of ethyl 5-(chloromethyl)furan-2-carboxylate (**FC**, 1.00g, 5.30mmol, Sigma-Aldrich), sodium azide (379.1mg, 5.83mmol, Sigma-Aldrich), and sodium iodate (catalytic amount, Sigma-Aldrich) in DMF at a temperature of about 25°C was stirred for 24h. The reaction mixture was extracted with EtOAc/water. The organic portion was separated, washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to provide a residue. The residue was chromatographed with a silica gel column eluted with 1:10 EtOAc:hexane to provide 950mg of the compound of formula **FD** as a pale yellow solid (yield 92%).

The identity of the compound of formula **FD**, ethyl 5-(azidomethyl)furan-2-carboxylate, was confirmed using ^{1}H NMR.

Compound **FD**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.14 (d, 1H, J=3.4Hz), 6.47 (d, 1H, J=3.4Hz), 4.39 (s, 2H), 4.37 (q, 2H, J=7.1Hz), 1.38 (t, 3H, J=7.1Hz).

Under a hydrogen atmosphere, a mixture of the compound of formula **FD** (952mg, 4.88mmol), 20% palladium on carbon (100mg, Sigma-Aldrich), and MeOH (10mL) was stirred at a temperature of about 25°C for 3.5hr. The Pd/C was filtered off, the mixture was washed with MeOH, and the filtrate was concentrated under reduced pressure to provide 843mg of the compound of formula **FE** as a brown oil (yield >98%).



347 185 186

Substituted-Quinoxaline-Type Piperidine Compound **185** was prepared by using methyl 1,4-dioxa-8-azaspiro[4.5]decane-6-carboxylate (**FI**) in place of serine amide hydrochloride (yield 67%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **185**, methyl 8-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)-1,4-dioxa-8-azaspiro[4.5]decane-6-carboxylate, was confirmed using LC/MS.

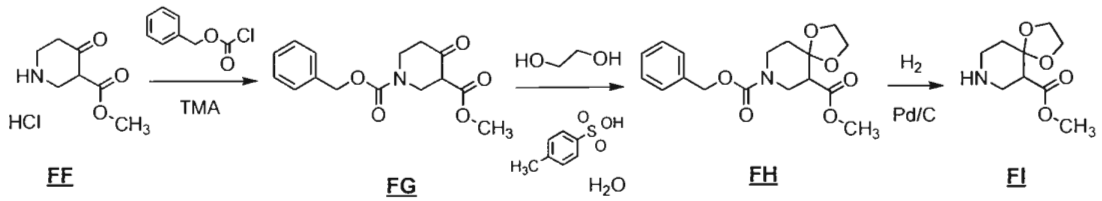
Substituted-Quinoxaline-Type Piperidine Compound **185**: LC/MS: *m/z*=565 $[M+H]^+$ (Calc: 564).

Substituted-Quinoxaline-Type Piperidine Compound **186** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **185** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **111** in Example 5 (yield 27%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **186**, 8-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)-1,4-dioxa-8-azaspiro[4.5]decane-6-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **186**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 12.25 (br, 1H), 7.37-7.43 (m, 2H), 7.28-7.35 (m, 1H), 7.19-7.21 (m, 1H), 5.05 (m, 1H), 4.30 (m, 1H), 4.09 (m, 1H), 3.92 (m, 4H), 3.61 (m, 2H), 2.68-2.73 (m, 1H), 1.40-2.45 (m, 25H); LC/MS: *m/z*=551 $[M+H]^+$ (Calc: 550).

The compound of formula **FI** was prepared as follows:



FF FG FH FI

After cooling a mixture of the compound of formula **FF** (methyl 4-oxopiperidine-3-carboxylate hydrochloride, 5.00g, 25.8mmol, Sigma-Aldrich) and TMA (9.00mL, 64.6mmol, Sigma-Aldrich) in DCM (50mL) to a temperature of 0°C, benzyl carbonochloridate (4.85g, 28.4mmol, Sigma-Aldrich) was added over a period of 10min. After addition, the reaction mixture was stirred for 1hr at a temperature of 0°C, warmed to a temperature of about 25°C, and stirred for 1hr more. Thereafter, the reaction mixture was extracted with DCM/water. The organic portion was separated, washed with 2N aqueous HCl, washed with saturated $NaHCO_3$, washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide 6.38g of the compound of formula **FG** as a colorless oil (yield 85%).

The identity of the compound of formula **FG**, 1-benzyl 3-methyl 4-oxopiperidine-1,3-dicarboxylate, was confirmed using ^1H NMR.

Compound **FG**: ^1H NMR: δ_H (400MHz, $CDCl_3$): 3.94-4.03 (m, 4H), 3.72 (s, 3H), 3.16-3.21 (m, 1H), 3.02-3.09 (m, 2H), 2.85-2.92 (m, 1H), 2.66-2.68 (m, 1H), 1.99-2.06 (m, 1H), 1.54-1.60 (m, 1H).

A reaction mixture of the compound of formula **FG** (6.38g, 21.9mmol), ethane-1,2-diol (3.66mL, 65.7mmol, Sigma-Aldrich), and 4-methylbenzenesulfonic acid monohydrate (200mg, Sigma-Aldrich) in toluene (150mL) was refluxed for 21hr. The reaction mixture was extracted with diethyl ether:water. The organic portion was separated, washed with saturated $NaHCO_3$, washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to provide a residue. The residue was chromatographed with a silica gel column eluted with a gradient of from 0%:100% EtOAc:n-hexane to 50%:50% EtOAc:n-hexane to provide 2.48g of the compound of formula **FH** as a colorless oil (yield 34%).

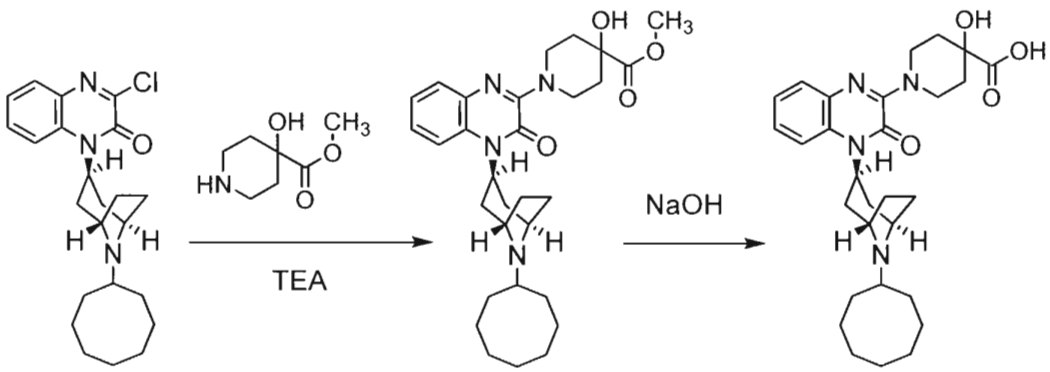
The identity of the compound of formula **FH**, 8-benzyl 6-methyl 1,4-dioxa-8-azaspiro[4.5]decane-6,8-dicarboxylate, was confirmed using LC/MS.

Compound **FH**: LC/MS: *m/z*=336 $[M+H]^+$ (Calc: 335), 358 $[M+Na]^+$ (Calc: 357).

Under a hydrogen atmosphere, a mixture of the compound of formula **FH** (2.48g, 7.40mmol), 20% palladium on carbon (200mg), and MeOH (50mL) was stirred at a temperature of about 25°C for 3hr. The Pd/C was filtered off, the mixture was washed with MeOH, and the filtrate was concentrated under reduced pressure to provide 1.50g of the compound of formula **FI** as a pale yellow oil (yield >98%).

The identity of the compound of formula **FI** was confirmed using ^{1}H NMR.

Compound **FI**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 11.99 (s, 1H), 7.32-7.40 (m, 5H), 5.16 (s, 2H), 4.14 (m, 2H), 3.78 (s, 3H), 3.63-3.66 (m, 2H), 2.40 (m, 2H).



347 **187** **188**

Substituted-Quinoxaline-Type Piperidine Compound **187** was prepared by using methyl 4-hydroxypiperidine-4-carboxylate (Sigma-Aldrich) in place of serine amide hydrochloride (yield 97%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **187**, methyl 1-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)-4-hydroxypiperidine-4-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

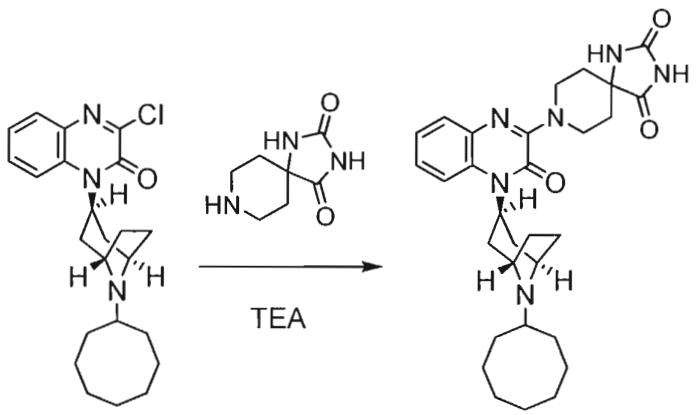
Substituted-Quinoxaline-Type Piperidine Compound **187**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 7.43 (1H, d, J=8.0Hz), 7.36 (1H, d, J=8.0Hz), 7.29 (1H, t, J=8.0Hz), 7.20 (1H, t, J=8.0Hz), 5.56 (1H, s), 5.20 (1H, br), 4.42 (2H, d, J=13.18Hz), 3.65 (3H, s), 3.65-3.60 (2H, m), 3.36 (2H, m), 2.36 (1H, m), 2.18 (2H, m), 2.02-1.30 (20H, m); LC/MS: *m/z*=523 $[M+H]^+$ (Calc: 522).

Substituted-Quinoxaline-Type Piperidine Compound **188** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **187** in a manner similar to the

preparation of Substituted-Quinoxaline-Type Piperidine Compound **111** in Example 5 (yield 84%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **188**, 1-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)-4-hydroxypiperidine-4-carboxylic acid, was confirmed using ^{1}H NMR and MS.

Substituted-Quinoxaline-Type Piperidine Compound **188**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 11.00-10.00 (1H, br) 7.74 (1H, d, J=8.0Hz), 7.45 (1H, d, J=8.0Hz), 7.26-7.22 (2H, m), 5.67 (1H, br), 5.90-5.10 (1H, br), 4.47 (2H, d, J=12.6Hz), 4.18 (2H, s), 3.34 (2H, m), 2.92 (1H, m), 2.54 (2H, m), 2.25 (6H, m), 2.01-1.40 (18H, m); LC/MS (100%, t_r=1.53min): *m/z*=509 $[M+H]^+$ (Calc: 508).

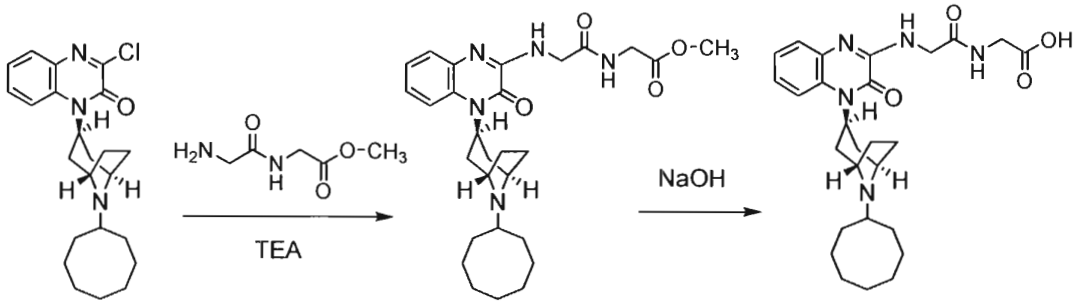


347 **189**

Substituted-Quinoxaline-Type Piperidine Compound **189** was prepared by using 1,3,8-triazaspiro[4.5]decane-2,4-dione (Sigma-Aldrich) in place of serine amide hydrochloride (yield 92%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **189**, 8-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)-1,3,8-triazaspiro[4.5]decane-2,4-dione, was confirmed using ^{1}H NMR and MS.

Substituted-Quinoxaline-Type Piperidine Compound **189**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 10.71 (1H, s), 8.63 (1H, s), 7.45 (1H, d, J=7.6Hz), 7.37 (1H, m), 7.31 (1H, m), 7.21 (1H, m), 5.40-5.10 (1H, br), 4.49 (2H, s), 3.62 (2H, s), 3.38 (2H, m), 2.70 (1H, s), 2.36 (1H, m), 2.19 (2H, m), 2.10-1.30 (22H, m); LC/MS (100%, t_r=1.53min): *m/z*=533 $[M+H]^+$ (Calc: 532).



347 **190** **191**

Substituted-Quinoxaline-Type Piperidine Compound **190** was prepared by using methyl 2-(2-aminoacetamido)acetate (Sigma-Aldrich) in place of serine amide hydrochloride (yield 66%).

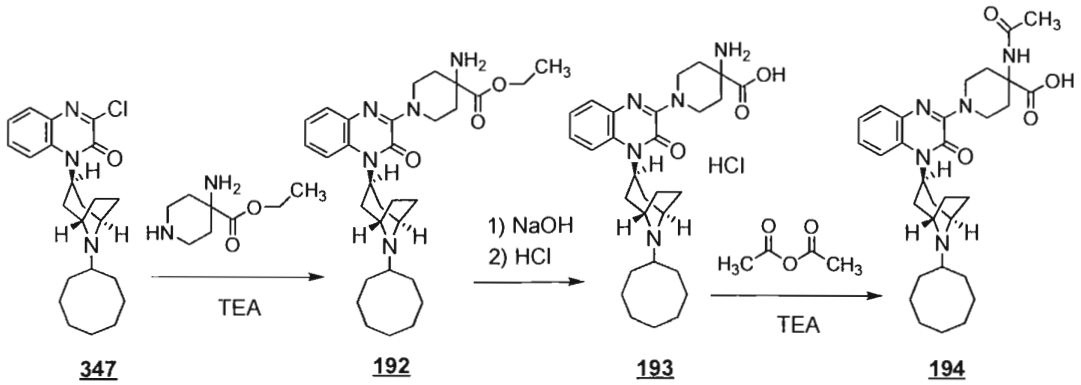
The identity of Substituted-Quinoxaline-Type Piperidine Compound **190**, methyl 2-(2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)acetamido)acetate, was confirmed using ^{1}H NMR and MS.

Substituted-Quinoxaline-Type Piperidine Compound **190**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 8.35 (1H, m), 7.70 (1H, m), 7.39 (2H, m), 7.27 (1H, m), 7.21 (1H, m), 5.00 (1H, br), 4.02 (2H, d, J=8.0Hz), 3.65 (2H, m), 3.63 (3H, s), 2.45-1.30 (19H, m); MS: *m/z*=510 $[M+H]^+$ (Calc: 509).

Substituted-Quinoxaline-Type Piperidine Compound **191** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **190** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **111** in Example 5 (yield 51%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **191**, 2-(2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)acetamido)acetic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **191**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 8.21 (1H, m), 7.69 (1H, m), 7.58 (1H, m), 7.40 (1H, d, J=8.0Hz), 7.26 (1H, m), 7.20 (1H, m), 5.40 (1H, br), 4.03 (2H, d, J=4.0Hz), 3.96 (2H, m), 3.75 (2H, d, J=4.0Hz), 2.70-2.40 (3H, m), 2.30-1.30 (20H, m); LC/MS (100%, t_r=1.31min): *m/z*=496 $[M+H]^+$ (Calc: 495).



Substituted-Quinoxaline-Type Piperidine Compound **192** was prepared by using ethyl 4-aminopiperidine-4-carboxylate (Sigma-Aldrich) in place of serine amide hydrochloride (yield 92%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **192**, ethyl 4-amino-1-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)piperidine-4-carboxylate, was confirmed using ^{1}H NMR and MS.

Substituted-Quinoxaline-Type Piperidine Compound **192**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 7.43 (1H, d, J=8.0Hz), 7.35 (1H, d, J=8.0Hz), 7.28 (1H, t, J=8.0Hz), 7.21 (1H, t, J=8.0Hz), 5.20 (1H, br), 4.10 (4H, m), 3.62 (4H, m), 2.35 (1H, m), 2.20 (2H, m), 2.10-1.40 (24H, m), 1.20 (3H, t, J=8.0Hz); MS: *m/z*=536 $[M+H]^+$ (Calc: 535).

The hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **193** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **192** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **174** in Example 7 (yield 89%).

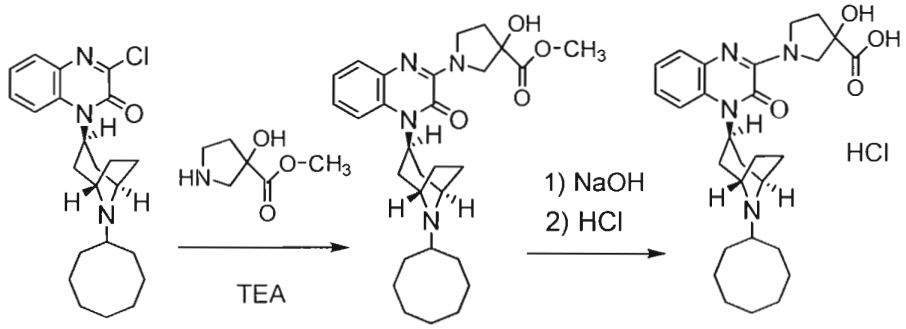
The identity of Substituted-Quinoxaline-Type Piperidine Compound **193**, 4-amino-1-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)piperidine-4-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **193**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 10.75 (0.9H, m), 10.11 (0.1H, m), 8.82 (3H, s), 7.92 (0.9H, d, J=8.62Hz), 7.79 (0.1H, d, J=8.0Hz), 7.53 (1H, d, J=8.0Hz), 7.30 (2H, m), 5.99-5.89 (0.9H, m), 5.10 (0.1H, m), 4.21-3.87 (8H, m), 2.92 (1H, s), 2.66-2.55 (2H, m), 2.36-1.23 (24H, m); LC/MS (98%, t_r=1.09min): *m/z*=508 $[M+H]^+$ (Calc: 507).

To a mixture of Substituted-Quinoxaline-Type Piperidine Compound **193** (130mg, 0.211mmol) and CH_2Cl_2 (4mL) at 0°C was added acetic anhydride (23.7mg, 0.232mmol, Sigma-Aldrich) and TEA (131μL, 0.948mmol). The reaction mixture was stirred at 0°C for 2h. After concentration under reduced pressure, the reaction mixture was diluted with water (2mL) to precipitate a white solid. The precipitate was filtered and rinsed with water to provide 38mg of Substituted-Quinoxaline-Type Piperidine Compound **194** as a white solid (yield 33%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **194**, 4-acetamido-1-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)piperidine-4-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **194**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 8.15 (1H, s), 7.45 (2H, m), 7.31 (1H, t, J=8.0Hz), 7.22 (1H, t, J=8.0Hz), 5.25 (1H, br), 4.36 (1H, d, J=12.0Hz), 3.90-3.20 (4H, m), 2.50 (1H, m), 2.30 (2H, m), 2.20-1.40 (24H, m), 1.87 (3H, s); LC/MS (100%, t_r=1.54min): *m/z*=550 $[M+H]^+$ (Calc: 549).



347 **195** **196**

Substituted-Quinoxaline-Type Piperidine Compound **195** was prepared by using methyl 3-hydroxypyrrolidine-3-carboxylate (Sigma-Aldrich) in place of serine amide hydrochloride (yield 55%).

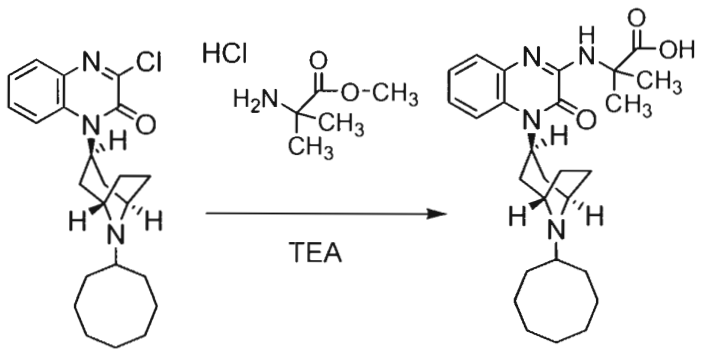
The identity of Substituted-Quinoxaline-Type Piperidine Compound **195**, methyl 1-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)-3-hydroxypyrrolidine-3-carboxylate, was confirmed using ^{1}H NMR and MS.

Substituted-Quinoxaline-Type Piperidine Compound **195**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 7.36 (1H, d, J=8.0Hz), 7.31 (1H, d, J=8.0Hz), 7.20 (1H, t, J=8.0Hz), 7.15 (1H, t, J=8.0Hz), 5.88 (1H, s), 5.10 (1H, br), 4.20 (2H, br), 3.72 (3H, s), 3.62 (2H, m), 3.35 (2H, m), 2.36 (1H, m), 2.30-1.40 (24H, m); MS: *m/z*=509 $[M+H]^+$ (Calc: 508).

The hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **196** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **195** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **174** in Example 7 (yield 90%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **196**, 1-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)-3-hydroxypyrrolidine-3-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **196**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 10.58 (0.9H, s), 9.80 (0.1H, s), 7.83 (0.9H, m), 7.74 (0.1H, m), 7.65 (1H, s), 7.25 (2H, m), 5.85 (0.9H, m), 5.05 (0.1H, m), 4.60-3.80 (6H, m), 2.98 (1H, m), 2.62 (2H, m), 2.40-1.30 (22H, m); LC/MS (100%, t_r=1.34min): *m/z*=495 $[M+H]^+$ (Calc: 494.5).

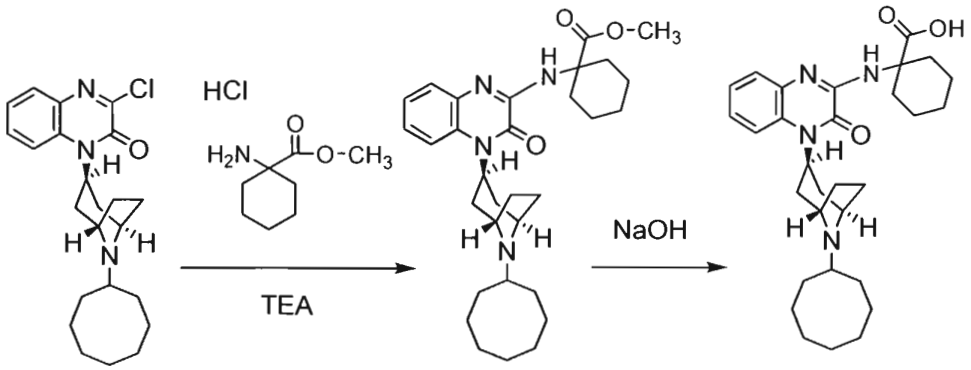


347 **197**

Substituted-Quinoxaline-Type Piperidine Compound **197** was prepared by using methyl 2-amino-2-methylpropanoate hydrochloride (Sigma-Aldrich) in place of serine amide hydrochloride (yield 30%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **197**, 2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)-2-methylpropanoic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **197**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 7.58 (1H, br), 7.52 (1H, s), 7.35 (1H, d, J=8.0Hz), 7.22 (2H, m), 5.40 (1H, br), 3.99 (2H, br), 2.65 (1H, m), 2.50 (2H, m), 2.40-1.40 (20H, m), 1.61 (6H, s); LC/MS (100%, t_r=1.81min): *m/z*=467 $[M+H]^+$ (Calc: 466.5).



347 **198** **199**

Substituted-Quinoxaline-Type Piperidine Compound **198** was prepared by using methyl 1-aminocyclohexanecarboxylate hydrochloride (Sigma-Aldrich) in place of serine amide hydrochloride (yield 35%).

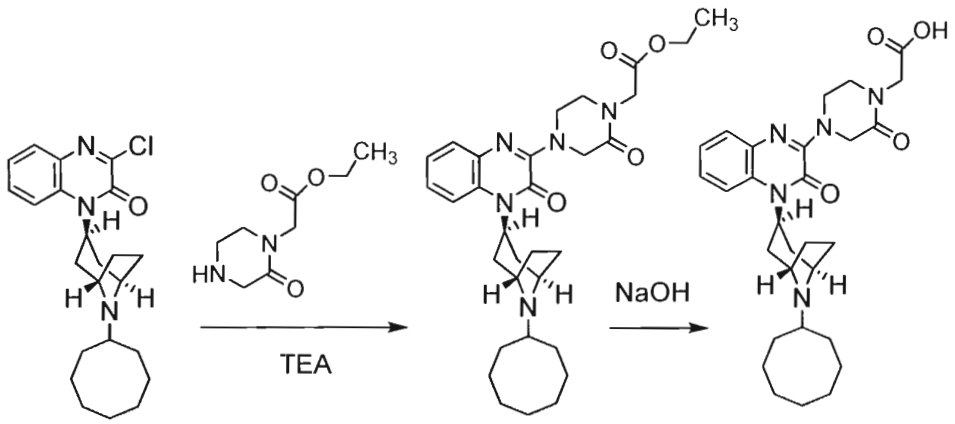
The identity of Substituted-Quinoxaline-Type Piperidine Compound **198**, methyl 1-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)cyclohexanecarboxylate, was confirmed using ^{1}H NMR and MS.

Substituted-Quinoxaline-Type Piperidine Compound **198**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 7.40 (1H, d, J=8.0Hz), 7.26 (2H, m), 7.20 (1H, m), 7.05 (1H, s), 5.00 (1H, br), 3.65 (2H, m), 3.56 (3H, s), 2.40-1.20 (33H, m); MS: *m/z*=521 $[M+H]^+$ (Calc: 520).

Substituted-Quinoxaline-Type Piperidine Compound **199** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **198** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **111** in Example 5 (yield 81%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **199**, 1-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)cyclohexanecarboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **199**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 7.70 (1H, br), 7.30 (1H, d, J=8.0Hz), 7.25 (1H, t, J=8.0Hz), 7.21 (1H, t, J=8,0Hz), 6.88 (1H, s), 5.60 (1H, br), 4.02 (2H, br), 2.80-1.30 (31H, m); LC/MS (100%, t_r=2.04min): *m/z*=507 $[M+H]^+$ (Calc: 506.5).



347 **200** **201**

Substituted-Quinoxaline-Type Piperidine Compound **200** was prepared by using ethyl 2-(2-oxopiperazin-1-yl)acetate (Sigma-Aldrich) in place of serine amide hydrochloride (yield 89%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **200**, ethyl 2-(4-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)-2-oxopiperazin-1-yl)acetate, was confirmed using ^{1}H NMR and MS.

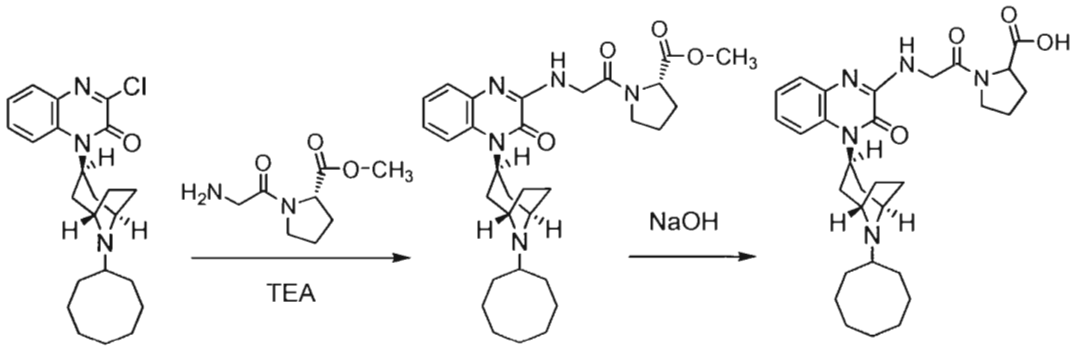
Substituted-Quinoxaline-Type Piperidine Compound **200**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.55 (1H, d, J=8.0Hz), 7.41 (1H, d, J=8.0Hz), 7.27 (1H, t, J=8.0Hz), 7.21 (1H, t, J=8.0Hz), 5.20 (1H, br), 4.59 (2H, s), 4.28 (2H, m), 4.20 (2H, m), 3.67 (2H, m), 3.60 (2H, m), 2.40-2.00 (7H, m), 1.90-1.40 (16H, m), 1.27 (3H, t, J=8.0Hz); MS: *m/z*=550 $[M+H]^+$ (Calc: 549).

Substituted-Quinoxaline-Type Piperidine Compound **201** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **200** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **111** in Example 5 (yield 94%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **201**, 2-(4-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)-2-oxopiperazin-1-yl)acetic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **201**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 7.54 (1H, m), 7.48 (1H, d, J=8.0Hz), 7.34 (1H, t, J=8.0Hz), 7.24 (1H, t, J=8,0Hz), 5.40 (1H, m), 4.44 (2H, s), 4.13 (2H, m), 4.04 (2H, s), 3.85 (2H, m), 3.53 (2H, m), 2.67 (1H,

m), 2.37 (2H, m), 2.20-1.35 (20H, m); LC/MS (100%, t_r=1.52min): *m/z*=522 $[M+H]^+$ (Calc: 521.5).



347 **202** **203**

Substituted-Quinoxaline-Type Piperidine Compound **202** was prepared by using (*S*)-methyl 1-(2-aminoacetyl)pyrrolidine-2-carboxylate (Sigma-Aldrich) in place of serine amide hydrochloride (yield 56%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **202**, (*S*)-methyl 1-(2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)acetyl)pyrrolidine-2-carboxylate, was confirmed using ^{1}H NMR and MS.

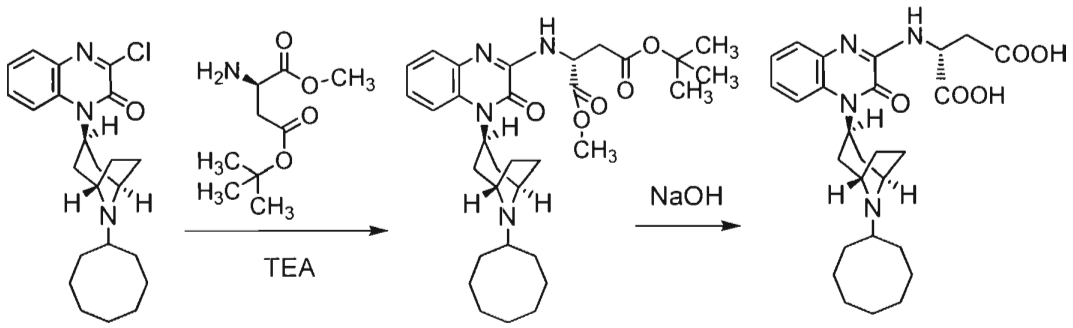
Substituted-Quinoxaline-Type Piperidine Compound **202**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.51 (1H, d, J=8.0Hz), 7.41 (1H, d, J=8.0Hz), 7.20-7.05 (3H, m), 5.20 (1H, br), 4.57 (1H, m), 4.29 (2H, d, J=8.0Hz), 3.73 (2H, s), 3.65 (2H, m), 2.84 (3H, s), 2.40-1.40 (27H, m); MS: *m/z*=550 $[M+H]^+$ (Calc: 549).

Substituted-Quinoxaline-Type Piperidine Compound **203** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **202** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **111** in Example 5 (yield 77%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **203**, 1-(2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)acetyl)pyrrolidine-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **203**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 7.69 (1H, br), 7.45 (2H, m), 7.23 (2H, m), 5.60 (1H, br), 4.68 (0.2H, m), 4.30-3.80

(4.8H, m), 3.65 (2H, m), 2.90-1.30 (27H, m); LC/MS (100%, t_r=1.56min): *m/z*=536 $[M+H]^+$ (Calc: 535.5).



347 **204** **205**

Substituted-Quinoxaline-Type Piperidine Compound **204** was prepared by using (*R*)-4-*tert*-butyl 1-methyl 2-aminosuccinate (Sigma-Aldrich) in place of serine amide hydrochloride (yield 28%).

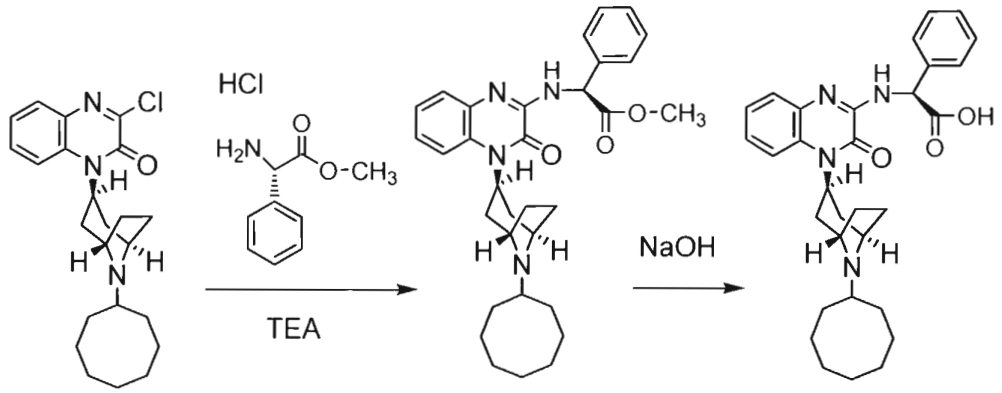
The identity of Substituted-Quinoxaline-Type Piperidine Compound **204**, (*R*)-4-*tert*-butyl 1-methyl 2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)succinate, was confirmed using LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **204**: LC/MS: *m/z*=567 $[M+H]^+$ (Calc: 567).

Substituted-Quinoxaline-Type Piperidine Compound **205** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **204** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **111** in Example 5 (yield 66%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **205**, (*R*)-2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)succinic acid was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **205**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 1.35-2.37 (24H, m), 2.73 (1H, d, J=15.72Hz), 3.62 (2H, s), 4.29 (1H, dd, J=10.65, 4.56Hz), 5.11-5.42 (1H, m), 7.15-7.29 (2H, m), 7.36-7.44 (3H, m); LC/MS (98%, t_r=1.50min): *m/z*=497 $[M+H]^+$ (Calc: 497).



347 **206** **207**

Substituted-Quinoxaline-Type Piperidine Compound **206** was prepared by using (*S*)-methyl 2-amino-2-phenylacetate hydrochloride (Sigma-Aldrich) in place of serine amide hydrochloride (yield 54%).

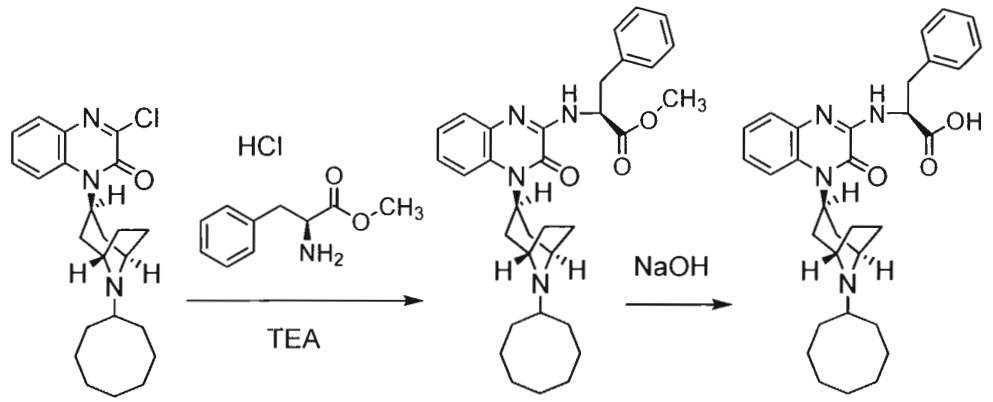
The identity of Substituted-Quinoxaline-Type Piperidine Compound **206**, (*S*)-methyl 2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)-2-phenylacetate, was confirmed using LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **206**: LC/MS: *m/z*=529 $[M+H]^+$ (Calc: 529).

Substituted-Quinoxaline-Type Piperidine Compound **207** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **206** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **111** in Example 5 (yield 15%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **207**, (*S*)-2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)-2-phenylacetic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **207**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 1.32-2.73 (22H, m), 2.94 (1H, s), 4.24 (2H, s), 5.14 (0.1H, s), 5.61 (1H, d, J=6.59Hz), 5.69 (0.9H, s), 7.21-7.54 (9H, m), 7.73 (1H, dd, J=6.59, 2.03Hz), 9.18 (0.1H, s), 9.94 (0.9H, s), 13.27 (1H, s); LC/MS (98%, t_r=2.05min): *m/z*=515 $[M+H]^+$ (Calc: 515).



347 **208** **209**

Substituted-Quinoxaline-Type Piperidine Compound **208** was prepared by using (*S*)-methyl 2-amino-3-phenylpropanoate hydrochloride (Sigma-Aldrich) in place of serine amide hydrochloride (yield 86%).

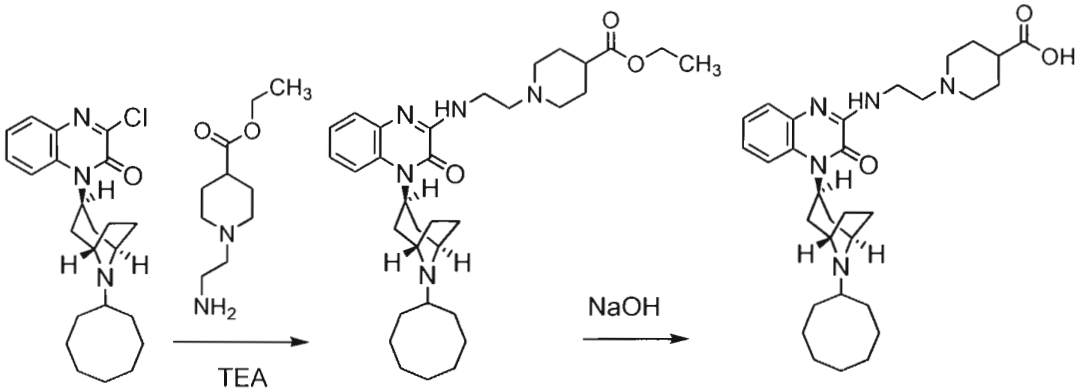
The identity of Substituted-Quinoxaline-Type Piperidine Compound **208**, (*S*)-methyl 2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)-3-phenylpropanoate, was confirmed using LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **208**: LC/MS: *m/z*=542 $[M+H]^+$ (Calc: 543).

Substituted-Quinoxaline-Type Piperidine Compound **209** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **208** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **111** in Example 5 (yield 33%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **209**, (*S*)-2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)-3-phenylpropanoic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **209**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 1.32-2.40 (23H, m), 3.19-3.29 (2H, m), 3.75 (2H, s), 4.64 (1H, dd, J=12.17, 7.1Hz), 5.23 (1H, br s), 7.26-7.12 (7H, m), 7.49-7.31 (3H, m); LC/MS (98%, t_r=2.04min): *m/z*=529 $[M+H]^+$ (Calc: 529).



347 **210** **211**

Substituted-Quinoxaline-Type Piperidine Compound **210** was prepared by using ethyl 1-(2-aminoethyl)piperidine-4-carboxylate (Sigma-Aldrich) in place of serine amide hydrochloride (yield 77%).

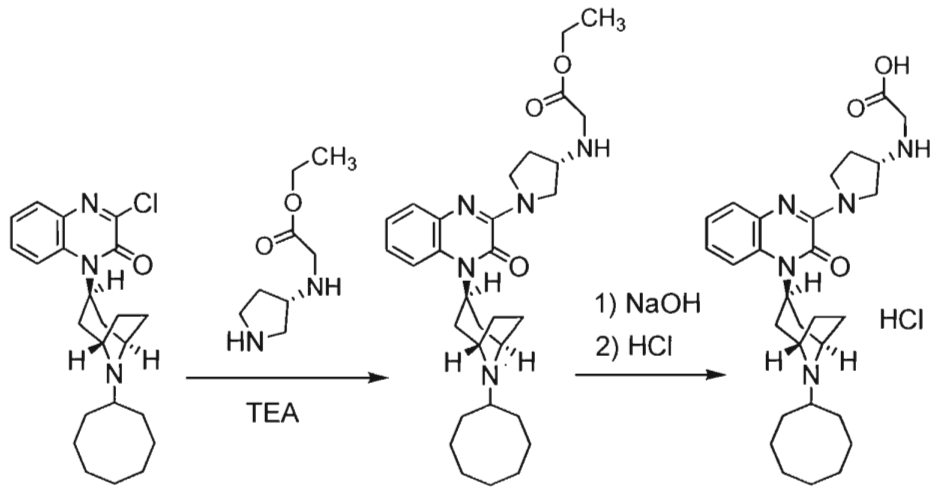
The identity of Substituted-Quinoxaline-Type Piperidine Compound **210**, ethyl 1-(2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)ethyl)piperidine-4-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **210**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 1.26 (3H, t, J=7.1Hz), 1.35-2.43 (30H, m), 2.61 (2H, t, J=6.08Hz), 2.92 (2H, d, J=11.15Hz), 3.59 (2H, q, J=5.75Hz), 3.67 (2H, br s), 4.14 (2H, q, J=6.93Hz), 5.18 (1H, br s), 6.71 (1H, br s), 7.15-7.22 (2H, m), 7.38-7.45 (1H, m), 7.49-7.55 (1H, m); LC/MS: *m/z*=564 $[M+H]^+$ (Calc: 564).

Substituted-Quinoxaline-Type Piperidine Compound **211** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **210** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **111** in Example 5 (yield 79%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **211**, 1-(2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)ethyl)piperidine-4-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **211**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 1.32-2.56 (32H, m), 2.86 (2H, d, J=11.15Hz), 3.46 (2H, d, J=5.58Hz), 3.62 (2H, s), 5.03 (1H, br s), 7.15-7.25 (2H, m), 7.31-7.42 (3H, m), 12.16 (1H, br s); LC/MS (t_r=0.84min): *m/z*=536 $[M+H]^+$ (Calc: 536).



Substituted-Quinoxaline-Type Piperidine Compound **278** was prepared by using (*S*)-ethyl 2-(pyrrolidin-3-ylamino)acetate (Sigma-Aldrich) in place of serine amide hydrochloride (yield 80%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **278**, ethyl 2-((*S*)-1-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)pyrrolidin-3-ylamino)acetate, was confirmed by ^{1}H NMR and LC/MS.

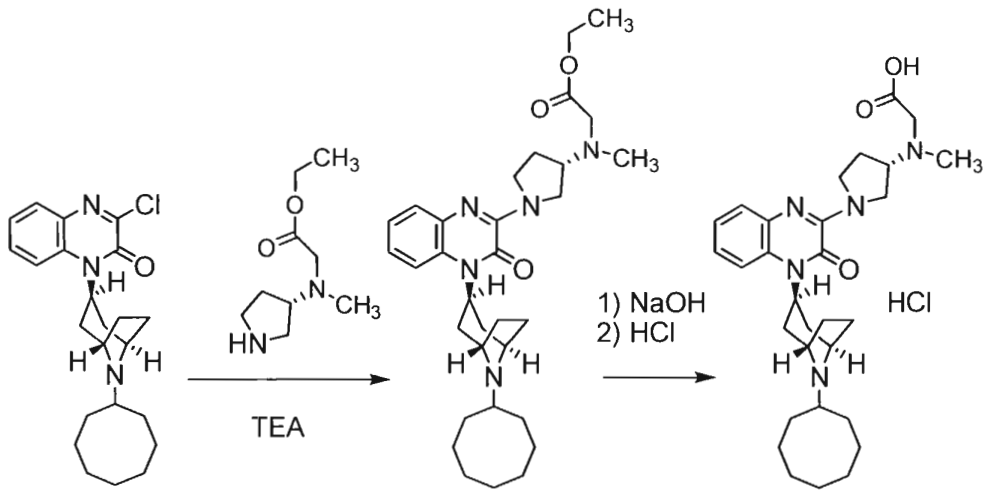
Substituted-Quinoxaline-Type Piperidine Compound **278**: ^{1}H NMR: δ_H ($CDCl_3$): 7.44 (1H, m), 7.31 (1H, m), 7.13-7.12 (2H, m), 4.17 (2H, q, J=8.0Hz), 4.15-3.60 (4H, m), 3.65 (2H, m), 3.43 (2H, s), 3.40 (1H, m), 2.38-2.00 (7H, m), 1.86-1.40 (18H, m), 1.26 (3H, t, J=8.0Hz); LC/MS: *m/z*=536 $[M+H]^+$ (Calc: 535.7).

The hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **279** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **278** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **174** in Example 7 (yield 47%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **279**, 2-((*S*)-1-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)pyrrolidin-3-ylamino)acetic acid, was confirmed by ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **279**: ^{1}H NMR: δ_H (DMSO-d_6): 10.78 (0.9H, d, J=7.6Hz), 10.2 (0.1H, m), 9.71 (2H, s), 7.88 (0.9H, d, J=7.6Hz), 7.75 (0.1H,

m), 7.53 (1H, s), 7.23 (2H, m), 5.92 (1H, m), 4.22-3.91 (9H, m), 2.92 (1H, m), 2.65-2.60 (2H, m), 2.40-1.20 (22H, m); LC/MS (97%, t_r=1.16min): *m/z*=508 $[M+H]^+$ (Calc: 507.6).



347 **283** **284**

Substituted-Quinoxaline-Type Piperidine Compound **283** was prepared by using (*S*)-ethyl 2-(methyl(pyrrolidin-3-yl)amino)acetate (Sigma-Aldrich) in place of serine amide hydrochloride (yield 97%).

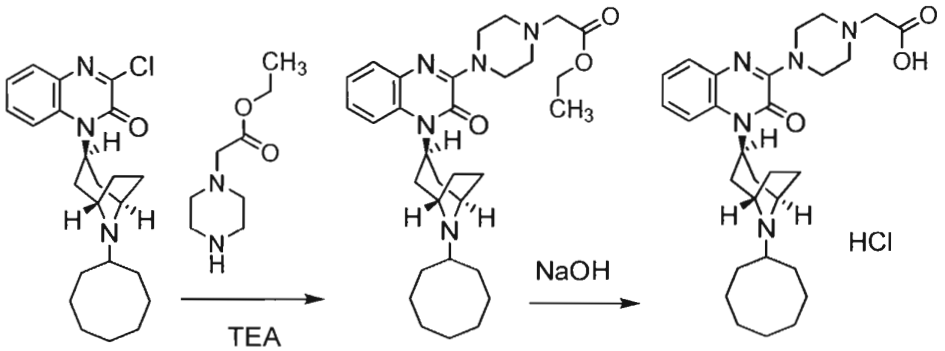
The identity of Substituted-Quinoxaline-Type Piperidine Compound **283**, ethyl 2-(((*S*)-1-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)pyrrolidin-3-yl)(methyl)amino)acetate, was confirmed by ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **283**: ^{1}H NMR: δ_H ($CDCl_3$): 7.44 (1H, m), 7.33 (1H, m), 7.13 (2H, m), 5.30 (1H, br), 4.20 (2H, q, J=8.0Hz), 3.65 (2H, s), 3.39 (4H, m), 2.49 (3H, s), 2.40-1.40 (27H, m) 1.38 (3H, t, J =8.0Hz); LC/MS: *m/z*=550 $[M+H]^+$ (Calc: 549.7).

The hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **284** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **283** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **174** in Example 7 (yield 98%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **284**, 2-(((*S*)-1-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)pyrrolidin-3-yl)(methyl)amino)acetic acid, was confirmed by ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **284**: ^{1}H NMR: δ_H (DMSO-d_6): 11.00 (1H, br), 10.79 (0.9H, m), 10.2 (0.1H, m), 7.88 (0.9H, d, J=7.6Hz), 7.70 (0.1H, m), 7.50 (1H, d, J=7.6Hz), 7.22 (2H, m), 5.93 (1H, s), 4.40-3.60 (7H, m), 2.93 (3H, s), 2.70-1.40 (27H, m); LC/MS (99%, t_r=1.13min); LC/MS: *m/z*=522 $[M+H]^+$ (Calc: 521.6).



347 **373** **337**

Substituted-Quinoxaline-Type Piperidine Compound **373** was prepared by using ethyl 2-(piperazin-1-yl)acetate (Sigma-Aldrich) in place of serine amide hydrochloride (yield 81%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **373**, ethyl 2-(4-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)piperazin-1-yl)acetate, was confirmed using ^{1}H NMR and LC/MS.

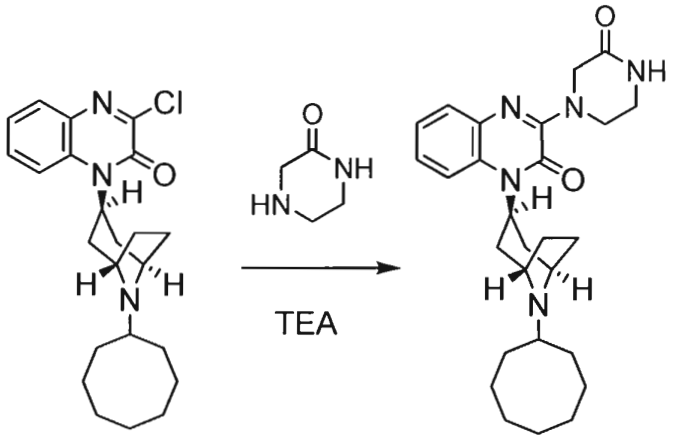
Substituted-Quinoxaline-Type Piperidine Compound **373**: ^{1}H NMR: δ_H (DMSO-d_6): 1.19 (3H, t, *J*=7.6Hz), 1.32-2.40 (23H, m), 2.64 (4H, t, *J*=4.56Hz), 3.27 (2H, s), 3.62 (2H, br s), 3.79 (4H, br s), 4.09 (2H, q, *J*=7.1Hz), 7.20 (1H, t, *J*=7.35Hz), 7.31 (1H, t, *J*=7.1Hz), 7.37 (1H, d, *J*=8.62Hz), 7.45 (1H, d, *J*=4.56Hz); LC/MS: *m/z*=536 $[M+H]^+$ (Calc: 536).

The hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **337** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **373** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **174** in Example 7 (yield 70%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **337**, 2-(4-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)piperazin-1-yl)acetic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **337**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 1.31-2.35 (22H, m), 2.61 (2H, dd, *J*=20.78, 11.66Hz), 2.93 (1H, s), 3.01 (4H, s),

3.59 (2H, s), 3.95 (4H, s), 4.21 (2H, s), 5.10 (0.1H, s), 5.83-5.96 (0.9H, m), 7.22-7.36 (2H, m), 7.48 (1H, dd, *J*=7.60, 1.52Hz), 7.78 (0.1H, d, *J*=8.62Hz), 7.90 (0.9H, d, *J*=8.11Hz), 9.84 (0.1H, s), 10.64 (0.9H, s), 12.18 (1H, br s); LC/MS (t_r=1.10min): *m/z*=508 $[M+H]^+$ (Calc: 508).

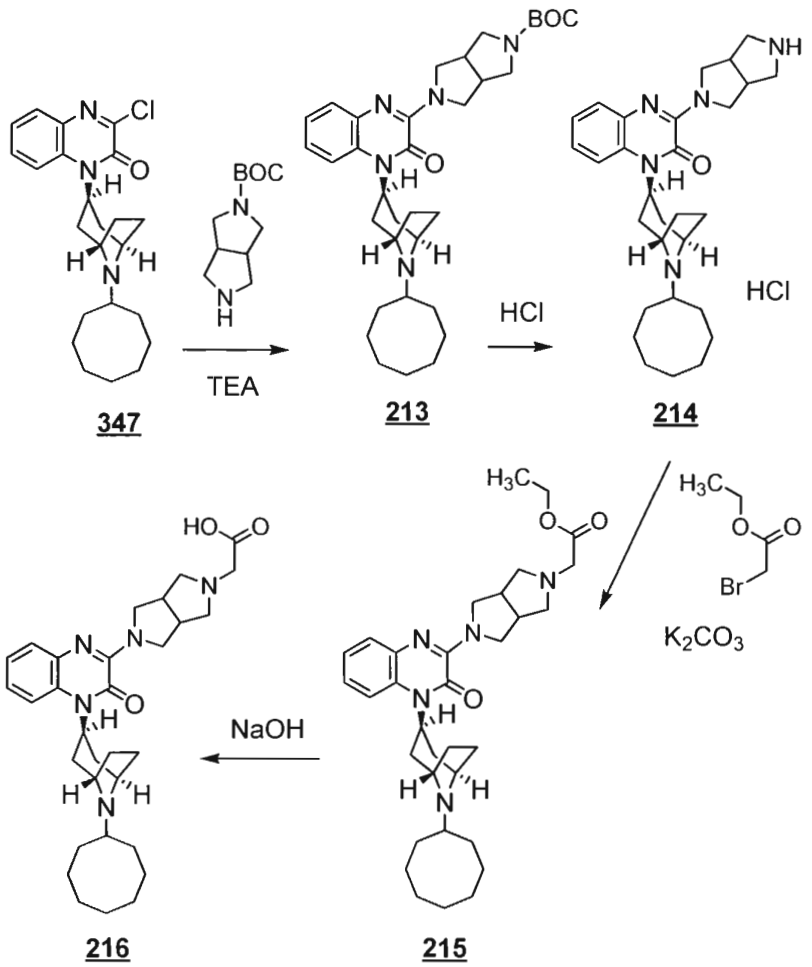


347 **212**

Substituted-Quinoxaline-Type Piperidine Compound **212** was prepared by using piperazin-2-one in place of serine amide hydrochloride (yield 99%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **212**, 1-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-(3-oxopiperazin-1-yl)quinoxalin-2(1*H*)-one, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **212**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 1.35-2.42 (23H, m), 3.57 (2H, s), 3.66 (2H, s), 4.17 (2H, s), 4.52 (2H, s), 5.19 (1H, br s), 6.53 (1H, br s), 7.18-7.32 (2H, m), 7.41 (1H, d, J=8.11Hz), 7.56 (1H, d, J=8.11Hz); LC/MS (t_r=1.66min): *m/z*=464 $[M+H]^+$ (Calc: 464).



Substituted-Quinoxaline-Type Piperidine Compound **213** was prepared by using *tert*-butyl hexahydropyrrolo[3,4-c]pyrrole-2(1*H*)-carboxylate in place of serine amide hydrochloride (yield 98%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **213**, *tert*-butyl 5-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **213**: ^{1}H NMR: δ_H (400MHz, DMSO) 7.34 (1H, d, J=8.0Hz), 7.28 (1H, d, J=8.0Hz), 7.18 (1H, t, J=8.0Hz), 7.15 (1H, d, J=8.0Hz), 5.10 (1H, br), 4.08 (2H, br), 3.80-3.50 (4H, m), 3.18 (2H, m), 2.80 (2H, m), 2.34 (1H, m), 2.16 (2H, m), 2.10-1.45 (22H, m), 1.39 (9H, s); LC/MS: *m/z*=576 $[M+H]^+$ (Calc: 575.3).

The hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **214** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **213** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **5** in Example 7 (yield 99%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **214**, 1-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-(hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)quinoxalin-2(1*H*)-one, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **214**: ^{1}H NMR: δ_H (400MHz, DMSO): 10.73 (1H, m), 9.69 (1H, m), 9.62 (1H, m), 7.88 (1H, d, J=8.0Hz), 7.65 (1H, d, J=8.0Hz), 7.28 (2H, m), 5.88 (1H, m), 4.22 (2H, m), 4.20-3.90 (4H, m), 3.45 (2H, m), 3.15 (4H, m), 2.90 (1H, m), 2.60 (2H, m), 2.40-1.30 (20H, m); LC/MS: *m/z*=476 $[M+H]^+$ (Calc: 475.3).

At a temperature of about 25°C, ethyl 2-bromoacetate (55mg, 0.328mmol, Sigma-Aldrich) and K_2CO_3 (151mg, 1.094mmol) were added to a mixture of Substituted-Quinoxaline-Type Piperidine Compound **214** (150mg, 0.273mmol) in DMF (4mL). The resulting reaction mixture was stirred at about 25°C for 3h. The reaction mixture was diluted with water (5mL) and extracted three times with EtOAc (10mL for each extraction). The organic portions were combined, washed with saturated aqueous NaCl (10mL), dried ($MgSO_4$), and concentrated under reduced pressure to provide a residue. The residue was chromatographed with a silica gel column eluted with a gradient of from 100%:0% $CHCl_3$:MeOH to 90%:10% $CHCl_3$:MeOH to provide 135mg of Substituted-Quinoxaline-Type Piperidine Compound **215** as a white amorphous solid (yield 88%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **215**, ethyl 2-(5-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)acetate, was confirmed using ^{1}H NMR and LC/MS.

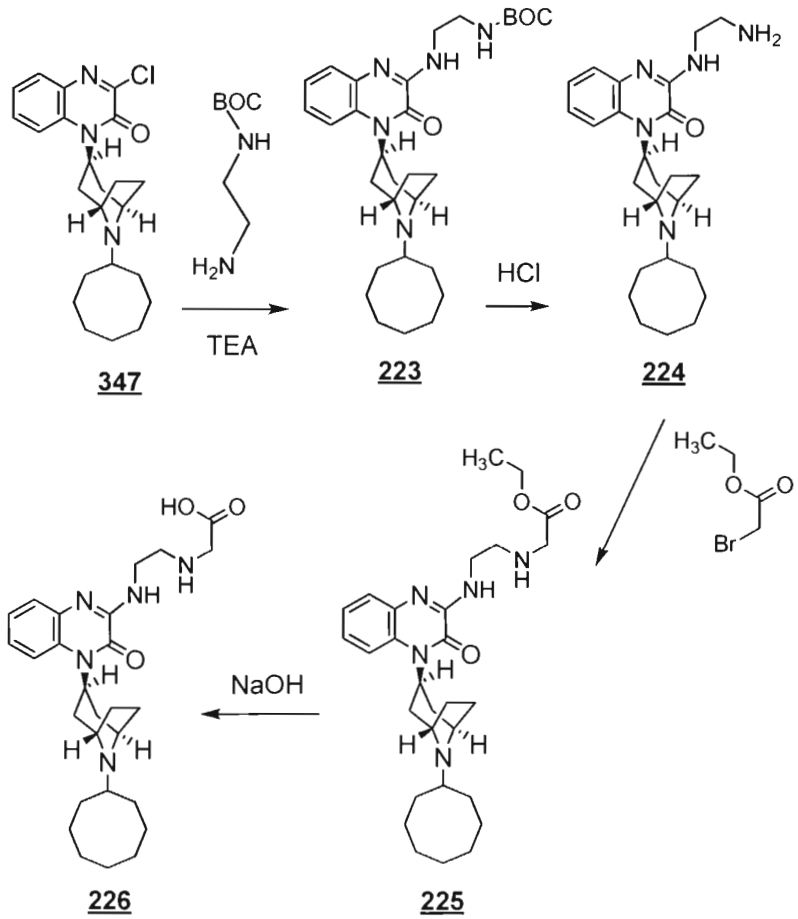
Substituted-Quinoxaline-Type Piperidine Compound **215**: ^{1}H NMR: δ_H (400MHz, DMSO): 10.40 (1H, m), 7.73 (1H, m), 7.39 (1H, d, J=8.0Hz), 7.20 (2H, m), 5.70 (1H, m), 4.30-3.80 (8H, m), 3.20-2.80 (6H, m), 2.80-1.30 (23H, m); LC/MS: *m/z*=562 $[M+H]^+$ (Calc: 561.3).

Substituted-Quinoxaline-Type Piperidine Compound **216** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **215** in a manner similar to the

preparation of Substituted-Quinoxaline-Type Piperidine Compound **111** in Example 5 (yield 70%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **216**, 2-(5-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)acetic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **216**: ^{1}H NMR: δ_H (400MHz, DMSO): 10.40 (1H, m), 7.73 (1H, m), 7.39 (1H, d, J=8.0Hz), 7.20 (2H, m), 5.70 (1H, m), 4.30-3.80 (8H, m), 3.20-2.80 (6H, m), 2.80-1.30 (23H, m); LC/MS (100%, t_r=1.20min): *m/z*=534 $[M+H]^+$ (Calc: 533.5).



In a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **216**, Substituted-Quinoxaline-Type Piperidine Compound **226** was prepared by

using *tert*-butyl 2-aminoethylcarbamate in place of *tert*-butyl-hexahydropyrrolo[3,4-c]pyrrole-2(1*H*)-carboxylate (yield 17% for four steps).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **223**, *tert*-butyl 2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)ethylcarbamate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **223**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 1.36-2.38 (32H, m), 3.18 (2H, q, J=5.91Hz), 3.42 (2H, q, J=5.91Hz), 3.63 (2H, br s), 5.06 (1H, br s), 6.91-6.94 (1H, m), 7.16-7.24 (2H, m), 7.38 (2H, t, J=6.08Hz), 7.56 (1H, s); LC/MS: *m/z*=524 $[M+H]^+$ (Calc: 524).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **224**, 3-(2-aminoethylamino)-1-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)quinoxalin-2(1*H*)-one, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **224**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 1.41-2.37 (24H, m), 2.75 (2H, t, J=6.34Hz), 3.36 (2H, t, J=6.08Hz), 3.57 (2H, s), 3.62 (2H, br s), 5.08 (1H, br s), 7.17-7.21 (2H, m), 7.36-7.39 (2H, m), 7.50-7.52 (1H, m); LC/MS: *m/z*=424 $[M+H]^+$ (Calc: 424).

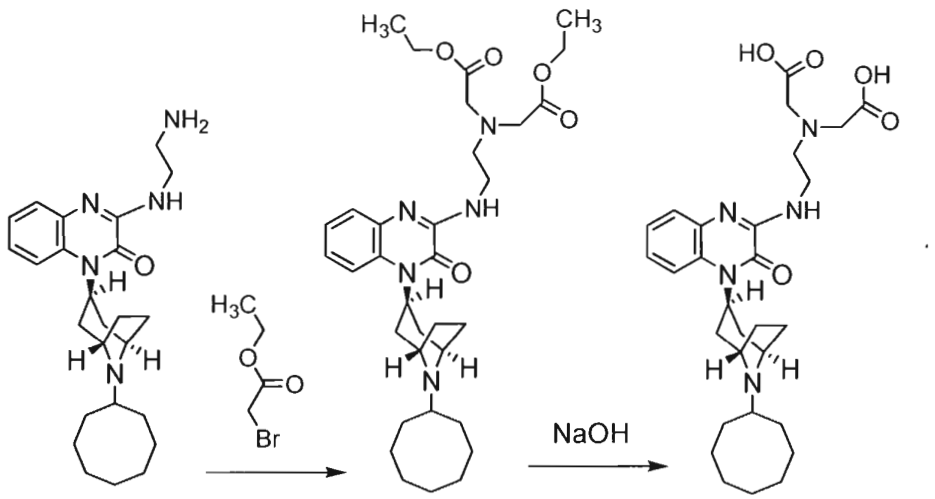
The identity of Substituted-Quinoxaline-Type Piperidine Compound **225**, ethyl 2-(2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)ethylamino)acetate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **225**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 1.19 (3H, t, J=6.84Hz), 1.98 (22H, dt, J=188.24, 72.62Hz), 2.74 (2H, d, J=6.59Hz), 2.77-2.78 (1H, m), 2.90 (2H, d, J=6.59Hz), 3.37 (2H, d, J=6.59Hz), 3.63 (2H, s), 4.04-4.11 (2H, m), 5.08 (1H, s), 7.16-7.25 (2H, m), 7.38 (2H, dd, J=12.67, 8.62Hz), 7.49 (1H, d, J=5.07Hz), 7.96 (1H, d, J=5.58Hz); LC/MS: *m/z*=255.5 $[M+2H]^{2+}$ (Calc: 255.5).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **226**, 2-(2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)ethylamino)acetic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **226**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 1.98 (23H, dtt, J=301.97, 81.62, 34.22Hz), 3.14 (2H, d, J=5.07Hz), 3.43 (2H, s), 3.62 (2H, d, J=5.07Hz), 4.17 (2H, s), 5.61 (1H, br s), 7.12 (1H, s), 7.20 (1H, d, J=7.6Hz), 7.43

(1H, d, J=7.6Hz), 7.57 (1H, s), 7.94 (1H, s), 10.72 (1H, brs); LC/MS (t_r=1.01min): *m/z*=482 $[M+H]^+$ (Calc: 481.6).



224 **227** **228**

To a mixture of Substituted-Quinoxaline-Type Piperidine Compound **224** (38mg, 0.090mmol) and DMF (1mL) at a temperature of about 25°C was added a solution of ethyl 2-bromoacetate (0.187mL, 0.188mmol) in MeCN (1mL). The resulting reaction mixture was stirred at about 25°C for 2h. The reaction mixture was diluted with water and extracted twice with EtOAc (20mL for each extraction). The organic portions were combined, washed with brine, dried ($MgSO_4$), filtrated, and concentrated under reduced pressure to provide a residue. The residue was chromatographed with a silica gel column (Yamazen, S (amino)) eluted with a gradient of from 95%:5% hexanes:EtOAc to 75%:25% hexanes:EtOAc to provide 28.8mg of Substituted-Quinoxaline-Type Piperidine Compound **227** as a yellow solid (yield 54%).

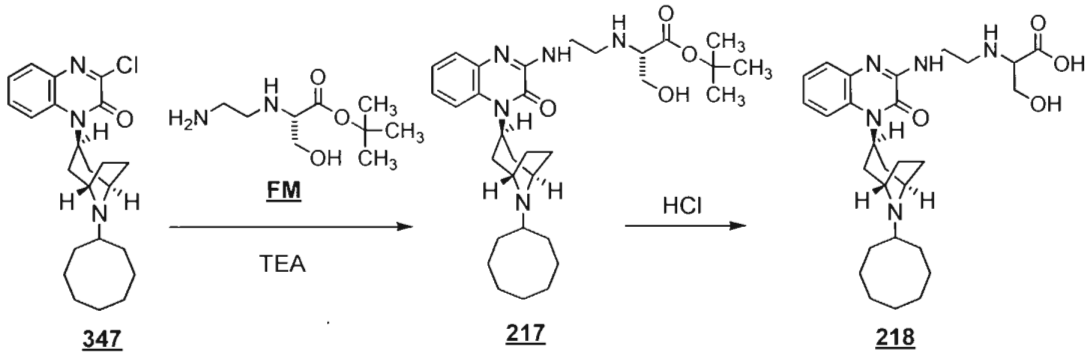
The identity of Substituted-Quinoxaline-Type Piperidine Compound **227**, diethyl 2,2'-(2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)ethylazanediyl)diacetate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **227**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 1.17 (3H, t, J=7.1Hz), 1.18 (3H, t, J=7.1Hz), 1.31-2.42 (23H, m), 2.91 (2H, s), 3.42 (2H, s), 3.58 (4H, d, J=3.55Hz), 3.64 (2H, s), 4.02-4.11 (4H, m), 5.05 (1H, br s), 7.15-7.26 (2H, m), 7.34-7.40 (2H, m), 7.42-7.48 (1H, m); LC/MS: *m/z*=298.5 $[M+2H]^{2+}$ (Calc: 298.5).

Substituted-Quinoxaline-Type Piperidine Compound **228** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **227** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **111** in Example 5 (yield 56%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **228**, 2,2'-(2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)ethylazanediyl)diacetic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **228**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 1.31-2.81 (22H, m), 2.88-2.98 (2H, m), 3.40-3.47 (2H, m), 3.51 (4H, s), 4.24 (2H, s), 5.11 (0.1H, s), 5.65 (0.9H, s), 7.19-7.26 (2H, m), 7.38-7.43 (1H, m), 7.58-7.64 (2H, m), 7.67-7.75 (2H, br m), 9.22 (0.1H, s), 9.95 (0.9H, s), 12.33 (1H, br s); LC/MS (t_r=1.36min): *m/z*=540 $[M+H]^+$ (Calc: 540).



347 **217** **218**

Substituted-Quinoxaline-Type Piperidine Compound **217** was prepared by using (*S*)-*tert*-butyl 2-(2-aminoethylamino)-3-hydroxypropanoate (**FM**) in place of serine amide hydrochloride (yield 99%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **217**, (*S*)-*tert*-butyl 2-(2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)ethylamino)-3-hydroxypropanoate, was confirmed using ^{1}H NMR and LC/MS.

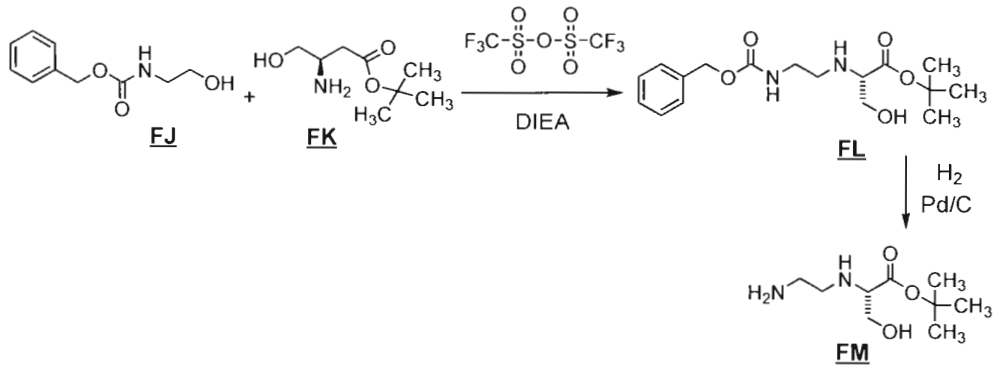
Substituted-Quinoxaline-Type Piperidine Compound **217**: ^{1}H NMR: δ_H ($CDCl_3$): 1.36-2.42 (32H, m), 2.77-2.85 (1H, m), 2.93 (1H, br s), 3.02-3.10 (1H, m), 3.33 (1H, dd, J=6.59, 4.56Hz), 3.52-3.58 (2H, m), 3.62-3.81 (4H, m), 5.15 (1H, br s), 6.64 (1H, br s), 7.17-7.23 (2H, m), 7.39-7.45 (1H, m), 7.50-7.56 (1H, m); LC/MS: *m/z*=568 $[M+H]^+$ (Calc: 568).

Under a nitrogen atmosphere, to a mixture of Substituted-Quinoxaline-Type Piperidine Compound **217** (260mg, 0.458mmol) and dioxane (6mL) at a temperature of about 25°C was added 4N HCl in dioxane (2mL, 8.00mmol). The resulting reaction mixture was warmed to 50°C and stirred for 4h. The mixture was filtrated with a Hirsch funnel, washed with dioxane, dried under reduced pressure for 8h at 85°C, then chromatographed by a reverse phase chromatography apparatus (Gilson Inc, Middletown WI). The collected fraction was dried under reduced pressure to provide 112mg of Substituted-Quinoxaline-Type Piperidine Compound **218** (yield 48%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **218**, 2-(2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)ethylamino)-3-hydroxypropanoic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **218**: ^{1}H NMR: δ_H (DMSO-d_6): 1.29-2.40 (21H, m), 2.53-2.73 (2H, m), 2.90 (1H, br s), 3.22 (3H, t, J=5.32Hz), 3.62-3.75 (3H, m), 3.84 (2H, ddd, J=25.73, 11.79, 3.93Hz), 4.16 (2H, d, J=24.33Hz), 5.12 (0.1H, br s), 5.78 (0.9H, br s), 7.12-7.23 (2H, m), 7.44 (1H, d, J=7.1Hz), 7.68-7.78 (1H, m), 8.00 (1H, t, J=5.58Hz), 9.84 (0.1H, br s), 10.76 (0.9H, br s); LC/MS (t_r=1.09min): *m/z*=512 $[M+H]^+$ (Calc: 512).

The compound of formula **FM** was prepared as follows:



Under a nitrogen atmosphere, to a mixture of benzyl 2-hydroxyethylcarbamate (**FJ**, 1000mg, 5.12mmol) and CH_2Cl_2 (13mL) at a temperature of from -20°C to -17°C were added DIEA (2340µL, 13.40mmol) and trifluoromethanesulfonic anhydride (909µL, 5.38mmol). The resulting reaction mixture was stirred for 1h at a temperature of -20°C. Thereafter, (*R*)-*tert*-butyl 3-amino-4-hydroxybutanoate (**FK**, 1239mg, 7.68mmol, Sigma-Aldrich) in CH_2Cl_2 (5mL) was slowly added. The resulting reaction mixture was stirred for 4h as its temperature warmed

from -20°C to -5°C. Thereafter, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ then extracted 3 times with $CHCl_3$ (30mL for each extraction). The organic portions were combined, washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was chromatographed with an amino-silica gel column (Yamazen Corp. W091-01) eluted with a gradient of from 20%:80% EtOAc:n-hexane to 80%:20% EtOAc:n-hexane to provide 921mg of the compound of formula **FL** as a yellow oil (yield 53%).

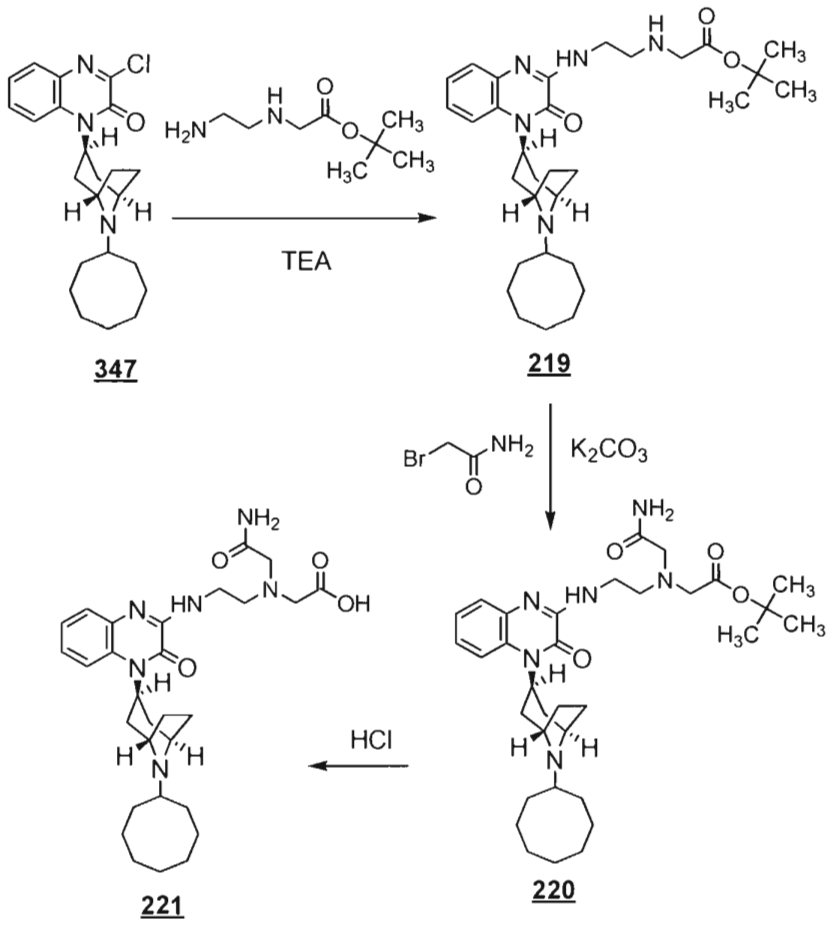
The identity of the compound of formula **FL**, (*S*)-*tert*-butyl 2-(2-(benzyloxycarbonylamino)ethylamino)-3-hydroxypropanoate, was confirmed using ^1H NMR and LC/MS.

Compound **FL**: ^1H NMR: δ_H (400MHz, $CDCl_3$): 1.46 (9H, s), 2.61-2.70 (1H, m), 2.82-2.91 (1H, m), 3.16-3.27 (2H, m), 3.30-3.42 (1H, m), 3.54 (1H, dd, J=10.90, 6.84Hz), 3.74 (1H, dd, J=10.65, 4.56Hz), 5.10 (2H, s), 5.21 (1H, br s), 7.31-7.37 (5H, m); LC/MS: *m/z*=339 $[M+H]^+$ (Calc: 339).

Under a hydrogen atmosphere, a mixture of the compound of formula **FL** (906mg, 2.68mmol), 10% palladium on carbon, 50% wet (285mg, 0.134mmol), and MeOH (10mL) was stirred at a temperature of about 25°C for 3h. The Pd/C was filtered off, the mixture was washed with MeOH, and the filtrate was concentrated under reduced pressure to provide 651mg of the compound of formula **FM** as a pale yellow solid (yield >98%).

The identity of the compound of formula **FM**, (*S*)-*tert*-butyl 2-(2-aminoethylamino)-3-hydroxypropanoate, was confirmed using ^1H NMR and LC/MS.

Compound **FM**: ^1H NMR: δ_H (400MHz, $CDCl_3$): 1.47 (9H, s), 2.55-2.64 (1H, m), 2.78-2.86 (3H, m), 3.27 (1H, dd, J=6.84, 4.31Hz), 3.55 (1H, dd, J=10.65, 6.59Hz), 3.77 (1H, dd, J=10.90, 4.31Hz); LC/MS: *m/z*=205 $[M+H]^+$ (Calc: 205).



347 219 220 221

Substituted-Quinoxaline-Type Piperidine Compound **219** was prepared by using *tert*-butyl 2-(2-aminoethylamino)acetate (Sigma-Aldrich) in place of serine amide hydrochloride (yield 86%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **219**, *tert*-butyl 2-(2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)ethylamino)acetate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **219**: ^{1}H NMR: δ_H ($CDCl_3$): 1.35-1.89 (2H, m), 1.98-2.03 (1H, m), 2.13-2.42 (4H, m), 2.91 (2H, t, J=5.83Hz), 3.34 (2H, s), 3.61 (2H, q, J=5.91Hz), 3.66 (2H, br s), 5.13 (1H, br s), 6.69 (1H, s), 7.16-7.22 (2H, m), 7.38-7.44 (1H, m), 7.49-7.55 (1H, m); LC/MS: *m/z*=538 $[M+H]^+$ (Calc: 538).

To a mixture of Substituted-Quinoxaline-Type Piperidine Compound **219** (305mg, 0.567mmol) and MeCN (5mL) at a temperature of about 25°C was added 2-bromoacetamide (86mg, 0.624mmol, Sigma-Aldrich) and K_2CO_3 (86mg, 0.624mmol). The resulting reaction

mixture was warmed to 60°C and stirred for 3h. The reaction mixture was diluted with water and extracted twice with $CHCl_3$ (20mL for each extraction). The organic portions were combined, washed with brine, dried ($MgSO_4$), filtrated, and concentrated under reduced pressure to provide a residue. The residue was chromatographed with a silica gel column (Yamazen, M (amino)) eluted with a gradient of from 60%:40% hexanes:EtOAc to 0%:100% hexanes:EtOAc to provide a fractions. The fractions were combined and concentrated under reduced pressure to provide a colorless amorphous solid which was chromatographed with a silica gel column (Yamazen, M (amino)) eluted with a gradient of from 99%:1% $CHCl_3$:(MeOH:NH_3=10:1) to 90%:10% $CHCl_3$:(MeOH:NH_3=10:1) to provide 252mg of Substituted-Quinoxaline-Type Piperidine Compound **220** (yield 75%).

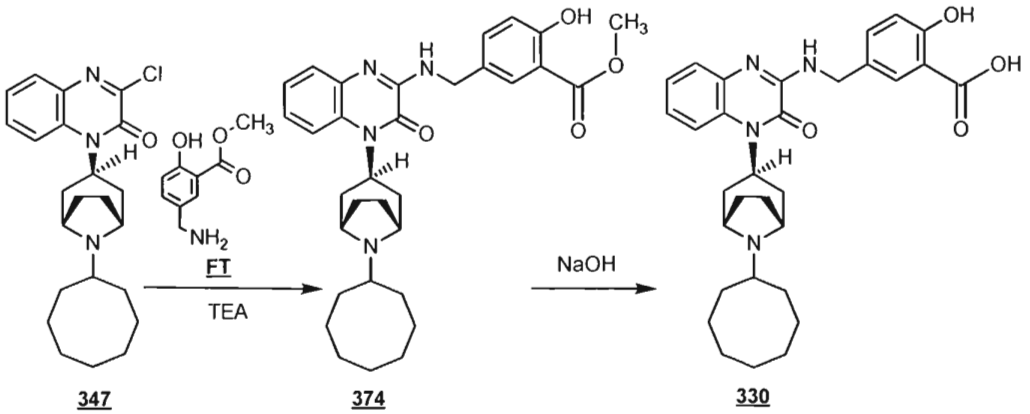
The identity of Substituted-Quinoxaline-Type Piperidine Compound **220**, *tert*-butyl 2-((2-amino-2-oxoethyl)(2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)ethyl)amino)acetate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **220**: ^{1}H NMR: δ_H ($CDCl_3$): 1.35-2.41 (32H, m), 2.96 (2H, t, J=4.82Hz), 3.33 (2H, s), 3.38 (2H, s), 3.57-3.63 (2H, m), 3.66 (2H, br s), 5.18 (1H, br s), 5.40 (1H, br s), 6.65 (1H, br s), 7.17-7.23 (2H, m), 7.38-7.44 (1H, m), 7.47-7.53 (1H, m), 7.55 (1H, br s); LC/MS: *m/z*=595 $[M+H]^+$ (Calc: 595).

Substituted-Quinoxaline-Type Piperidine Compound **221** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **220** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **218** (yield 96%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **221**, 2-((2-amino-2-oxoethyl)(2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)ethyl)amino)acetic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **221**: ^{1}H NMR: δ_H (CD_3OD): 1.35-2.43 (20H, m), 2.61-2.74 (2H, m), 2.95-3.12 (3H, m), 3.34-3.71 (6H, m), 4.17 (2H, br s), 5.45 (1H, br s), 7.25-7.15 (2H, m), 7.46 (1H, d, J=7.6Hz), 7.58 (1H, d, J=8.11Hz); LC/MS (t_r=1.06min): *m/z*=539 $[M+H]^+$ (Calc: 539).

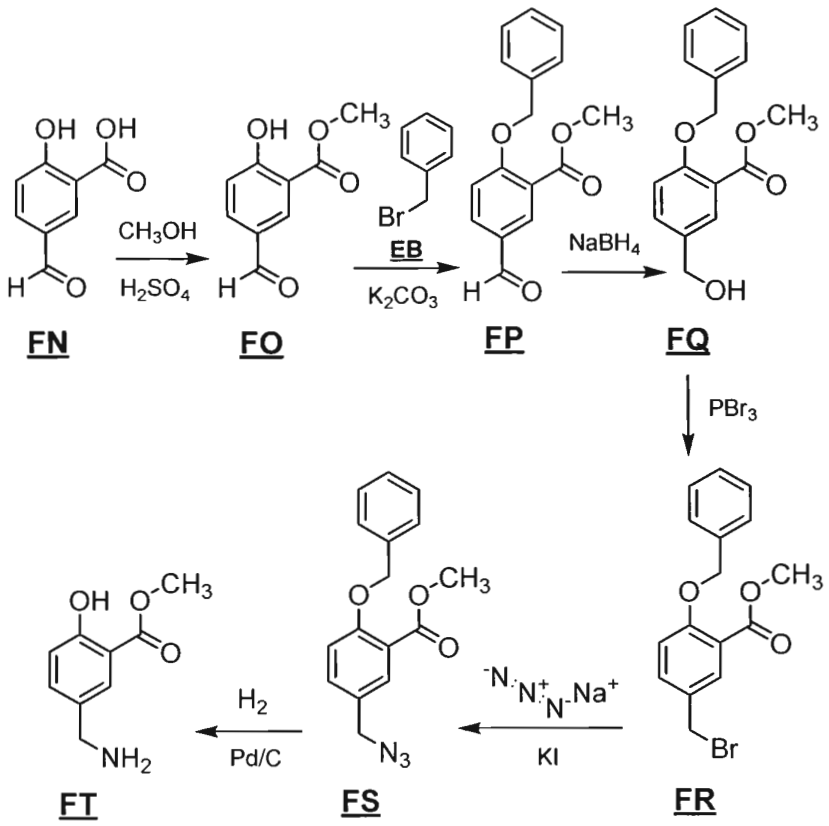


Substituted-Quinoxaline-Type Piperidine Compound **374**, methyl 5-((4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)methyl)-2-hydroxybenzoate, was prepared by using methyl 5-(aminomethyl)-2-hydroxybenzoate (**FT**) in place of serine amide hydrochloride. Substituted-Quinoxaline-Type Piperidine Compound **211** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **374** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **111** in Example 5 (yield 9% for two steps).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **330**, 5-((4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)methyl)-2-hydroxybenzoic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **330**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 13.97 (br, 1H), 11.16 (s, 1H), 10.49 (s, 1H), 8.51 (br, 1H), 7.78-7.91 (m, 2H), 7.59-7.62 (m, 1H), 7.49 (m, 1H), 7.23-7.25 (m, 2H), 6.90-6.92 (m, 1H), 5.85-5.90 (m, 1H), 4.45-4.57 (m, 2H), 4.19-4.36 (m, 2H), 2.92 (m, 1H), 2.59-2.64 (m, 2H), 1.16-2.34 (m, 20H); LC/MS: m/z=568 $[M+H]^+$ (Calc: 567).

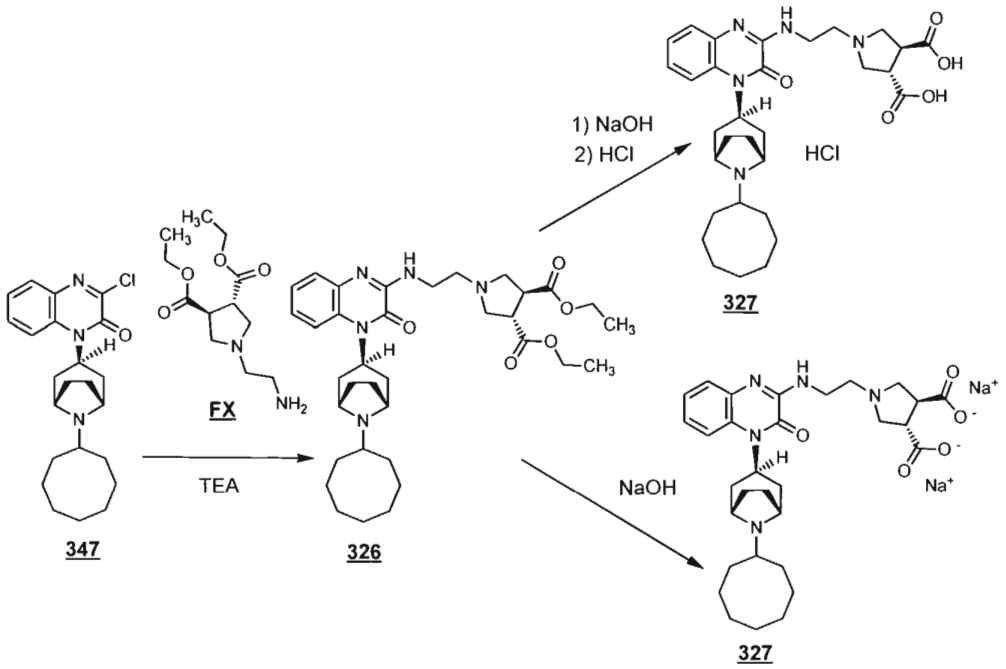
Methyl 5-(aminomethyl)-2-hydroxybenzoate (**FT**) was prepared as follows:



A reaction mixture of 5-formyl-2-hydroxybenzoic acid (**FN**, 5.00g, 30.1mmol, Sigma-Aldrich), concentrated H_2SO_4 (2.00mL), and MeOH (50mL) was stirred at reflux for 24h. Thereafter, the mixture was concetrated under reduced pressure to provide 5.36g of the compound of formula **FO**, methyl 5-formyl-2-hydroxybenzoate, as colorless oil (yield 99%). A reaction mixture of the compound of formula **FO** (5.36g, 29.7mmol), the compound of formula **EB** (3.89mL, 32.8mmol), K_2CO_3 (4.93g, 35.7mmol), and acetone (150mL) was stirred at reflux for 22h. Thereafter, the mixture was concentrated under reduced pressure to provide 4.92g of the compound of formula **FP**, methyl 2-(benzyloxy)-5-formylbenzoate, as a white solid (yield 61%). A reaction mixture of the compound of formula **FP** (4.40g, 16.3mmol), sodium tetrahydroborate (738mg, 19.5mmol), and THF (50mL) was stirred for 1h at a temperature of 0°C, warmed to a temperature of about 25°C, and stirred for 1h more. Thereafter, the reaction mixture was partitioned between EtOAc and water. The organic portion was separated, washed with saturated aqueous $NaHCO_3$, washed with brine, dried (Na_2SO_4), filtered, concentrated under reduced pressure, and chromatographed with a silica gel column eluted with a gradient of from 100%:0% hexane:EtOAc to 50%:50% hexane:EtOAc to

provide 3.98g of the compound of formula **FQ**, methyl 2-(benzyloxy)-5-(hydroxymethyl)benzoate, as a colorless oil (yield 90%).

A reaction mixture of the compound of formula **FQ** (3.98g, 14.6mmol), phosphorus tribromide (687mL, 7.31mmol, Sigma-Aldrich), and diethyl ether (100mL) was stirred for 1h at a temperature of 0°C. Thereafter, the reaction mixture was partitioned between diethyl ether and water. The organic portion was separated, washed with saturated aqueous $NaHCO_3$, washed with brine, dried (Na_2SO_4), filtered, concentrated under reduced pressure to provide 4.90g of the compound of formula **FR**, methyl 2-(benzyloxy)-5-(bromomethyl)benzoate, as a white solid (yield >99%). A reaction mixture of the compound of formula **FR** (4.90g, 14.6mmol), sodium azide (1.05g, 16.1mmol), potassium iodide (catalytic amount, Sigma-Aldrich), and DMF (100mL) was stirred for 20h at a temperature of about 25°C. Thereafter, the reaction mixture was partitioned between EtOAc and water. The organic portion was separated, washed with saturated aqueous $NaHCO_3$, washed with brine, dried (Na_2SO_4), filtered, concentrated under reduced pressure, and chromatographed with a silica gel column eluted with a gradient of from 100%:0% hexane:EtOAc to 50%:50% hexane:EtOAc to provide 2.82g of the compound of formula **FS**, methyl 5-(azidomethyl)-2-(benzyloxy)benzoate, as a colorless oil (yield 65%). Under a hydrogen atmosphere, a mixture of the compound of formula **FS** (1.28g, 4.30mmol), 20% palladium on carbon by weight (120mg), MeOH (5mL), and EtOAc (10mL) was stirred at a temperature of about 25°C for 5h. The Pd/C was filtered off with a CELITE pad, the mixture was washed with EtOAc, then concentrated under reduced pressure to provide a first residue. The first residue was suspended in MeOH, the insoluble solid filtered off, and the filtrate concentrated under reduced pressure to provide a second residue. The second residue was washed with EtOAc to provide 438mg of the compound of formula **FT** as a brown solid (yield 56%).



Substituted-Quinoxaline-Type Piperidine Compound **326** was prepared by using (3*S*,4*S*)-diethyl 1-(2-aminoethyl)pyrrolidine-3,4-dicarboxylate (**FX**) in place of serine amide hydrochloride (yield 75%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **326**, (3*S*,4*S*)-diethyl 1-(2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)ethyl)pyrrolidine-3,4-dicarboxylate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **326**: ^{1}H NMR: δ_H (400MHz, CD_3OD): 7.51 (m, 2H), 7.25 (m, 2H), 5.10 (s, br, 1H), 4.12 (dd, 4H), 3.7 (s, br, 2H), 3.60(m, 1H), 3.42 (m, 2H), 2.89 (m, 2H), 2.75 (m, 2H), 2.55 (s, br, 1H), 2.38-1.35 (m, 22H), 1.25 (t, 6H); LC/MS: *m/z*=566 $[M+H]^+$ (Calc: 565).

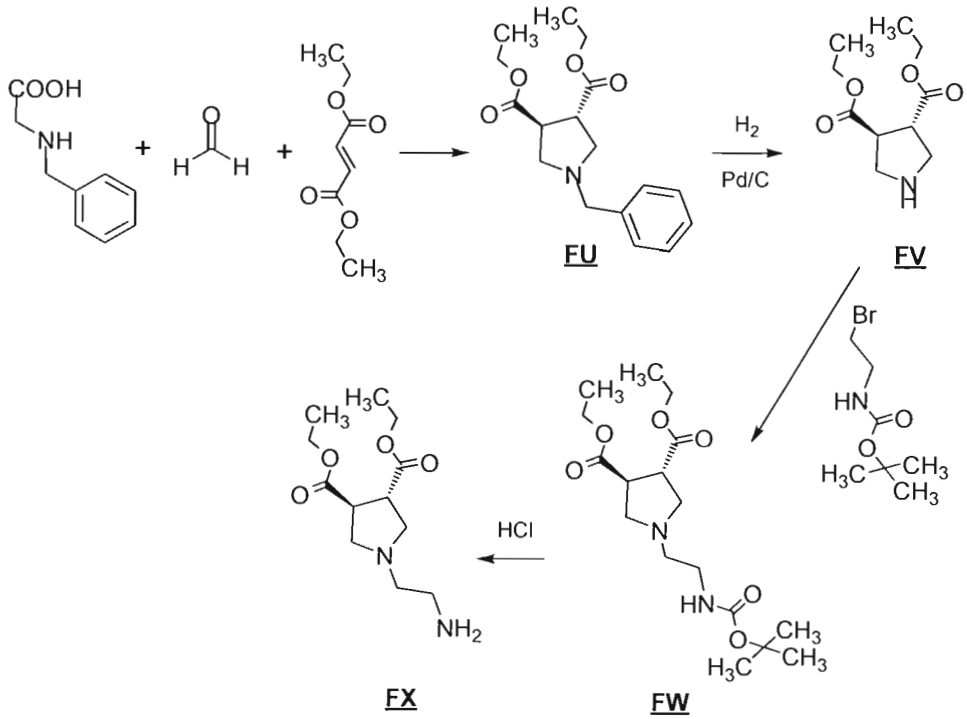
The hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **327** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **326** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **174** in Example 7 (yield 60%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **327**, (3*S*,4*S*)-1-(2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)ethyl)pyrrolidine-3,4-dicarboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **327**: ^{1}H NMR: δ_H (400MHz, CD_3OD):. 7.36-7.38 (m, 2H), 7.12-7.06 (m, 2H), 5.27-5.09 (s, br. 1H), 3.60 (s, br, 2H), 3.57-3.45 (m, 2H), 2.89 (t, J=8.8Hz, 2H), 2.82-2.78 (m, 2H), 2.72-2.53 (m, 3H), 2.46-2.36 (s, br, 1H), 2.27-1.36 (m, 22H); LC/MS: *m/z*=566 $[M+H]^+$ (Calc: 565).

The sodium salt of Substituted-Quinoxaline-Type Piperidine Compound **327** was prepared as follows. To a mixture of Substituted-Quinoxaline-Type Piperidine Compound **326** (65mg, 0.1mmol) and 95% ethanol (3mL) at a temperature of about 25°C was added 2N aqueous NaOH (0.1mL). The resulting reaction mixture was stirred at about 25°C for 2h after which a white precipitate formed. The precipitate was collected and dried under reduced pressure to provide 42.1mg of the sodium salt of Substituted-Quinoxaline-Type Piperidine Compound **327** (yield 71%).

The compound of formula **FX** was prepared as follows:



To a mixture of diethyl fumarate (8.68g, 50.4mmol, Sigma-Aldrich) and toluene (800mL) at 105°C was added dropwise over 1h a mixture of formaldehyde, in the form of paraformaldehyde, (10.2g, 339mmol (based on formaldehyde monomer molecular weight), Sigma-Aldrich) and 2-(benzylamino)acetic acid (12.2g, 60.5mmol, Sigma-Aldrich). The resulting reaction mixture was refluxed for 16h in an apparatus comprising a Dean-Stark trap.

After concentration under reduced pressure, the residue was dissolved in hexanes, filtered, and concentrated under reduced pressure to provide a brown oil. Flash chromatography of the oil with a silica gel column eluting with 1:5 EtOAc:hexanes provided 13.8g of the compound of formula **FU** as a colorless oil (yield 74%).

The identity of the compound of formula **FU**, (3*S*,4*S*)-diethyl 1-benzylpyrrolidine-3,4-dicarboxylate, was confirmed using TLC and LC/MS.

Compound **FU**: TLC (SiO_2) 1:1 EtOAc:hexanes: Rf=0.8 with UV detection, Dragendorff's reagent; LC/MS: *m/z*=306 $[M+H]^+$ (Calc: 305).

Under a hydrogen atmosphere, a mixture of the compound of formula **FU** (4.08g, 13.4mmol), 10% palladium on carbon (4.7g), and MeOH was stirred at a temperature of about 25°C for 2h. The Pd/C was filtered off with a CELITE pad and the filtrate was concentrated under reduced pressure to provide 2.89g of the compound of formula **FV** as a pale yellow oil (yield >98%).

The identity of the compound of formula **FV**, (3*S*,4*S*)-diethyl pyrrolidine-3,4-dicarboxylate, was confirmed using TLC and LC/MS.

Compound **FV**: TLC (SiO_2) 1:3 EtOAc:hexanes: Rf=0.1 with UV detection, Dragendorff's reagent; LC/MS: *m/z*=216 $[M+H]^+$ (Calc: 215).

To a mixture of the compound of formula **FV** (2.4g, 11.2mmol) and dry DMF (150mL) at a temperature of about 25°C was added *tert*-butyl 2-bromoethylcarbamate (2.7g, 12.3mmol, Sigma-Aldrich) and TEA (22.4mmol, 3.1mL). The resulting reaction mixture was heated to 60°C and stirred for 18h at that temperature. Thereafter the solids were filtered off, the filtrate was washed with brine, and the aqueous phase was extracted three times with with EtOAc (100mL for each extraction). The organic portions were combined, dried ($MgSO_4$), and concentrated under reduced pressure to provide an oil. Flash chromatography of the oil with a silica gel column eluting with 9:1 CH_2Cl_2:MeOH provided 2.59g of the compound of formula **FW** as a pale yellow oil (yield 65%).

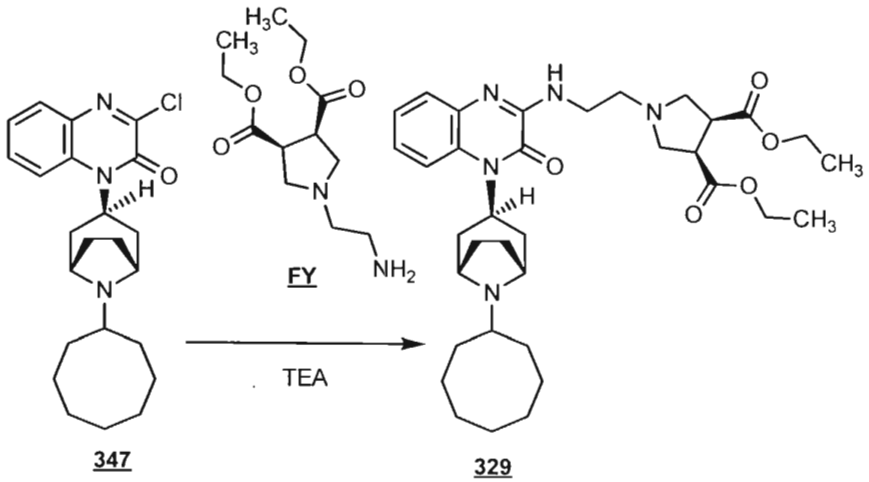
The identity of the compound of formula **FW**, (3*S*,4*S*)-diethyl 1-(2-(*tert*-butoxycarbonylamino)ethyl)pyrrolidine-3,4-dicarboxylate, was confirmed using TLC and LC/MS.

Compound **FW**: TLC (SiO_2) 5:1 EtOAc:hexanes: Rf=0.6 with UV detection, Dragendorff's reagent; LC/MS: *m/z*=359 $[M+H]^+$ (Calc: 358).

To a mixture of the compound of formula **FW** (1.5g, 4.2mmol) and EtOAc at 0°C was added slowly 4N HCl in EtOAc (4.5mL). After heating to a temperature of about 25°C and stirring for 2h, the reaction mixture became cloudy, indicating the formation of an HCl salt. After concentration under reduced pressure, the residue was washed with diethyl ether and the solids were filtered off and the dried under reduced pressure for 16h to provide 1.08g of the compound of formula **FX** as a white solid (yield 90%).

The identity of the compound of formula **FX** was confirmed using LC/MS.

Compound **FX**: LC/MS: *m/z*=259 $[M+H]^+$ (Calc: 258).



347 **329**

Substituted-Quinoxaline-Type Piperidine Compound **329** was prepared by using (3*R*,4*S*)-diethyl 1-(2-aminoethyl)pyrrolidine-3,4-dicarboxylate (**FY**) in place of serine amide hydrochloride (yield 86%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **329**, (3*R*,4*S*)-diethyl 1-(2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)ethyl)pyrrolidine-3,4-dicarboxylate, was confirmed using ^1H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **329**: ^1H NMR: δ_H (400MHz, CD_3OD): 7.49-5.56 (m, 1H), 7.45-7.49 (s, br, 1H), 7.25-7.22 (m, 2H), 6.77-6.67 (s, br, 1H), 5.64-4.86 (s, br., 1H), 4.17-4.12(dd, J=9.1, 8.2Hz, 4H), 3.72 (s, br, 2H), 3.62-3.58 (dd, J=5.8,

11.5Hz, 2H), 3.32-3.24 (m, 4H), 2.82-2.74 (m, 4H), 2.5-1.25(m, 23H), 1.15(t, J=7.1Hz, 6H); LC/MS: *m/z*=566 $[M+H]^+$ (Calc: 565).

In a manner similar to the above preparation of the compound of formula **FX**, the compound of formula **FY** was prepared except that diethyl maleate (Sigma-Aldrich) was used in place of diethyl fumarate (yield 30% for four steps).

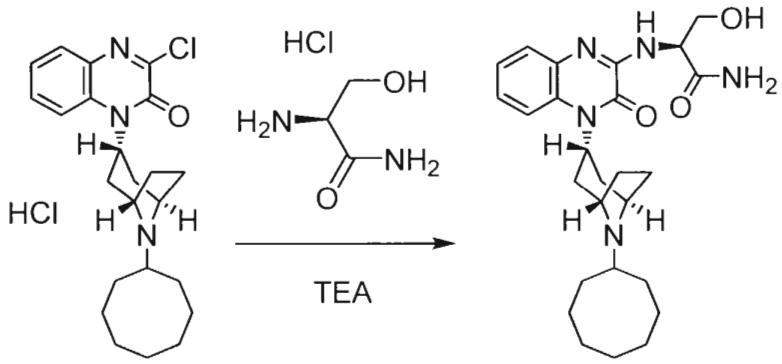
The identity of the compound of formula **FY** was confirmed using LC/MS.

Compound **FY**: LC/MS: *m/z*=259 $[M+H]^+$ (Calc: 258).

5.17 Example 17

In a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **347** from the compound of formula **EH** in Example 14, Substituted-Quinoxaline-Type Piperidine Compound **403**, *i.e.*, 3-chloro-1-((*exo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)quinoxalin-2(1*H*)-one or the *exo* isomer, was prepared from the compound of formula **EI**.

In a manner similar to Example 15, the following Substituted-Quinoxaline-Type Piperidine Compound was prepared from Substituted-Quinoxaline-Type Piperidine Compound **403** (yield 61%).



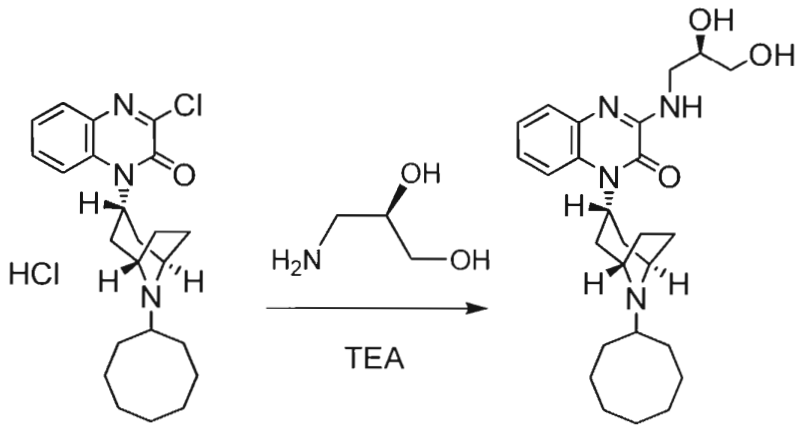
403 **104**

The identity of Substituted-Quinoxaline-Type Piperidine Compound **104**, (2*S*)-2-(4-((*exo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)-3-hydroxypropanamide, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **104**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 7.70 (1H, s), 7.49 (1H, s), 7.38 (1H, t, J=4.82Hz), 7.19 (4H, m), 5.02 (2H, m),

4.47-4.43 (1H, m), 3.68 (4H, m), 2.81 (2H, m), 1.58 (21H, m); LC/MS (96%, t_r=1.14min): *m/z*=468.2 $[M+H]^+$ (Calc: 467.6).

In a manner similar to the above preparation of Substituted-Quinoxaline-Type Piperidine Compound **104**, the following Substituted-Quinoxaline-Type Piperidine Compound was prepared from Substituted-Quinoxaline-Type Piperidine Compound **403** except that (*R*)-3-amino-1,2-propanediol (Sigma-Aldrich) was used in place of serine amide hydrochloride (yield 70%).

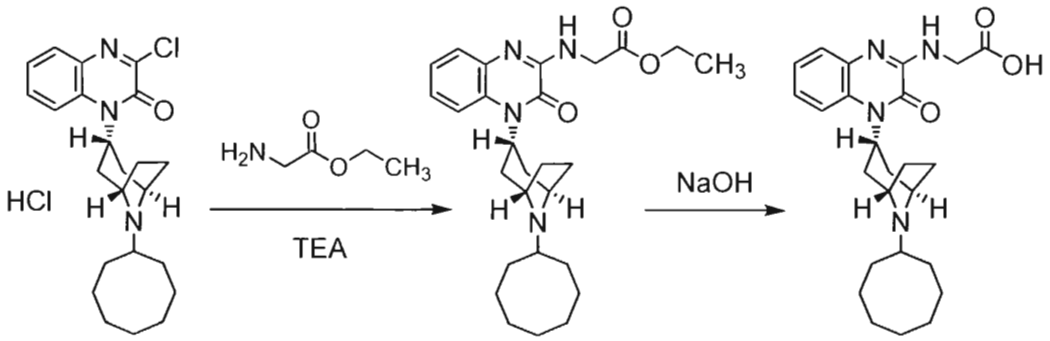


403 **105**

The identity of Substituted-Quinoxaline-Type Piperidine Compound **105**, 1-((*exo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-((*R*)-2,3-dihydroxypropylamino)quinoxalin-2(1*H*)-one, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **105**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 9.38 (0.1H, s), 7.69 (0.9H, s), 7.31 (4H, m), 5.00 (1.5H, d, J=5.07Hz), 4.71 (1H, t, J=5.58Hz), 4.28 (0.5H, s), 3.71 (1H, t, J=5.83Hz), 3.55 (2H, t, J=6.59Hz), 3.39 (3H, m), 2.80 (2H, br), 1.64 (23H, m); LC/MS (100%, t_r=1.14min): *m/z*=455.2 $[M+H]^+$ (Calc: 454.6).

In a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compounds **144** and **106** in Example 16, the following Substituted-Quinoxaline-Type Piperidine Compounds were prepared from Substituted-Quinoxaline-Type Piperidine Compound **403**.



403 **146** **110**

The identity of Substituted-Quinoxaline-Type Piperidine Compound **146**, ethyl 2-(4-((*exo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)acetate, was confirmed using ^{1}H NMR.

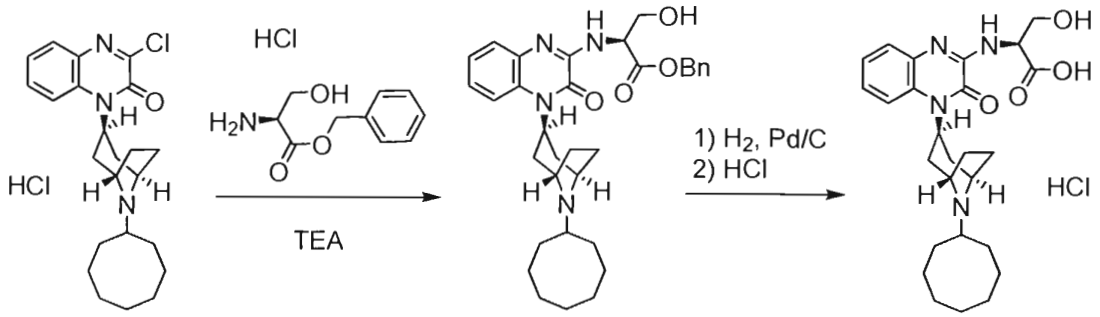
Substituted-Quinoxaline-Type Piperidine Compound **146**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 7.92 (1H, s), 7.68 (1H, s), 7.36 (1H, dd, J=7.60, 2.03Hz), 7.21 (2H, q, J=7.94Hz), 4.98 (1H, br), 4.15-4.08 (2H, m), 3.55 (2H, s), 2.80 (2H, s), 1.57 (23H, m).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **110**, 2-(4-((*exo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)acetic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **110**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 7.68 (1H, s), 7.53 (1H, t, J=5.32Hz), 7.40-7.38 (1H, m), 7.23-7.17 (2H, m), 5.02 (1H, br), 3.85 (2H, d, J=5.07Hz), 3.66 (2H, s), 2.82 (2H, s), 1.97-1.41 (21H, m); LC/MS (98%, t_r=1.38min): *m/z*=439.2 $[M+H]^+$ (Calc: 438.6).

5.18 Example 18

In a manner similar to Example 15, the following Substituted-Quinoxaline-Type Piperidine Compounds were prepared from Substituted-Quinoxaline-Type Piperidine Compound **347**.



347 **147** **100**

Substituted-Quinoxaline-Type Piperidine Compound **147** was prepared by using L-serine benzyl ester (*i.e.*, (*S*)-benzyl 2-amino-3-hydroxypropanoate hydrochloride, Sigma-Aldrich) in place of serine amide hydrochloride (yield 93%).

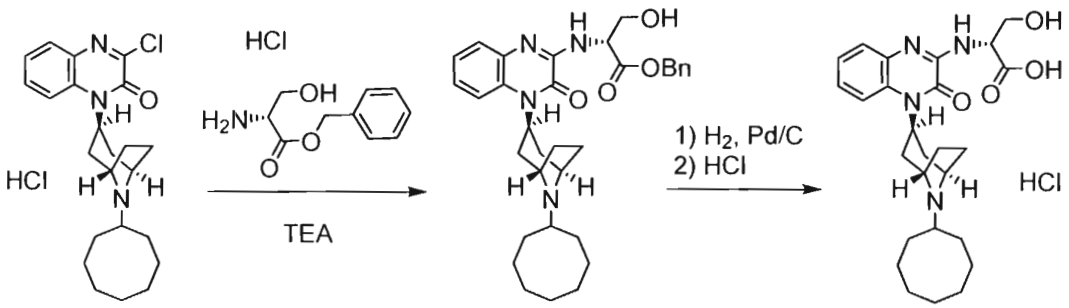
The identity of Substituted-Quinoxaline-Type Piperidine Compound **147**, (2*S*)-benzyl 2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)-3-hydroxypropanoate, was confirmed using ^{1}H NMR.

Substituted-Quinoxaline-Type Piperidine Compound **147**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 7.39-7.28 (9H, m), 4.68-4.64 (1H, m), 4.49 (2H, d, J=6.08Hz), 4.04-3.87 (2H, m), 3.62 (2H, t, J=5.58Hz), 2.37 (1H, s), 2.28-2.18 (2H, m), 2.03 (4H, d, J=34.47Hz), 1.79-1.39 (17H, m).

Under a hydrogen atmosphere, a mixture of Substituted-Quinoxaline-Type Piperidine Compound **147** (176mg, 0.32mmol), 10% palladium on carbon (20mg), and MeOH (5mL) was stirred at a temperature of about 25°C for 3hr. After the Pd/C was filtered off, the mixture was washed with EtOAc and the filtrate was concentrated under reduced pressure. The resulting solid was chromatographed with a silica gel column eluted with a gradient of from 95:5:0.5 $CHCl_3$:MeOH:aqueous ammonia to 4:1:0.1 $CHCl_3$:MeOH:aqueous ammonia to provide Substituted-Quinoxaline-Type Piperidine Compound **100** as a colorless solid. Acidifying the solid with 2N aqueous HCl (2mL) provided a white precipitate which was collected by filtration and washed twice with water (3mL for each wash) to provide 67mg of the hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **100** as a colorless solid (yield 45%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **100**, (2*S*)-2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)-3-hydroxypropanoic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **100**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 10.48 (1H, s), 7.88 (1H, d, J=7.6Hz), 7.41 (2H, m), 7.26 (2H, m), 5.91 (1H, t, J=9.38Hz), 4.61-4.57 (1H, m), 4.21 (2H, s), 3.90 (2H, m), 2.94 (1H, s), 2.69 (2H, m), 2.40-1.38 (22H, m); LC/MS (98%, t_r=1.42min): *m/z*=469.2 $[M+H]^+$ (Calc: 468.6).



347 **150** **115**

Substituted-Quinoxaline-Type Piperidine Compound **150** was prepared by using D-serine benzyl ester (*i.e.*, (*R*)-benzyl 2-amino-3-hydroxypropanoate hydrochloride, Sigma-Aldrich) in place of serine amide hydrochloride (yield 62%).

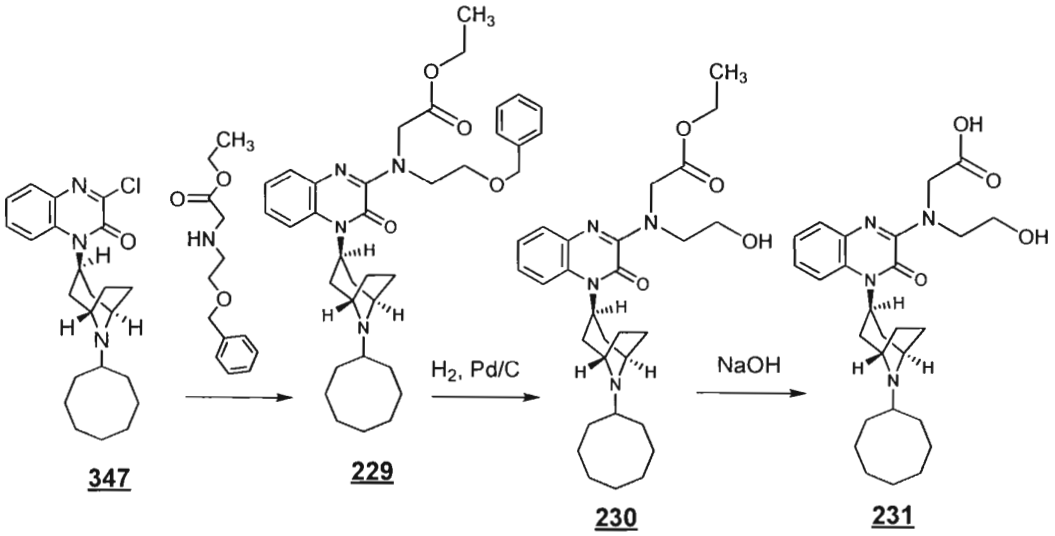
The identity of Substituted-Quinoxaline-Type Piperidine Compound **150**, (2*R*)-benzyl 2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)-3-hydroxypropanoate, was confirmed using MS.

Substituted-Quinoxaline-Type Piperidine Compound **150**: MS: *m/z*=559.3 $[M+H]^+$ (Calc: 558.3).

In a manner similar to the above preparation of the hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **100** from Substituted-Quinoxaline-Type Piperidine Compound **147**, the hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **115** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **150** (yield 93%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **115**, (2*R*)-2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)-3-hydroxypropanoic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **115**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 10.60 (0.9H, d, J=5.07Hz), 9.79 (0.1H, s), 7.92 (0.9H, d, J=7.6Hz), 7.81 (0.1H, d, J=8.11Hz), 7.49-7.45 (2H, m), 7.28-7.23 (2H, m), 6.00-5.91 (0.9H, m), 5.16 (0.1H, s), 4.65-4.62 (1H, m), 4.20 (2H, s), 3.94-3.90 (2H, m), 2.94 (1H, s), 2.78-2.61 (2H, m), 2.28 (6H, m), 2.02-1.37 (14H, m); LC/MS (100%, t_r=1.39min): *m/z*=469.2 $[M+H]^+$ (Calc: 468.6)



347 **229** **230** **231**

Substituted-Quinoxaline-Type Piperidine Compound **229** was prepared by using ethyl 2-(2-(benzyloxy)ethylamino)acetate (Sigma-Aldrich) in place of serine amide hydrochloride (yield 76%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **229**, ethyl 2-((2-(benzyloxy)ethyl)(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)amino)acetate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **229**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.43 (1H, d, J=8.0Hz), 7.35-7.20 (6H, m), 7.18 (2H, m), 5.20 (1H, m), 4.60 (2H, m), 4.51 (2H, s), 4.14 (1H, q, H=8.0Hz), 4.06 (2H, m), 3.86 (2H, m), 3.63 (2H, m), 2.36 (1H, m), 2.25 (2H, m), 2.10-1.90 (4H, m), 1.90-1.40 (16H, m), 1.25 (3H, t, J=8.0Hz); LC/MS: *m/z*=601 $[M+H]^+$ (Calc: 600.3).

Substituted-Quinoxaline-Type Piperidine Compound **230** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **229** in a manner similar to that described above except that the acid treatment was omitted (yield 48%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **230**, ethyl 2-((4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)(2-hydroxyethyl)amino)acetate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **230**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.45 (1H, d, J=8.0Hz), 7.35 (1H, d, J=8.0Hz), 7.20 (1H, m), 7.15 (1H, m), 5.15 (1H, br), 4.39 (2H, m), 4.25 (2H, q, J=8.0Hz), 4.02 (2H, m), 3.89 (2H, m), 3.64 (2H, m), 2.40-1.30 (23H, m), 1.31 (3H, t, J=8.0Hz); LC/MS: *m/z*=511 $[M+H]^+$ (Calc: 510.3).

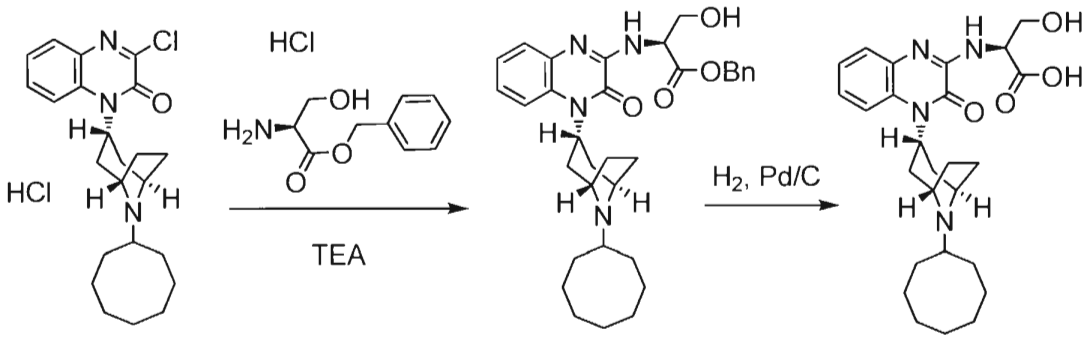
Substituted-Quinoxaline-Type Piperidine Compound **231** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **230** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **111** in Example 5 (yield 62%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **231**, 2-((4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)(2-hydroxyethyl)amino)acetic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **231**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 7.35 (2H, m), 7.24 (1H, t, J=8.0Hz), 7.16 (1H, t, J=8.0Hz), 5.20 (1H, br), 4.48 (2H, m), 3.82 (2H, m), 3.72 (2H, m), 3.66 (2H, m), 2.60-1.30 (23H, m); LC/MS (100%, t_r=1.47min): *m/z*=483 $[M+H]^+$ (Calc: 482.3).

5.19 Example 19

In a manner similar to Example 17 except that L-serine benzyl ester hydrochloride was used, the following Substituted-Quinoxaline-Type Piperidine Compound was prepared from Substituted-Quinoxaline-Type Piperidine Compound **403** (yield 50%).



403 **151** **107**

The identity of Substituted-Quinoxaline-Type Piperidine Compound **151**, (2*S*)-benzyl 2-(4-((*exo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)-3-hydroxypropanoate, was confirmed using MS.

Substituted-Quinoxaline-Type Piperidine Compound **151**: MS: *m/z*=559.3 $[M+H]^+$ (Calc: 558.7).

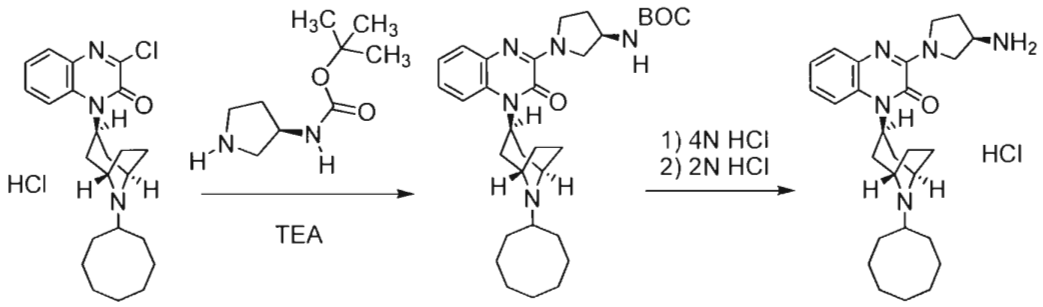
In a manner similar to Example 18 except that the acidification was omitted, Substituted-Quinoxaline-Type Piperidine Compound **107** was prepared from the compound of formula **151** (yield 63%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **107**, (2*S*)-2-(4-((*exo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)-3-hydroxypropanoic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **107**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 7.75 (1H, s), 7.40 (1H, dd, J=7.10, 2.03Hz), 7.26 (3H, m), 4.99 (1H, s), 4.45 (1H, t, J=3.8Hz), 3.86 (4H, m), 2.91 (2H, s), 1.79 (21H, m); LC/MS (100%, t_r=1.33min): *m/z*=469.2 $[M+H]^+$ (Calc: 468.6).

5.20 Example 20

In a manner similar to Example 15, Substituted-Quinoxaline-Type Piperidine Compound **152** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **347**.



347 **152** **101**

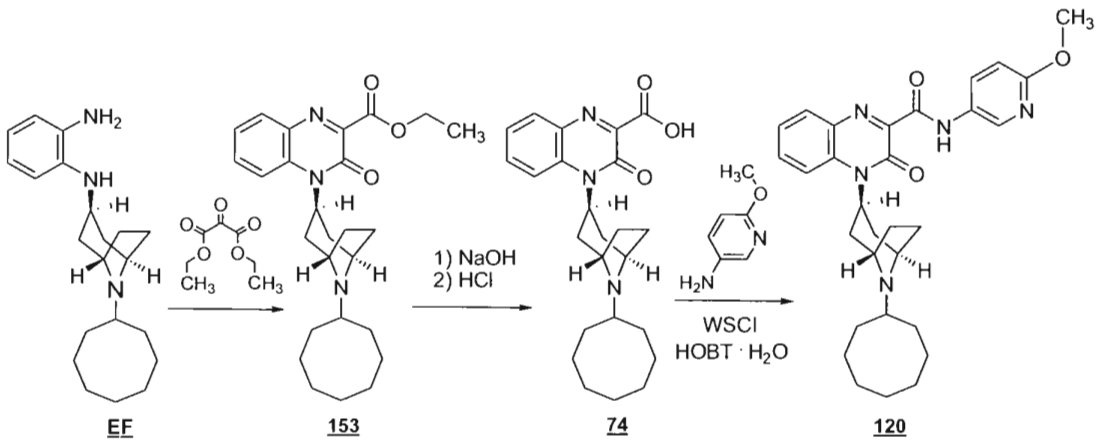
Substituted-Quinoxaline-Type Piperidine Compound **152**, *i.e.*, *tert*-butyl (3*R*)-1-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)pyrrolidin-3-ylcarbamate, was prepared by using (*R*)-*tert*-butyl pyrrolidin-3-ylcarbamate

(Sigma-Aldrich) in place of serine amide hydrochloride. In a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **5** in Example 7, the free Substituted-Quinoxaline-Type Piperidine Compound **101** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **152**. Thereafter, the hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **101** was prepared in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **174** in Example 7 (overall yield 84%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **101**, 3-((*R*)-3-aminopyrrolidin-1-yl)-1-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)quinoxalin-2(1*H*)-one, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **101**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 10.67 (1H, s), 8.40 (3H, s), 7.85 (1H, d, J=9.12Hz), 7.49 (1H, d, J=6.08Hz), 7.22 (2H, td, J=8.49, 5.24Hz), 5.89 (1H, t, J=9.38Hz), 4.22-3.86 (9H, m), 2.92 (1H, s), 2.61 (2H,m), 2.27-1.37 (22H, m); LC/MS (98%, t_r=0.78min): *m/z*=450.2 $[M+H]^+$ (Calc: 449.6).

5.21 Example 21



In a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **70** from the compound of formula **AB** in Example 12, Substituted-Quinoxaline-Type Piperidine Compound **153** was prepared from diethyl 2-oxomalonate and the compound of formula **EF** (yield 40%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **153**, ethyl 4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR.

Substituted-Quinoxaline-Type Piperidine Compound **153**: ^{1}H NMR: δ_H (300MHz, $CDCl_3$): 7.91 (1H, d, J=8.1Hz), 7.63-7.55 (2H, m), 7.34 (1H, t, J=7.4Hz), 5.21 (1H, br s), 4.50 (2H, q, J=7.1Hz), 3.66 (2H, br s), 2.43-2.15 (5H, m), 2.07-1.93 (2H, m), 1.88-1.35 (20H, m).

Substituted-Quinoxaline-Type Piperidine Compound **74** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **153** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **111** in Example 5 (yield 63%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **74**, 4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **74**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 10.38 (1H, br s), 8.06 (1H, d, J=8.6Hz), 7.89 (1H, d, J=7.6Hz), 7.76 (1H, t, J=7.6Hz), 7.47 (1H, t, J=7.6Hz), 6.00-5.91 (1H, m), 4.24 (2H, br s), 2.99-2.89 (1H, m), 2.67-2.59 (2H, m), 2.38-1.38 (20H, m); LC/MS (99%, t_r=1.02min): *m/z*=410.2 $[M+H]^+$ (Calc: 409).

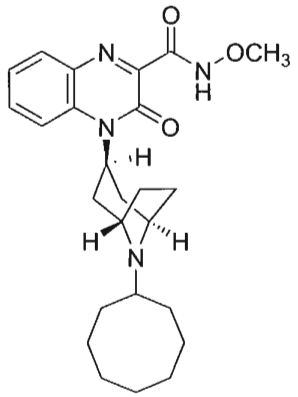
At a temperature of about 25°C, a reaction mixture of Substituted-Quinoxaline-Type Piperidine Compound **74** (150mg, 0.37mmol), 6-methoxypyridin-3-amine (0.55mmol, Sigma-Aldrich), WSCI (0.74mmol), and HOBT · H_2O (0.74mmol, Sigma-Aldrich) in DMF (4mL) was stirred for 4hr. The mixture was quenched with saturated aqueous $NaHCO_3$, extracted three times with EtOAc/water (40mL for each extraction), washed twice with water (20mL for each wash), dried ($MgSO_4$), and concentrated under reduced pressure to provide a yellow solid. The solid was triturated with 4:1:0.5 Et_2O:n-hexane:EtOAc (20mL), sonicated, and filtrated to provide a yellow solid. The solid was dried under reduced pressure at 70°C for 12hr to provide 133mg of Substituted-Quinoxaline-Type Piperidine Compound **120** (yield 70%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **120**, 4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-*N*-(6-methoxypyridin-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **120**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 10.82 (1H, s), 8.47 (1H, d, J=2.53Hz), 8.02 (1H, dd, J=8.87, 2.79Hz), 7.92 (1H, d, J=8.11Hz), 7.77 (1H, d, J=7.1Hz), 7.65 (1H, d, J=8.62Hz), 7.46 (1H, t, J=7.6Hz), 6.88 (1H, d, J=8.62Hz), 5.29 (1H, s), 3.85 (3H, s), 3.65 (2H, s), 2.30-1.37 (23H, m); LC/MS (100%, t_r=1.73min): *m/z*=516.2 $[M+H]^+$ (Calc: 515.7).

5.22 Example 22

In a manner similar to Example 21, the following Substituted-Quinoxaline-Type Piperidine Compounds ("*endo*" isomers) were prepared from Substituted-Quinoxaline-Type Piperidine Compound **74**.

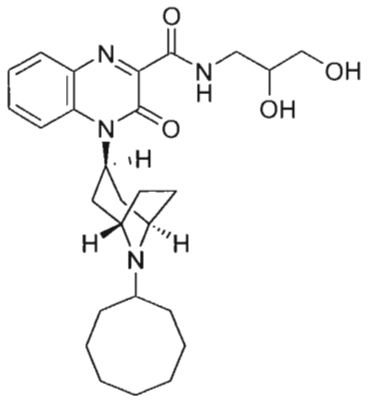


121

Substituted-Quinoxaline-Type Piperidine Compound **121** was prepared by using *O*-methylhydroxylamine (Sigma-Aldrich) in place of 4-methoxyaniline (yield 54%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **121**, 4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-*N*-hydroxy-3-oxo-3,4-dihydroquinoxaline-2-carboxamide, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **121**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 11.71 (1H, s), 7.89 (1H, d, J=7.6Hz), 7.77 (1H, s), 7.44 (1H, s), 5.26 (0.8H, s), 4.23 (0.2H, s), 3.74 (3H, s), 3.58 (2H, m), 2.39-1.39 (23H, m); LC/MS (98%, t_r=1.20min): *m/z*=439.2 $[M+H]^+$ (Calc: 438.6).

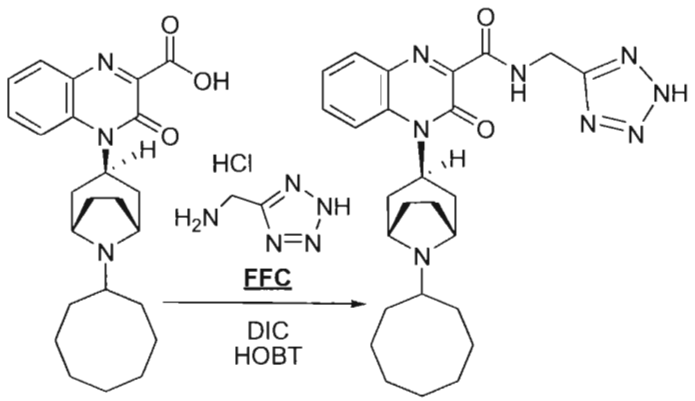


125

Substituted-Quinoxaline-Type Piperidine Compound **125** was prepared by using 3-amino-1,2-propanediol (Sigma-Aldrich) in place of 4-methoxyaniline (yield 16%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **125**, 4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-*N*-(2,3-dihydroxypropyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **125**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 10.09 (1H, s), 8.17 (1H, d, J=8.11Hz), 7.67 (2H, m), 7.43 (1H, t, J=7.6Hz), 5.30 (1H, br), 3.93 (1H, t, J=4.82Hz), 3.69 (6H, m), 2.37-1.22 (25H, m); LC/MS (96%, t_r=1.00min): *m/z*=483.2 $[M+H]^+$ (Calc: 482.6).



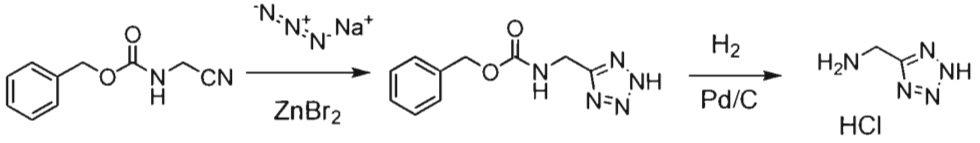
74 **317**

Substituted-Quinoxaline-Type Piperidine Compound **317** was prepared by using (2*H*-tetrazol-5-yl)methanamine hydrochloride (**FFC**) in place of 4-methoxyaniline and DIC in place of WSCI (yield 29%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **317**, *N*-((2*H*-tetrazol-5-yl)methyl)-4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **317**: ^{1}H NMR: δ_H (400MHz, CD_3OD): 8.06 (d, 1H, J=7.9Hz), 7.83-7.84 (m, 2H), 7.52-7.56 (m, 1H)5.57-5.59 (m, 1H), 5.01 (s, 2H), 4.38 (m, 2H), 3.15 (m, 1H)2.77-2.80 (m, 2H), 1.47-2.54 (m, 20H); LC/MS: *m/z*=491 $[M+H]^+$ (Calc: 490).

(2*H*-tetrazol-5-yl)methanamine hydrochloride (**FFC**) was prepared as follows:



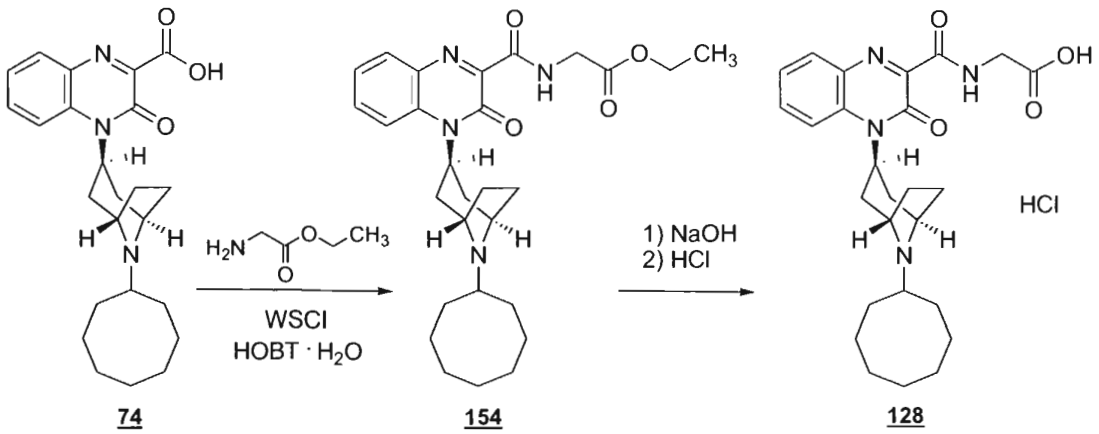
FFA **FFB** **FFC**

A mixture of benzyl cyanomethylcarbamate (**FFA**, 2.00g, 10.5mmol, Sigma-Aldrich), sodium azide (1.37g, 21.0mmol), zinc bromide (1.18g, 5.26mmol, Sigma-Aldrich), 2-propanol (15mL), and water (30mL) at a temperature of about 25°C was stirred for 15h. To the reaction mixture was added 2N aqueous HCl (7mL). The mixture was partitioned between EtOAc and water, the organic portion was separated, washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to provide 1.51g of the compound of formula **FFB** as a white solid (yield 61%).

The identity of the compound of formula **FFB**, benzyl (2*H*-tetrazol-5-yl)methylcarbamate, was confirmed using LC/MS.

Compound **FFB**: LC/MS: *m/z*=234 $[M+H]^+$ (Calc: 233).

Under a hydrogen atmosphere, a mixture of the compound of formula **FFC** (754mg, 3.23mmol), 20% palladium on carbon (50mg), and MeOH (8mL) was stirred at a temperature of about 25°C for 1h. The Pd/C was filtered off with a CELITE pad, the mixture was washed with MeOH, then concentrated under reduced pressure to provide 438mg of the compound of formula **FFC** as a yellow oil (yield >98%).



74 154 128

Substituted-Quinoxaline-Type Piperidine Compound **154** was prepared by using glycine ethyl ester in place of 4-methoxyaniline (yield 96%).

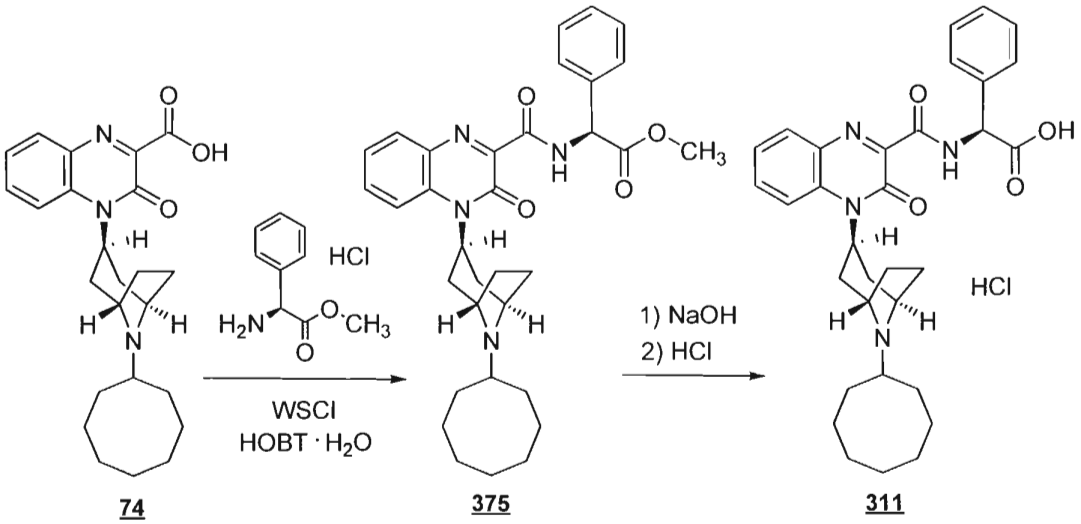
The identity of Substituted-Quinoxaline-Type Piperidine Compound **154**, ethyl 2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamido)acetate, was confirmed using ^{1}H NMR.

Substituted-Quinoxaline-Type Piperidine Compound **154**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 9.25 (1H, m), 7.90 (1H, t, J=4.06Hz), 7.76 (1H, t, J=7.1Hz), 7.62 (1H, d, J=8.62Hz), 7.44 (1H, t, J=7.6Hz), 5.23 (1H, br), 4.13 (4.2H, m), 3.65 (2H, s), 2.37-1.45 (23H, m), 1.23 (3H, t, J=7.1Hz).

The hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **128** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **154** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **174** in Example 7 (yield 30%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **128**, 2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamido)acetic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **128**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 12.78-12.74 (1H, m), 10.33 (0.9H, br), 9.38 (0.1H, s), 9.10 (1H, t, J=5.58Hz), 8.04 (1H, d, J=8.11Hz), 7.92 (1H, dd, J=7.86, 1.27Hz), 7.76 (1H, t, J=7.35Hz), 7.47 (1H, t, J=7.6Hz), 5.93 (0.9H, t, J=9.12Hz), 5.20 (0.1H, s), 4.25 (2H, s), 4.03 (2H, d, J=5.58Hz), 2.94 (1H, s), 2.61 (2H, m), 2.35-1.37 (20H, m); LC/MS (96%, t_r=1.18min): *m/z*=467.3 $[M+H]^+$ (Calc: 466.6).



74 375 311

Substituted-Quinoxaline-Type Piperidine Compound **375** was prepared by using (*S*)-(+)-methyl 2-amino-2-phenylacetate hydrochloride in place of 4-methoxyaniline (yield 49%).

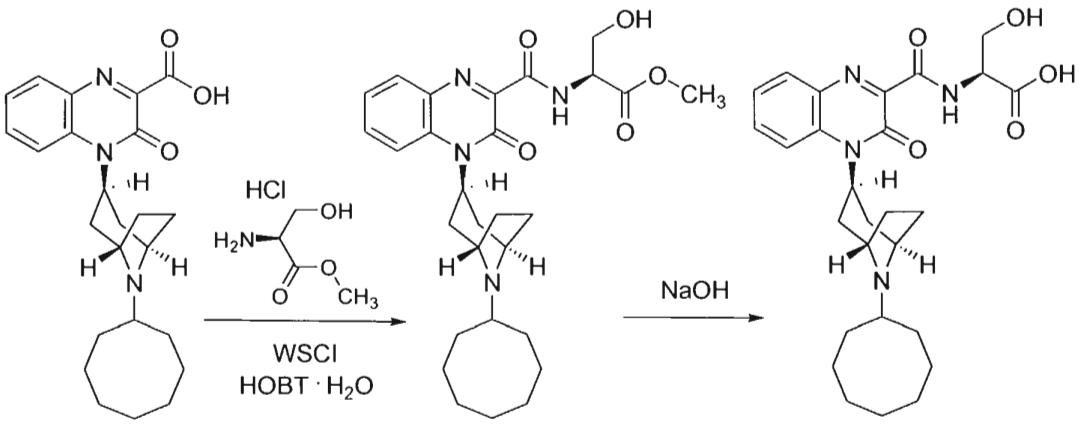
The identity of Substituted-Quinoxaline-Type Piperidine Compound **375**, (*S*)-methyl 2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamido)-2-phenylacetate, was confirmed using LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **375**: LC/MS: *m/z*=557 $[M+H]^+$ (Calc: 556).

The hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **311** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **375** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **174** in Example 7 (yield 30%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **311**, (*S*)-2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamido)-2-phenylacetic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **311**: ^{1}H NMR: δ_H (400MHz, CD_3OD): 7.69-7.96 (m, 3H), 7.24-7.45 (m, 6H), 5.61 (s, 1H), 5.21-5.55 (m, 1H), 4.19-4.27 (m, 2H), 3.03-3.04 (m, 1H), 1.33-2.76 (m, 22H); LC/MS: *m/z*=543 $[M+H]^+$ (Calc: 542).



74 155 129

Substituted-Quinoxaline-Type Piperidine Compound **155** was prepared by using L-serine methyl ester hydrochloride (*i.e.*, (*S*)-methyl 2-amino-3-hydroxypropanoate hydrochloride, Sigma-Aldrich) in place of 4-methoxyaniline (yield >98%).

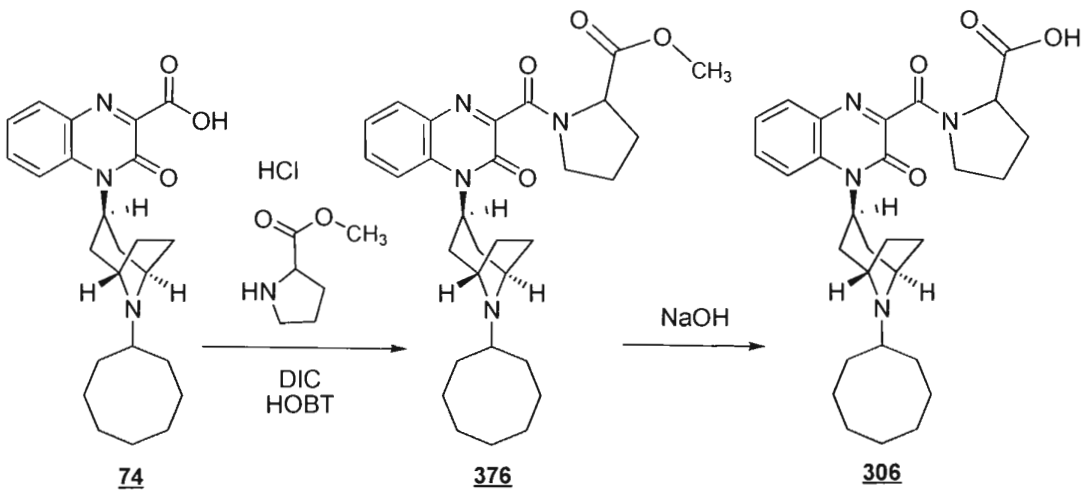
The identity of Substituted-Quinoxaline-Type Piperidine Compound **155**, (2*S*)-methyl 2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamido)-3-hydroxypropanoate, was confirmed using ^{1}H NMR.

Substituted-Quinoxaline-Type Piperidine Compound **155**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 9.44 (1H, m), 7.92 (1H, d, J=8.11Hz), 7.77 (1H, t, J=7.35Hz), 7.62 (1H, d, J=8.62Hz), 7.45 (1H, t, J=7.6Hz), 5.22 (1H, br), 5.21 (1H, t, J=5.58Hz), 4.61-4.56 (1H, m), 3.86-3.81 (1H, m), 3.70 (6H, m), 1.89 (23H, m).

Substituted-Quinoxaline-Type Piperidine Compound **129** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **155** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **111** in Example 5 (yield 78%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **129**, (2*S*)-2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamido)-3-hydroxypropanoic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **129**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 9.30 (1H, s), 7.92 (1H, dd, J=7.86, 1.27Hz), 7.72 (2H, m), 7.44 (1H, t, J=7.86Hz), 5.36 (1H, br), 4.44-4.40 (1.1H, m), 3.77 (4H, m), 2.34 (2H, m), 2.08 (4H, m), 1.91-1.40 (17H, m); LC/MS (98%, t_r=1.15min): *m/z*=497.2 $[M+H]^+$ (Calc: 496.6).



Substituted-Quinoxaline-Type Piperidine Compound **376** was prepared by using methyl pyrrolidine-2-carboxylate hydrochloride (Bachem Americas, Inc., Torrance, CA) in place of 4-methoxyaniline and DIC in place of WSCI (yield 29%).

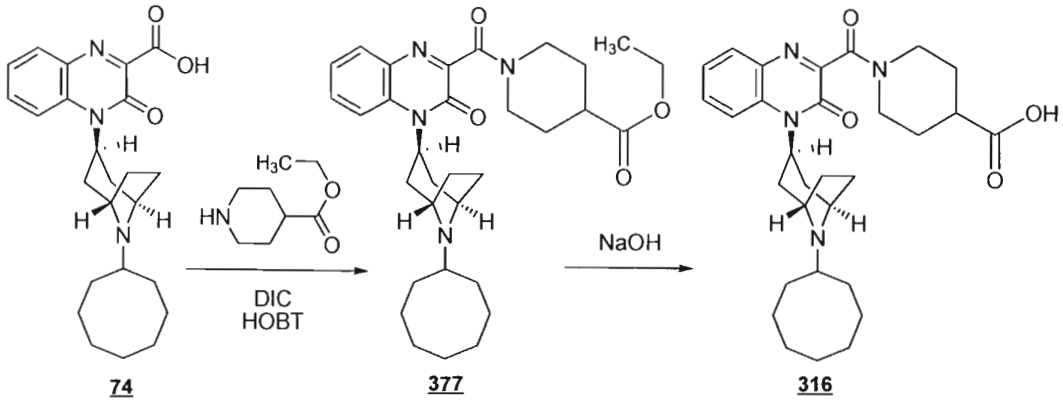
The identity of Substituted-Quinoxaline-Type Piperidine Compound **376**, methyl 1-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carbonyl)pyrrolidine-2-carboxylate, was confirmed using LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **376**: LC/MS: *m/z*=521 $[M+H]^+$ (Calc: 520).

Substituted-Quinoxaline-Type Piperidine Compound **306** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **376** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **111** in Example 5 (yield 40%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **306**, 1-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carbonyl)pyrrolidine-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **306**: ^{1}H NMR: δ_H (400MHz, CD_3OD): 7.39-7.90 (m, 4H), 5.28-5.50 (m, 1H), 4.35-4.42 (m, 1H), 3.54-3.79 (m, 5H), 1.45-2.35 (m, 24H); LC/MS: *m/z*=507 $[M+H]^+$ (Calc: 506).



74 377 316

Substituted-Quinoxaline-Type Piperidine Compound **377** was prepared by using ethyl piperidine-4-carboxylate (Sigma-Aldrich) in place of 4-methoxyaniline and DIC in place of WSCI (yield 29%).

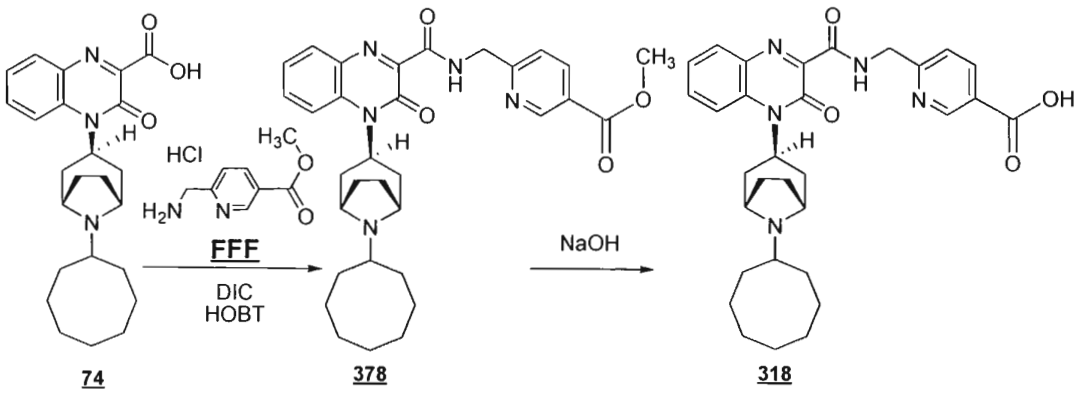
The identity of Substituted-Quinoxaline-Type Piperidine Compound **377**, ethyl 1-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carbonyl)piperidine-4-carboxylate, was confirmed using LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **377**: LC/MS: m/z=549 $[M+H]^+$ (Calc: 548).

Substituted-Quinoxaline-Type Piperidine Compound **316** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **377** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **111** in Example 5 (yield 23%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **316**, 1-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carbonyl)piperidine-4-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **316**: ^{1}H NMR: δ_H (400MHz, CD_3OD): 7.91 (dd, 1H, J=1.2Hz, 7.9Hz), 7.79-7.87 (m, 1H), 7.75-7.77 (m, 1H), 7.48-7.51 (m, 1H), 5.59-5.63 (m, 08H), 5.30 (m, 0.2H), 4.52 (m, 1H), 4.49 (m, 2H), 3.67-3.70 (m, 1H), 3.14-3.32 (m, 3H), 1.46-2.84 (m, 27H); LC/MS: m/z=521 $[M+H]^+$ (Calc: 520).



Substituted-Quinoxaline-Type Piperidine Compound **378** was prepared by using methyl 6-(aminomethyl)nicotinate hydrochloride (**FFF**) in place of 4-methoxyaniline and DIC in place of WSCI (yield 39%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **378**, methyl 6-((4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamido)methyl)nicotinate, was confirmed using LC/MS.

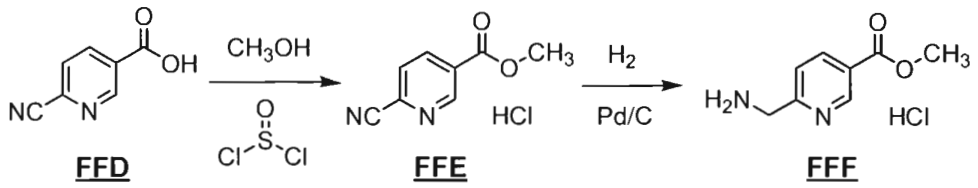
Substituted-Quinoxaline-Type Piperidine Compound **378**: LC/MS: *m/z*=558 $[M+H]^+$ (Calc: 557).

Substituted-Quinoxaline-Type Piperidine Compound **318** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **378** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **111** in Example 5 (yield 32%).

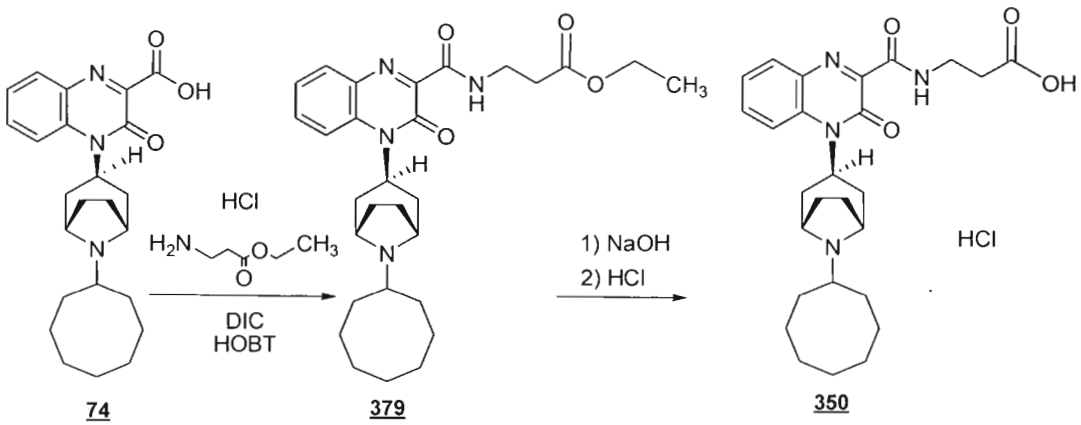
The identity of Substituted-Quinoxaline-Type Piperidine Compound **318**, 6-((4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamido)methyl)nicotinic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **318**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 9.43-9.46 (m, 1H), 9.03 (d, 1H, J=1.1Hz), 8.27 (dd, 1H, J=1.9Hz, 8.1Hz), 7.89 (d, 1H, J=7.7Hz), 7.67-7.75 (m, 2H), 7.59 (d, 1H, J=8.1Hz), 7.42-7.46 (m, 1H), 5.21-5.42 (m, 1H), 4.65 (d, 2H, J=5.7Hz), 3.65-3.76 (m, 2H), 1.42-2.35 (m, 23H); LC/MS: *m/z*=544 $[M+H]^+$ (Calc: 543).

Methyl 6-(aminomethyl)nicotinate hydrochloride (**FFF**) was prepared as follows:



To a mixture of 6-cyanonicotinic acid (**FFD**, 1.00g, 6.75mmol, Sigma-Aldrich) and DMF (4 drops) in $CHCl_3$ (20mL) at a temperature of about 25°C was added thionyl chloride (1.08mL, 14.85mmol). The reaction mixture was refluxed for 2h, then concentrated under reduced pressure to provide a residue. The residue was dissolved in MeOH (20mL), stirred at a temperature of about 25°C for 2h, then concentrated under reduced pressure to provide 1.34g of the compound of formula **FFE**, methyl 6-cyanonicotinate hydrochloride, as a pale yellow solid (yield >98%). Under a hydrogen atmosphere, a mixture of the compound of formula **FFE** (1.34g, 6.75mmol), 20% palladium on carbon (650mg), and MeOH (20mL) was stirred at a temperature of about 25°C for 16h. The Pd/C was filtered off with a CELITE pad, the mixture was washed with MeOH, then recrystalized from EtOAc/MeOH/hexane to provide 488.2mg of the compound of formula **FFF** as a purple solid (yield 36%).



Substituted-Quinoxaline-Type Piperidine Compound **379** was prepared by using ethyl 3-aminopropanoate hydrochloride (Sigma-Aldrich) in place of 4-methoxyaniline and DIC in place of WSCI (yield 73%).

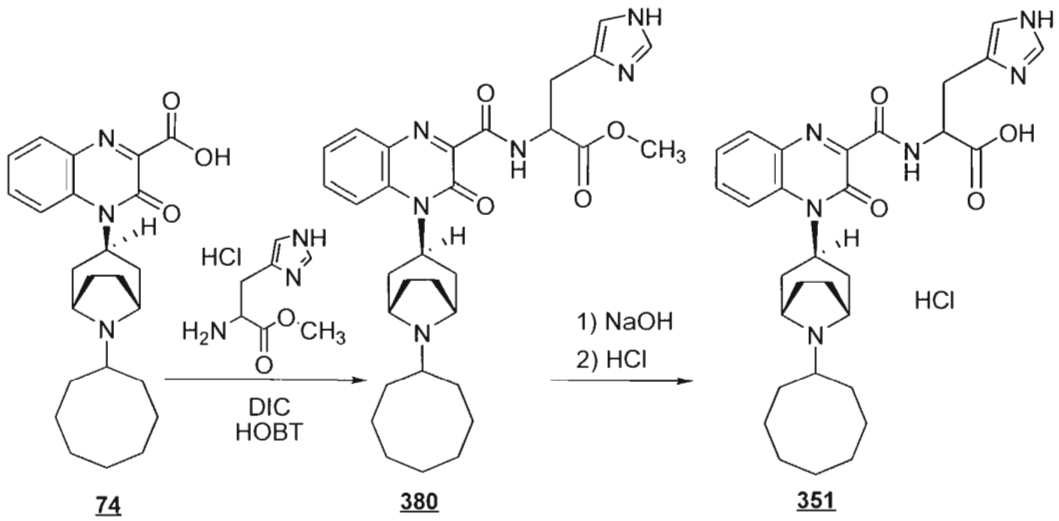
The identity of Substituted-Quinoxaline-Type Piperidine Compound **379**, ethyl 3-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamido)propanoate, was confirmed using LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **379**: LC/MS: *m/z*=509 $[M+H]^+$ (Calc: 508).

The hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **350** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **379** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **174** in Example 7 (yield 34%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **350**, 3-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamido)propanoic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **350**: ^{1}H NMR: δ_H (400MHz, CD_3OD): 7.92-7.94 (m, 1H), 7.67-7.74 (m, 2H), 7.38-7.42 (m, 1H), 5.50 (m, 1H), 4.25 (m, 2H), 3.63 (t, 2H, J=6.5Hz), 3.02-3.04 (m, 1H), 2.63-2.68 (m, 2H), 2.59 (t, 2H, J=6.5Hz), 2.28-2.57 (m, 6H), 1.35-1.86 (14H, m); LC/MS: *m/z*=481 $[M+H]^+$ (Calc: 480).



74 **380** **351**

Substituted-Quinoxaline-Type Piperidine Compound **380** was prepared by using methyl 2-amino-3-(1*H*-imidazol-4-yl)propanoate hydrochloride (Sigma-Aldrich) in place of 4-methoxyaniline and DIC in place of WSCI (yield 29%).

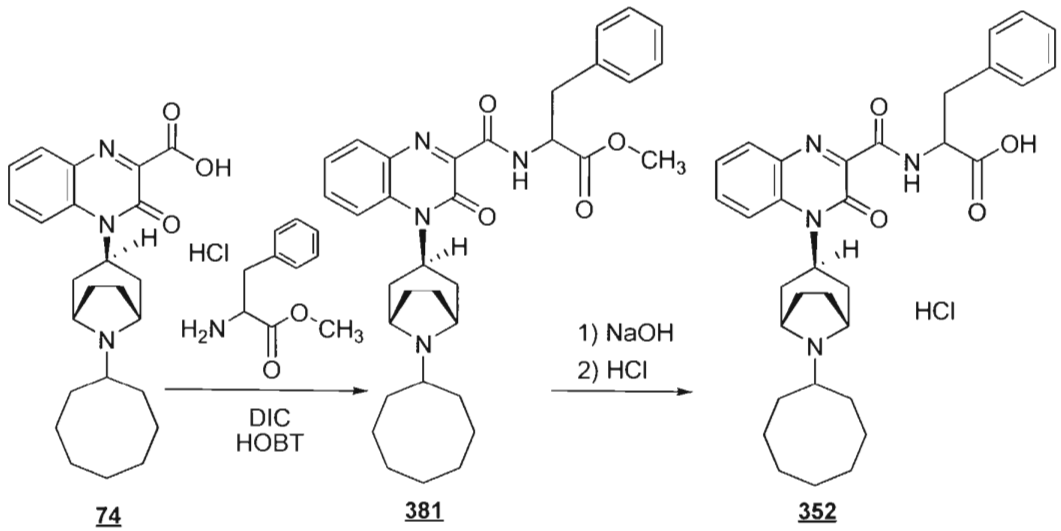
The identity of Substituted-Quinoxaline-Type Piperidine Compound **380**, methyl 2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamido)-3-(1*H*-imidazol-4-yl)propanoate, was confirmed using LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **380**: LC/MS: *m/z*=561 $[M+H]^+$ (Calc: 560).

The hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **351** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **380** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **174** in Example 7 (yield 34%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **351**, 2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamido)-3-(1*H*-imidazol-4-yl)propanoic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **351**: ^{1}H NMR: δ_H (400MHz, CD_3OD): 8.87 (s, 1H), 8.02 (m, 2H), 7.80-7.84 (m, 1H), 7.52 (m, 1H), 7.47 (s, 1H), 5.80 (m, 1H), 5.09 (m, 1H), 4.36 (m, 2H), 3.52-3.55 (m, 1H), 3.13 (m, 1H), 1.45-2.80 (m, 21H); LC/MS: *m/z*=547 $[M+H]^+$ (Calc: 546).



74 **381** **352**

Substituted-Quinoxaline-Type Piperidine Compound **381** was prepared by using methyl 2-amino-3-phenylpropanoate hydrochloride (Sigma-Aldrich) in place of 4-methoxyaniline and DIC in place of WSCI (yield 53%).

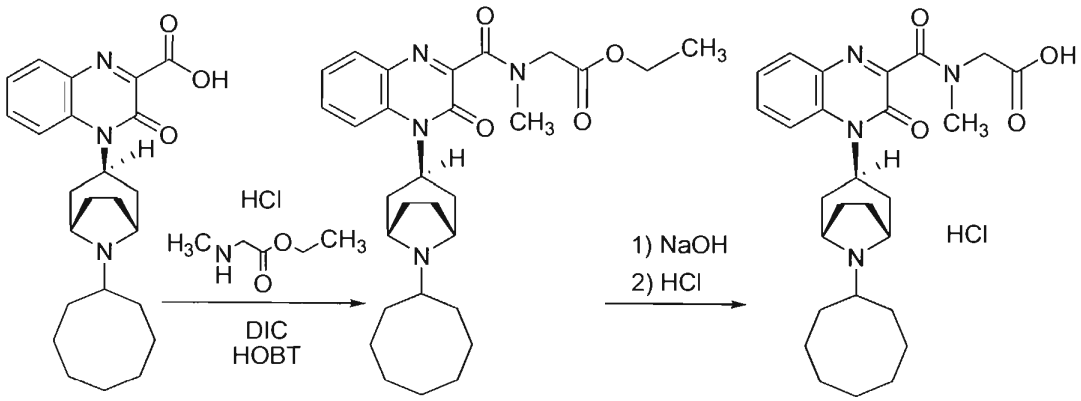
The identity of Substituted-Quinoxaline-Type Piperidine Compound **381**, methyl 2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamido)-3-phenylpropanoate, was confirmed using LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **381**: LC/MS: *m/z*=571 $[M+H]^+$ (Calc: 570).

The hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **352** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **381** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **174** in Example 7 (yield 15%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **352**, 2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamido)-3-phenylpropanoic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **352**: ^{1}H NMR: δ_H (400MHz, CD_3OD): 7.95-7.97 (m, 2H), 7.67-7.73 (m, 2H), 7.40-7.43 (m, 1H), 7.14-7.24 (m, 5H), 5.45 (m, 1H), 4.85-4.91 (m, 1H), 4.08-4.27 (m, 2H), 3.02-3.04 (m, 1H), 1.35-2.70 (22H, m); LC/MS: *m/z*=556 $[M+H]^+$ (Calc: 557).



74 **382** **307**

Substituted-Quinoxaline-Type Piperidine Compound **382** was prepared by using ethyl 2-(methylamino)acetate hydrochloride (Sigma-Aldrich) in place of 4-methoxyaniline and DIC in place of WSCI (yield 74%).

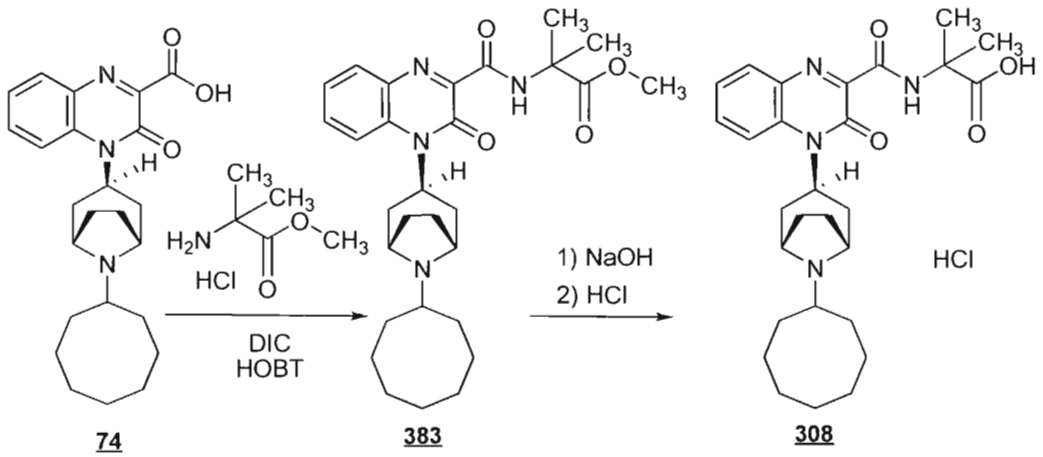
The identity of Substituted-Quinoxaline-Type Piperidine Compound **382**, ethyl 2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-*N*-methyl-3-oxo-3,4-dihydroquinoxaline-2-carboxamido)acetate, was confirmed using LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **382**: LC/MS: *m/z*=509 $[M+H]^+$ (Calc: 508).

The hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **307** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **382** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **174** in Example 7 (yield 23%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **307**, 2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-*N*-methyl-3-oxo-3,4-dihydroquinoxaline-2-carboxamido)acetic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **307**: ^{1}H NMR: δ_H (400MHz, CD_3OD): 7.78-7.96 (m, 3H), 7.46-7.52 (m, 1H), 5.29-5.64 (m, 1H), 4.18-7.90 (m, 4H), 3.11 (s, 3H), 1.46-2.88 (m, 21H); LC/MS: *m/z*=481 $[M+H]^+$ (Calc: 480).



Substituted-Quinoxaline-Type Piperidine Compound **383** was prepared by using methyl 2-amino-2-methylpropanoate hydrochloride (Sigma-Aldrich) in place of 4-methoxyaniline and DIC in place of WSCI (yield 49%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **383**, methyl 2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamido)-2-methylpropanoate, was confirmed using LC/MS.

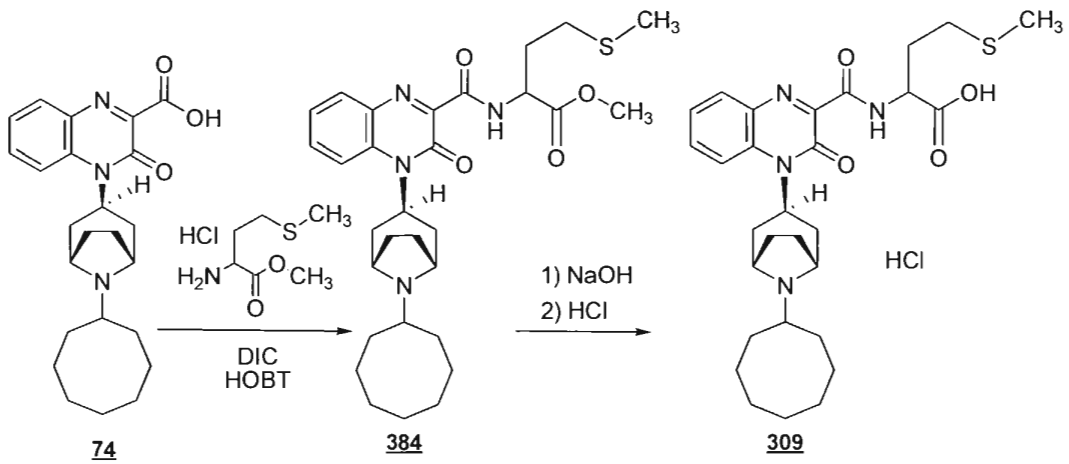
Substituted-Quinoxaline-Type Piperidine Compound **383**: LC/MS: *m/z*=509 $[M+H]^+$ (Calc: 508).

The hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **308** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **383** in a manner similar to

the preparation of Substituted-Quinoxaline-Type Piperidine Compound **174** in Example 7 (yield 16%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **308**, 2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamido)-2-methylpropanoic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **308**: ^{1}H NMR: δ_H (400MHz, CD_3OD): 8.06-8.13(m, 1H), 7.81-7.95 (m, 2H), 7.51-7.55 (m, 1H), 5.33-5.66 (m, 1H), 4.38 (m, 2H), 3.14-3.16 (m, 1H), 1.55-2.83 (m, 22H); LC/MS: *m/z*=495 $[M+H]^+$ (Calc: 494).



74 **384** **309**

Substituted-Quinoxaline-Type Piperidine Compound **384** was prepared by using methyl 2-amino-4-(methylthio)butanoate hydrochloride (Sigma-Aldrich) in place of 4-methoxyaniline and DIC in place of WSCI (yield 44%).

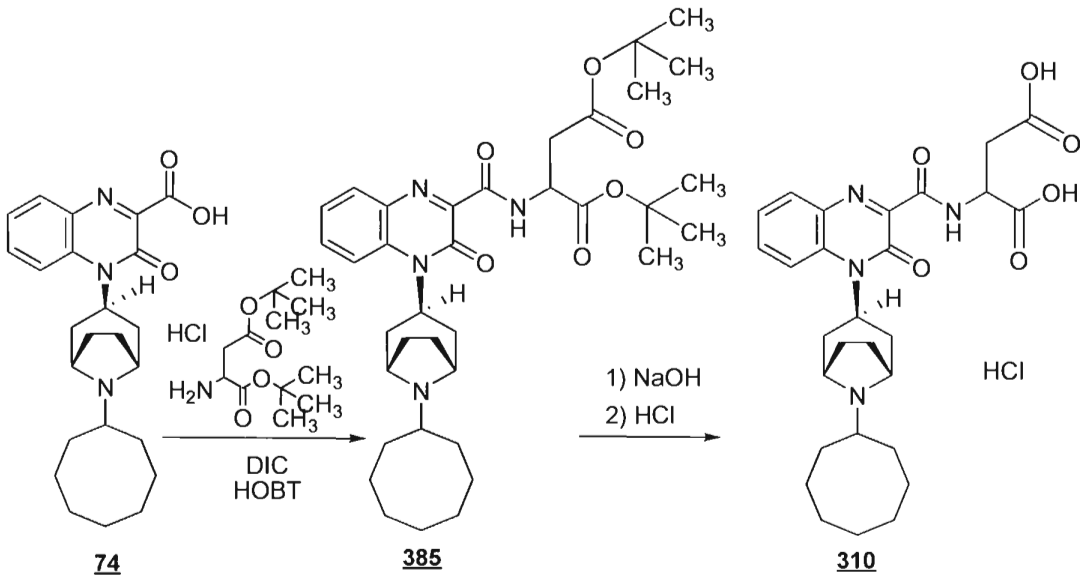
The identity of Substituted-Quinoxaline-Type Piperidine Compound **384**, methyl 2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamido)-4-(methylthio)butanoate, was confirmed using LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **384**: LC/MS: *m/z*=555 $[M+H]^+$ (Calc: 554).

The hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **309** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **384** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **174** in Example 7 (yield 9%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **309**, 2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamido)-4-(methylthio)butanoic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **309**: ^{1}H NMR: δ_H (400MHz, CD_3OD): 7.71-7.96 (m, 3H), 7.43 (m, 1H), 5.21-5.50 (m, 1H), 4.20-4.27 (m, 2H), 3.03-3.04 (m, 1H), 1.53-2.66 (m, 27H); LC/MS: *m/z*=541 $[M+H]^+$ (Calc: 540).



74 **385** **310**

Substituted-Quinoxaline-Type Piperidine Compound **385** was prepared by using di-*tert*-butyl 2-aminosuccinate hydrochloride (Bachem Americas, Inc.) in place of 4-methoxyaniline and DIC in place of WSCI (yield 47%).

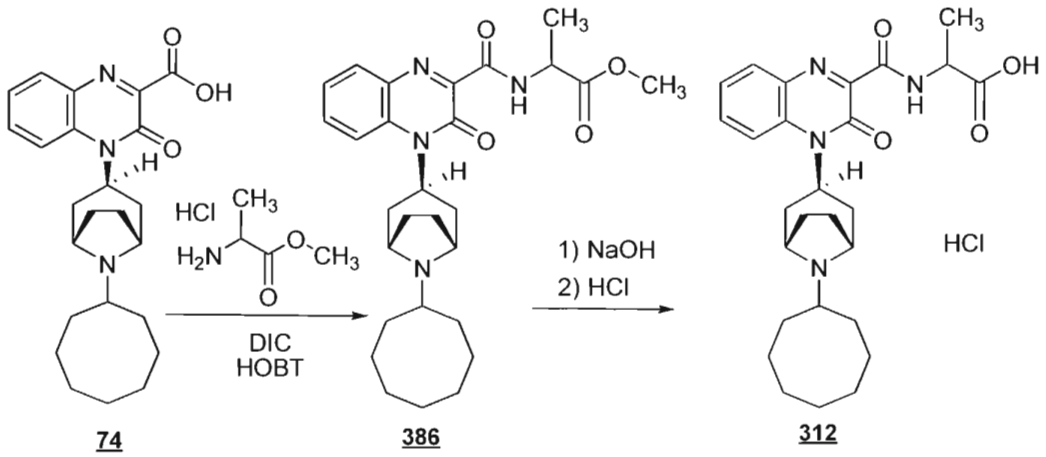
The identity of Substituted-Quinoxaline-Type Piperidine Compound **385**, di-*tert*-butyl 2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamido)succinate, was confirmed using LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **385**: LC/MS: *m/z*=637 $[M+H]^+$ (Calc: 636).

The hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **310** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **385** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **174** in Example 7 (yield 14%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **310**, 2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamido)succinic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **310**: ^{1}H NMR: δ_H (400MHz, CD_3OD): 8.08 (d, 1H, J=7.9Hz), 7.82-7.98 (m, 2H), 7.52-7.55 (m, 1H), 5.51-5.64 (m, 0.8H), 5.32 (m, 0.2H), 5.05 (t, 1H, J=4.8Hz), 4.30-4.38 (m, 2H), 2.98-3.16 (m, 3H), 1.46-2.83 (m, 22H); LC/MS: *m/z*=525 $[M+H]^+$ (Calc: 524).



74 **386** **312**

Substituted-Quinoxaline-Type Piperidine Compound **386** was prepared by using methyl 2-aminopropanoate hydrochloride (Sigma-Aldrich) in place of 4-methoxyaniline and DIC in place of WSCI (yield 38%).

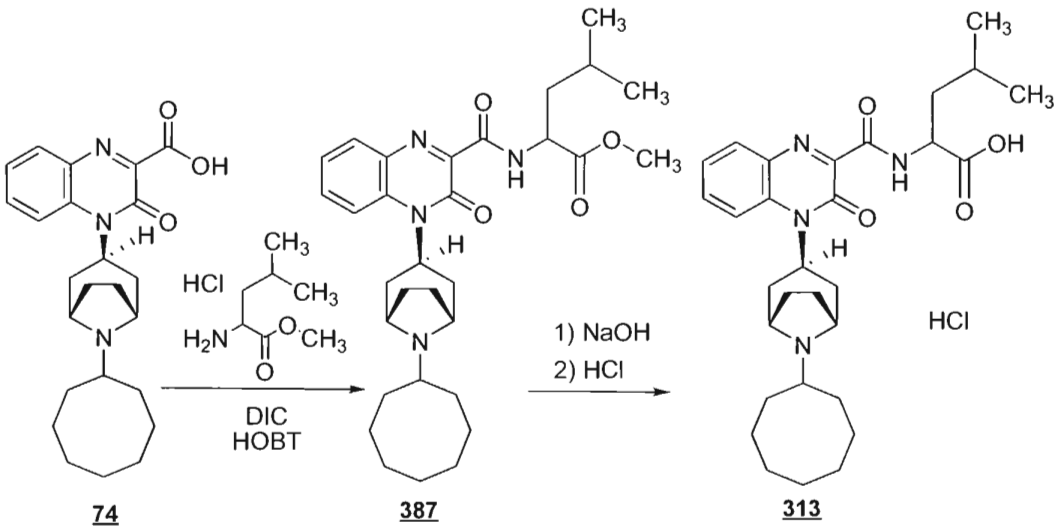
The identity of Substituted-Quinoxaline-Type Piperidine Compound **386**, methyl 2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamido)propanoate, was confirmed using LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **386**: LC/MS: *m/z*=495 $[M+H]^+$ (Calc: 494).

The hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **312** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **386** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **174** in Example 7 (yield 14%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **312**, 2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamido)propanoic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **312**: ^{1}H NMR: δ_H (400MHz, CD_3OD): 8.08-8.10 (m, 1H), 7.78-7.98 (m,2H), 7.53-7.56 (m, 1H), 5.31-5.53 (m, 1H), 4.71-4.74 (m, 1H), 4.13-4.39 (m, 2H), 3.14-3.23 (m, 1H), 1.31-2.81 (m, 25H); LC/MS: *m/z*=481 $[M+H]^+$ (Calc: 480).



74 **387** **313**

Substituted-Quinoxaline-Type Piperidine Compound **387** was prepared by using methyl 2-amino-4-methylpentanoate hydrochloride (Sigma-Aldrich) in place of 4-methoxyaniline and DIC in place of WSCI (yield 90%).

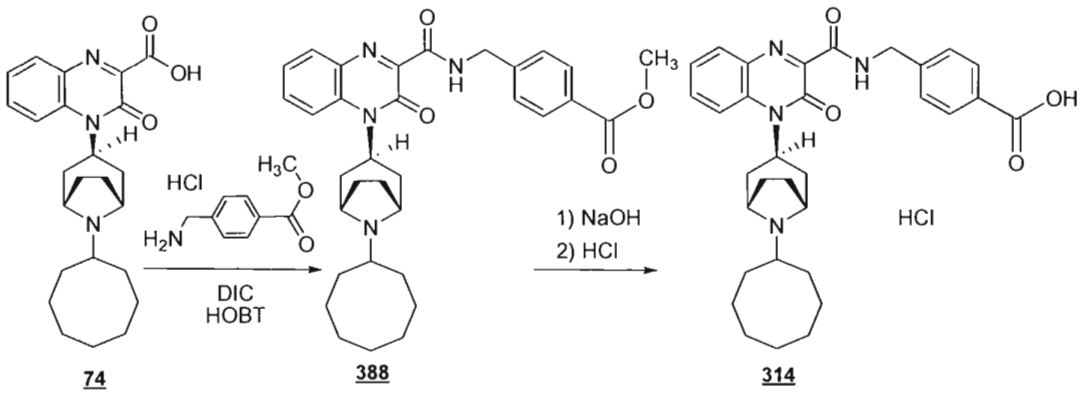
The identity of Substituted-Quinoxaline-Type Piperidine Compound **387**, methyl 2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamido)-4-methylpentanoate, was confirmed using LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **387**: LC/MS: *m/z*=537 $[M+H]^+$ (Calc: 536).

The hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **313** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **387** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **174** in Example 7 (yield 9%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **313**, 2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamido)-4-methylpentanoic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **313**: ^{1}H NMR: δ_H (400MHz, CD_3OD): 7.69-8.08 (m, 3H), 7.40-7.43 (m, 1H), 5.21-5.53 (m, 1H), 4.64-4.67 (m, 1H), 4.20-4.27 (m, 2H), 3.03-3.04 (m, 1H), 1.34-2.71 (m, 25H), 0.92 (d, 6H, J=5.8Hz); LC/MS: *m/z*=523 $[M+H]^+$ (Calc: 522).



Substituted-Quinoxaline-Type Piperidine Compound **388** was prepared by using methyl 4-(aminomethyl)benzoate hydrochloride (Sigma-Aldrich) in place of 4-methoxyaniline and DIC in place of WSCI (yield 47%).

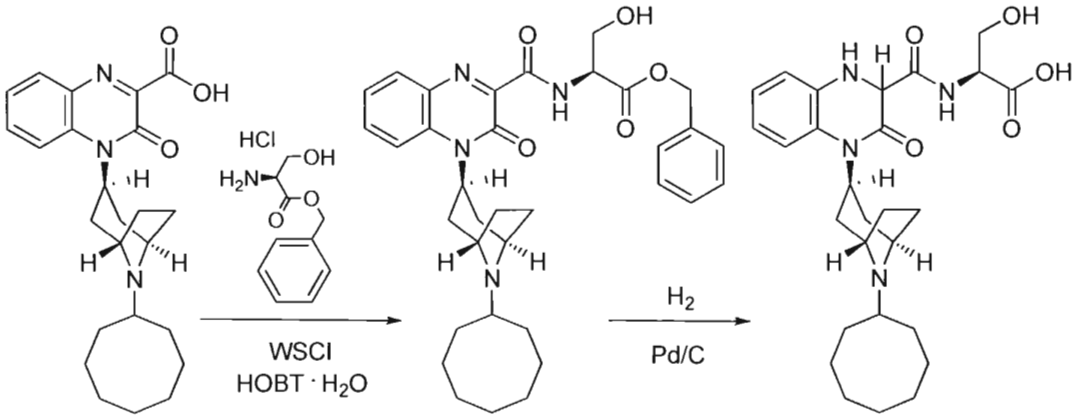
The identity of Substituted-Quinoxaline-Type Piperidine Compound **388**, methyl 4-((4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamido)methyl)benzoate, was confirmed using LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **388**: LC/MS: *m/z*=557 $[M+H]^+$ (Calc: 556).

The hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **314** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **388** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **174** in Example 7 (yield 73%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **314**, 4-((4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamido)methyl)benzoic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **314**: ^{1}H NMR: δ_H (400MHz, CD_3OD): 8.02-8.06 (m, 3H), 7.79-7.89 (m, 2H), 7.50-7.58 (m, 3H), 5.63-5.67 (m, 0.8H), 5.32 (m, 0.2H), 4.77 (s, 2H), 4.36 (m, 2H), 3.14-3.16 (m, 1H), 1.30-2.82 (m, 22H); LC/MS: *m/z*=543 $[M+H]^+$ (Calc: 542).



74 **156** **126**

Substituted-Quinoxaline-Type Piperidine Compound **156** was prepared by using L-serine benzyl ester in place of 4-methoxyaniline and DIC in place of WSCI (yield 95%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **156**, (2*S*)-benzyl 2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamido)-3-hydroxypropanoate, was confirmed using ^{1}H NMR.

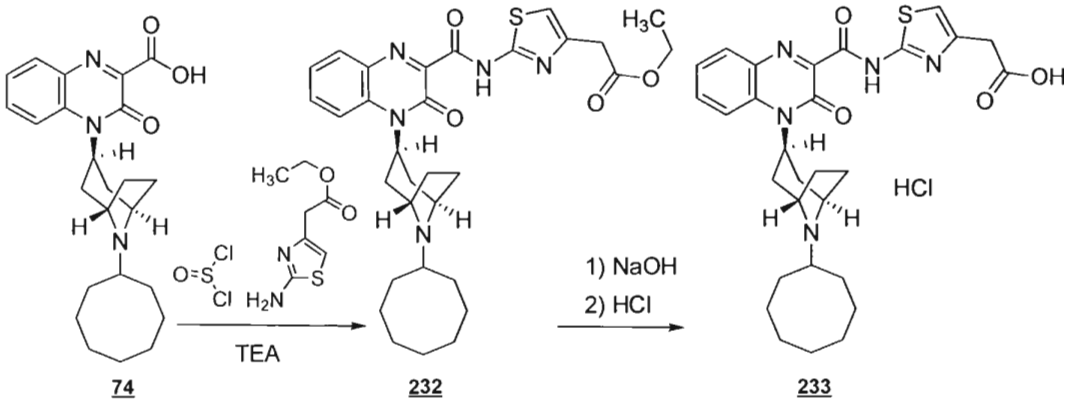
Substituted-Quinoxaline-Type Piperidine Compound **156**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 9.47 (1H, m), 7.90 (1H, m), 7.66 (1H, m), 7.61 (1H,m), 7.47-7.33 (8H, m), 5.26 (2H, t, J=4.2Hz), 5.20 (2H, s), 3.89-3.64 (5H, s), 2.44-1.43 (22H, m).

Substituted-Quinoxaline-Type Piperidine Compound **126** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **156** in a manner similar to the final step of Example 18 except that the acidification was omitted (yield 84%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **126**, (2*S*)-2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-1,2,3,4-tetrahydroquinoxaline-2-carboxamido)-3-hydroxypropanoic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **126**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 7.94 (1H, t, J=8.36Hz), 7.02 (1H, t, J=7.6Hz), 6.84 (2H, t, J=6.34Hz), 6.72 (1H, td, J=8.36, 3.72Hz), 6.50 (1H, d, J=15.21Hz), 4.83 (1H, s), 4.44 (1H, dd, J=6.84, 1.77Hz), 4.08 (1H, dq, J=16.22, 4.06Hz), 3.92 (2H, s), 3.69-3.61 (1H, m), 3.47 (1H, m), 2.71 (1H, s), 2.42 (1H, m), 2.18-1.39 (22H, m); LC/MS (100%, t_r=1.27min): *m/z*=499.2 $[M+H]^+$ (Calc: 498.6).

5.23 Example 23



74 232 233

Thionyl chloride (214μL, 0.293mmol) was added to a mixture of Substituted-Quinoxaline-Type Piperidine Compound **74** (120mg, 293mmol), a catalytic amount of DMF (5 drops), and $CHCl_3$ (2mL) at a temperature of about 25°C. The reaction mixture was refluxed for 2h then concentrated under reduced pressure to provide a residue. Ethyl 2-(2-aminothiazol-4-yl)acetate (71.0mg, 0.381mmol, Sigma-Aldrich) was added to a mixture of the residue and $CHCl_3$ (2mL). The reaction mixture was stirred at a temperature of about 25°C for 21h, 100μL of TEA was added, and the reaction mixture was stirred at at a temperature of about 25°C for 24h more. The mixture was partitioned between DCM and water. The organic portion was separated, washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide a residue. The residue was then chromatographed by preparative TLC (eluted with 10%:90% MeOH:DCM) to provide 84.5mg of Substituted-Quinoxaline-Type Piperidine Compound **232** as a pale yellow solid (yield 49.9%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **232**, ethyl 2-(2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamido)thiazol-4-yl)acetate, was confirmed using LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **232**: LC/MS: *m/z*=578 $[M+H]^+$ (Calc: 577).

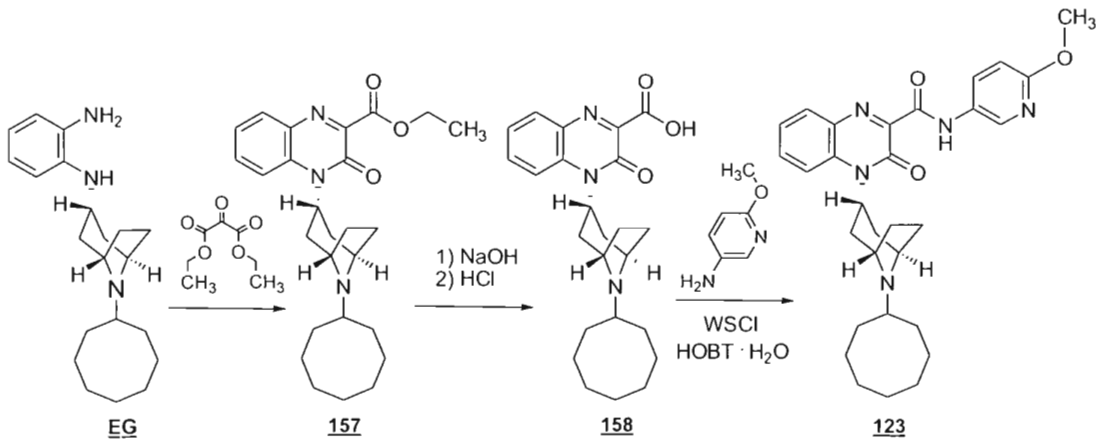
The hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **233** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **232** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **174** in Example 7 (yield 37%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **233**, 2-(2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamido)thiazol-4-yl)acetic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **233**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 12.64-12.87 (1H, br), 12.44 (1H, br), 10.43 (1H, br), 8.13 (1H, m), 7.97 (1H, dd, J=1.0, 7.9Hz), 7.80-7.84 (1H, m), 7.50-7.53 (1H, m), 7.13 (1H, s), 6.02 (1H, m), 4.26 (2H, m), 3.66 (2H, s), 2.94 (2H, m), 2.60-2.67 (2H, m), 1.39-2.41 (20H, m); LC/MS: *m/z*=550 $[M+H]^+$ (Calc: 549).

5.24 Example 24

In a manner similar to Example 21, the following Substituted-Quinoxaline-Type Piperidine Compounds ("*exo*" isomers) were prepared from from the compound of formula **EG**.



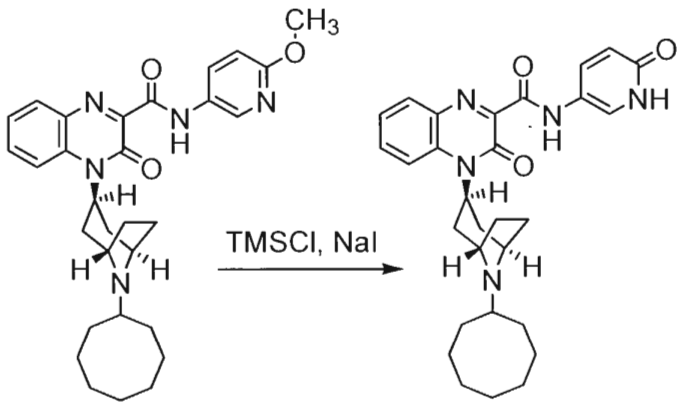
Substituted-Quinoxaline-Type Piperidine Compound **123** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **158** (4-((*exo*)-8-cyclooctyl-

8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid) (yield 82%), which was prepared from Substituted-Quinoxaline-Type Piperidine Compound **157** (ethyl 4-((*exo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate), which was prepared from the compound of formula **EG**.

The identity of Substituted-Quinoxaline-Type Piperidine Compound **123**, 4-((*exo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-*N*-(6-methoxypyridin-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **123**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 10.84 (1H, s), 8.45 (1H, d, J=2.53Hz), 7.98 (3H, dt, J=21.46, 8.24Hz), 7.76 (1H, s), 7.50 (1H, d, J=7.6Hz), 6.89 (1H, d, J=9.12Hz), 5.15 (1H, br), 4.29 (2H, br), 3.85 (3H, s), 2.85 (2H, br), 2.33-1.48 (21H, m); LC/MS (99%, t_r=1.63min): *m/z*=516.3 $[M+H]^+$ (Calc: 515.7).

5.25 Example 25



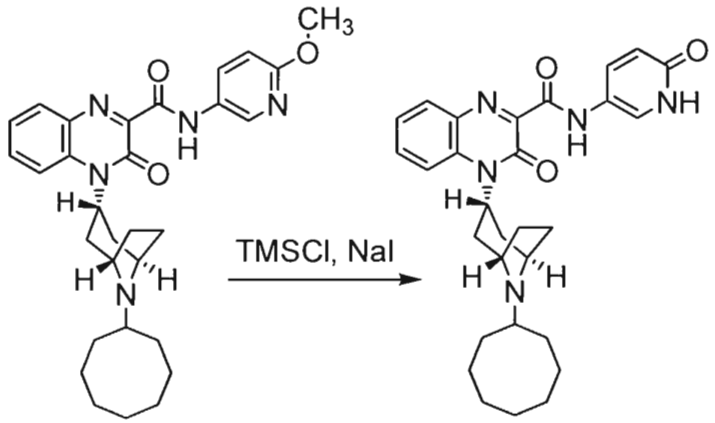
120 **122**

To a mixture of sodium iodide (1.29mmol, Sigma-Aldrich) in acetonitrile (7mL) was added TMSCl (1.29mmol, Sigma-Aldrich) and the mixture was stirred at a temperature of about 25°C for 30min. Thereafter, to the mixture was added Substituted-Quinoxaline-Type Piperidine Compound **120** (133mg, 0.26mmol) in acetonitrile (3mL). The resulting reaction mixture was heated with stirring at 80°C for 2.5h. After cooling to a temperature of about 25°C, the reaction mixture was extracted three times with EtOAc/water (30mL for each extraction). The organic portions were combined, washed with saturated aqueous Na_2SO_3 solution (10mL), brine (10mL), dried ($MgSO_4$), and concentrated under reduced pressure to

provide a yellow solid. The solid was chromatographed with a silica gel column eluted with a gradient of from 97%:3% $CHCl_3$:MeOH to 85%:15% $CHCl_3$:MeOH to provide 38mg of Substituted-Quinoxaline-Type Piperidine Compound **122** as a yellow solid (yield 30%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **122**, 4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-*N*-(6-oxo-1,6-dihydropyridin-3-yl)-3,4-dihydroquinoxaline-2-carboxamide, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **122**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 11.44 (0.9H, s), 10.59 (1H, s), 9.73 (0.1H, s), 8.02-7.46 (6H, m), 6.41 (1H, d, J=9.63Hz), 5.50 (1H, br), 4.27 (0.5H, s), 3.65 (1.5H, s), 2.36-1.45 (23H, m); LC/MS (98%, t_r=1.18min): *m/z*=502.2 $[M+H]^+$ (Calc: 501.6).



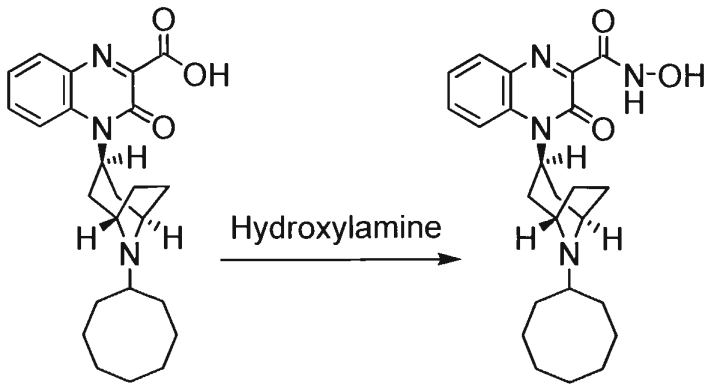
123 **124**

In a manner similar to the above preparation of Substituted-Quinoxaline-Type Piperidine Compound **122**, Substituted-Quinoxaline-Type Piperidine Compound **124** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **123** (yield 53%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **124**, 4-((*exo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-*N*-(6-oxo-1,6-dihydropyridin-3-yl)-3,4-dihydroquinoxaline-2-carboxamide, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **124**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 11.45 (1H, s), 10.61 (1H, s), 7.96 (3H, m), 7.75 (1H, s), 7.50 (2H, m), 6.42 (1H, d, J=9.63Hz), 5.13 (1H, br), 4.27 (0.5H, br), 3.59 (1.5H, br), 2.72 (2H, m), 2.00-1.47 (21H, m); LC/MS (96%, t_r=1.02min): *m/z*=502.2 $[M+H]^+$ (Calc: 501.6).

5.26 Example 26



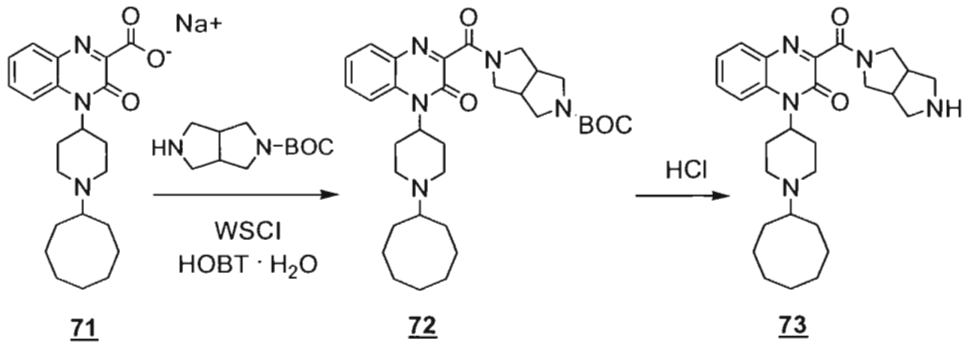
74 **127**

To a mixture of Substituted-Quinoxaline-Type Piperidine Compound **74** (100mg, 0.23mmol) in ethanol (3mL) was added dropwise at a temperature of about 25°C a 50% aqueous solution of hydroxylamine (1mL, Sigma-Aldrich). The resulting reaction mixture was stirred at a temperature of about 25°C for 4h. A yellow precipitate formed. Diethyl ether (20mL) was added to the precipitate which was then collected by filtration, washed twice with diethyl ether (5mL for each wash), and dried under reduced pressure a temperature of about 25°C for 12hr to provide 49mg of Substituted-Quinoxaline-Type Piperidine Compound **127** as a pale yellow solid (yield 51%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **127**, 4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-*N*-hydroxy-3-oxo-3,4-dihydroquinoxaline-2-carboxamide, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **127**: ^{1}H NMR: δ_H (400MHz, CD_3OD): 8.02 (1H, d, J=8.11Hz), 7.78 (2H, t, J=6.59Hz), 7.51-7.47 (1H, m), 5.44 (1H, s), 4.13 (2H, s), 2.95 (1H, s), 2.66-2.58 (2H, m), 2.33 (6H, m), 2.02-1.47 (15H, m); LC/MS (100%, t_r=1.05min): *m/z*=425.2 $[M+H]^+$ (Calc: 424.5).

5.27 Example 27



71 72 73

In a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **120** from Substituted-Quinoxaline-Type Piperidine Compound **74** in Example 21, Substituted-Quinoxaline-Type Piperidine Compound **72** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **71** (yield 70%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **72**, *tert*-butyl 5-(4-(1-cyclooctylpiperidin-4-yl)-3-oxo-3,4-dihydroquinoxaline-2-carbonyl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

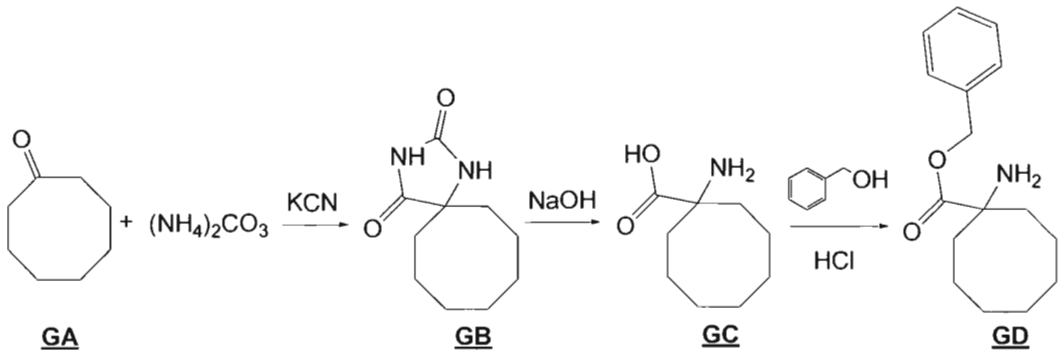
Substituted-Quinoxaline-Type Piperidine Compound **72**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 7.93 (1H, d, J=8Hz), 7.84 (1H, d, J=8Hz), 7.68 (1H, t, J=8Hz), 7.42 (1H, t, J=8Hz), 4.75 (1H, br), 3.69 (1H, s), 3.55-2.42 (16H, m), 1.71-1.40 (16H, m), 1.39 (9H, s); LC/MS: *m/z*=578.2 $[M+H]^+$ (Calc: 577.8).

Substituted-Quinoxaline-Type Piperidine Compound **73** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **72** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **5** in Example 7 (yield 72%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **73**, 1-(1-cyclooctylpiperidin-4-yl)-3-(octahydropyrrolo[3,4-*c*]pyrrole-2-carbonyl)quinoxalin-2(1*H*)-one, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **73**: ^{1}H NMR: δ_H (400MHz, DMSO): 7.93 (1H, d, J=8Hz), 7.83 (1H, d, J=4Hz), 7.68 (1H, t, J=4Hz), 7.42 (1H, t, J=8Hz), 4.72 (1H, br), 3.70 (1H, m), 3.48 (1H, m), 3.38 (1H, m), 3.09 (1H, m), 2.92-2.38 (13H, m), 1.73-1.43 (17H, m); LC/MS: *m/z*=478.1 $[M+H]^+$ (Calc: 477.6).

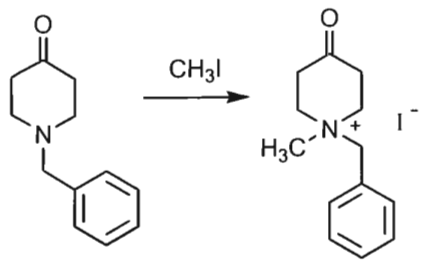
5.28 Example 28



GA GB GC GD

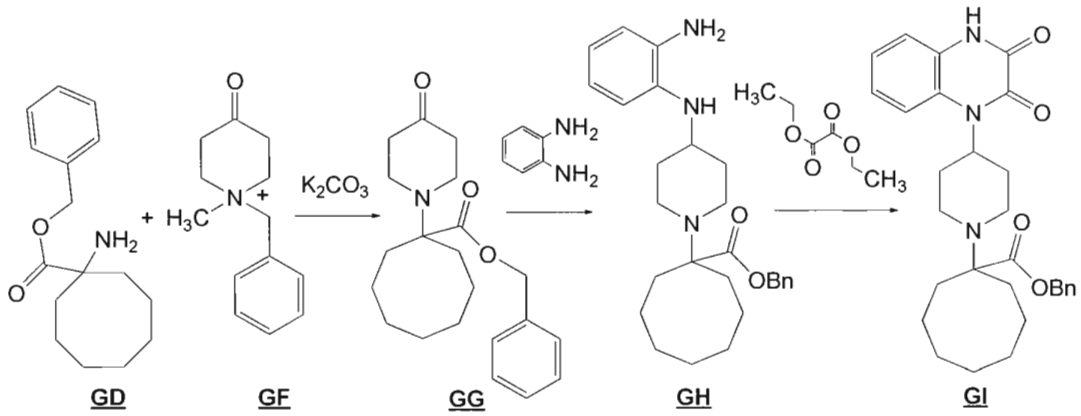
To a mixture of cyclooctanone (**GA**, 17g, 135mmol, Sigma-Aldrich) in ethanol (200mL) and water (200mL) were added KCN (17.5g, 269mmol, Sigma-Aldrich) followed by ammonium carbonate ($[NH_4]_2CO_3$, 51.8g, 539mmol, Sigma-Aldrich). The resulting reaction mixture was stirred at 80°C for 6h. The reaction mixture was evaporated to dryness under reduced pressure to provide a white solid precipitate which was filtered, collected, and dried for 16h to provide 15.9g of the compound of formula **GB**, 1,3-diazaspiro[4.7]dodecane-2,4-dione (yield 73%).

A mixture of the compound of formula **GB** (15.9g, 81mmol) in 2N NaOH was refluxed for 96hr. The reaction mixture was neutralized by the addition of 2N HCl to provide a white solid precipitate which was filtered and collected to provide the compound of formula **GC**, 1-aminocyclooctanecarboxylic acid. The compound of formula **GC** was dissolved with hot phenylmethanol (*i.e.*, phenylmethanol) then concentrated HCl was added. The resulting reaction mixture was refluxed for 16hr. After neutralizing the reaction mixture with 2N NaOH, the resulting mixture was extracted three times with 4:1 $CHCl_3$:MeOH. The organic portions were combined, washed with water, washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide 920mg of the compound of formula **GD**, benzyl 1-aminocyclooctanecarboxylate (yield 6% for two steps).



GE **GF**

The compound of formula **GF** was prepared in a manner similar to the preparation of the compound of formula **DB** in Example 13 except 1-benzylpiperidin-4-one (**GE**, Sigma-Aldrich) was used in place of tropinone and methyl iodide was used in place of dimethyl sulfate.



GD **GF** **GG** **GH** **GI**

At a temperature of 90°C, a mixture of the compound of formula **GF** (10mmol), MeOH (6mL) and water (20mL) was added dropwise to a mixture of the compound of formula **GD** (10mmol), K_2CO_3 (1mmol), MeOH (10mL) and water (4mL) over 20min. The resulting reaction mixture was stirred at 90°C for 48hr. After concentration under reduced pressure, the mixture was extracted three times with a mixture of EtOAc and water. The organic portions were combined, dried ($MgSO_4$), and concentrated under reduced pressure to provide a yellow oil. The resulting oil was chromatographed with a silica gel column eluted with a gradient of from 10%:90% EtOAc:n-hexane to 50%:50% EtOAc:n-hexane to provide the compound of formula **GG**, benzyl 1-(4-oxopiperidin-1-yl)cyclooctanecarboxylate.

Sodium triacetoxyborohydride (50mmol) was added to a mixture of the compound of formula **GG** (12.8mmol), and 1,2-phenylenediamine (3g, 27.8mmol) in 100mL of CH_2Cl_2 at a temperature of about 25°C. Thereafter, 3mL of acetic acid was added. The resulting mixture

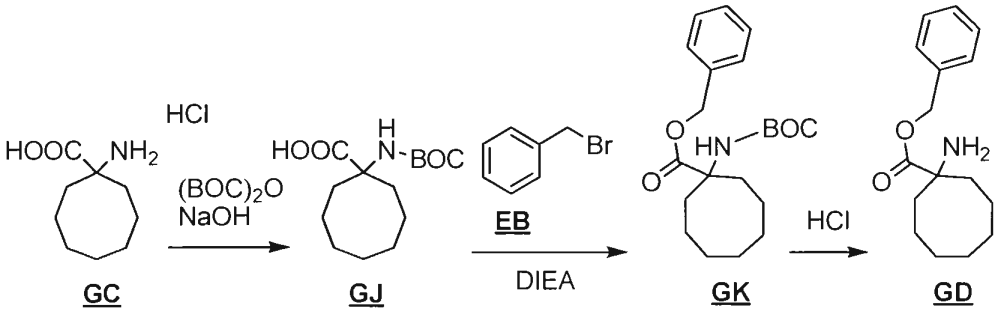
was stirred at a temperature of about 25°C for about 16h. MeOH (2mL) and water (25mL) were added and the mixture was neutralized with 28% aqueous ammonia to adjust the pH to about 8. The organic portion was separated, washed with brine (10mL), concentrated under reduced pressure, and chromatographed with a silica gel column eluted with 10:1:1 EtOAc:MeOH:TEA to provide the compound of formula **GH**, benzyl 1-(4-(2-aminophenylamino)piperidin-1-yl)cyclooctanecarboxylate.

A mixture of the compound of formula **GH** in 20mL of diethyl oxalate (Sigma-Aldrich) was heated at 140°C for 16h. After cooling to a temperature of about 25°C, the reaction mixture was diluted with EtOAc, washed with 2N aqueous NaOH (30mL), washed with brine (20mL), concentrated under reduced pressure, and chromatographed with a silica gel column eluted with 5:5:0.5:0.5 EtOAc:hexane:MeOH:TEA to provide the compound of formula **GI**.

The identity of the compound of formula **GI**, benzyl 1-(4-(2,3-dioxo-3,4-dihydroquinoxalin-1(2*H*)-yl)piperidin-1-yl)cyclooctanecarboxylate, was confirmed using ^{1}H NMR and LC/MS.

Compound **GI:** ^{1}H NMR: δ_H (300MHz, DMSO-d_6): 11.51 (1H, s), 7.47 (1H, d, J=8.1Hz), 7.41-7.33 (5H, m), 7.24-7.17 (3H, m), 5.17 (2H, s), 4.58 (1H, br), 3.24 (2H, d, J=11.1Hz), 2.76 (2H, d, J=9.3Hz), 2.33 (2H, t, J=10.8Hz), 2.01-1.47 (16H, m); LC/MS (100%, t_r=1.87min): *m/z*=490.2 $[M+H]^+$ (Calc: 489.3).

Alternatively, the compound of formula **GD** was prepared by the following route.



To a mixture of the hydrochloride of the compound of formula **GC** (414mg, 2.00mmol), aqueous 1N NaOH (4mL, 4.00mmol), and dioxane (4mL) at a temperature of about 25°C was added $(BOC)_2O$ (0.51mL, 2.2mmol). After the addition, the reaction mixture was stirred for 18h at a temperature of about 25°C. The mixture was quenched by pouring it

into aqueous 1N HCl and extracted with $CHCl_3$. The organic portion was dried (Na_2SO_4) and concentrated under reduced pressure to provide a white solid. The solid was triturated with *iso*-propyl ether and collected to provide 221mg of the compound of formula **GJ** as a colorless solid (yield 41%).

The identity of the compound of formula **GJ**, 1-(*tert*-butoxycarbonylamino)cyclooctanecarboxylic acid, was confirmed using ^{1}H NMR.

Compound **GJ**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 12.01 (1H, s), 6.90 (1H, s), 1.89-1.45 (14H, m), 1.35 (9H, s).

To a mixture of the compound of formula **GJ** (215mg, 0.792mmol) in DMF (1mL) at a temperature of about 25°C was added the compound of formula **EB** (0.103mmol, 0.871mmol) and DIEA (0.166mL, 0.950mmol). After the addition, the reaction mixture was stirred for 20h at a temperature of about 25°C. The mixture was quenched by pouring it into water. A white precipitate formed. The precipitate was collected, washed with dilute aqueous $NaHCO_3$, and washed with water to provide 240mg of the compound of formula **GK** as a white solid (yield 84%).

The identity of the compound of formula **GK**, benzyl 1-(*tert*-butoxycarbonylamino)cyclooctanecarboxylate, was confirmed using ^{1}H NMR.

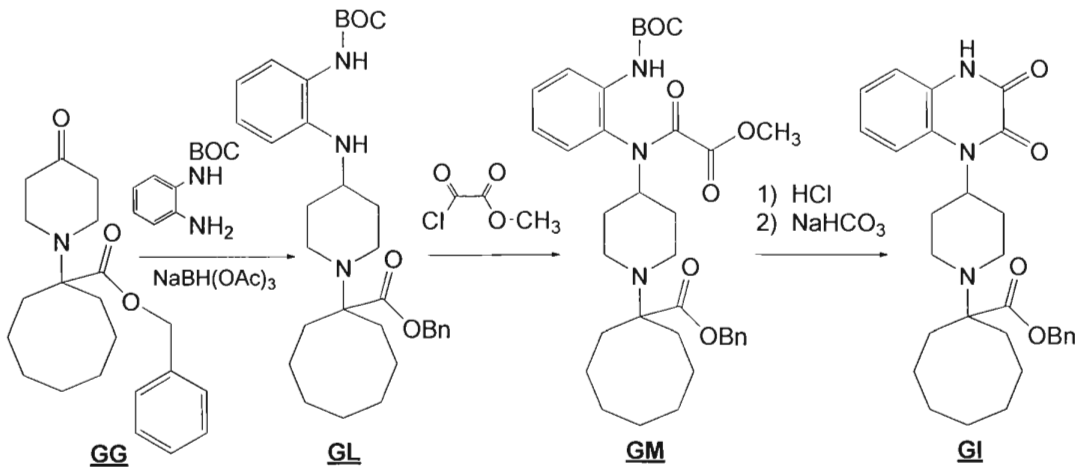
Compound **GK**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.37-7.34 (5H, m), 5.16 (2H, s), 4.69 (1H, s), 2.08-2.04 (4H, m), 1.57 (10H, d, J=8.06Hz), 1.43 (9H, s).

The compound of formula **GD** was prepared from the compound of formula **GK** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **5** in Example 7 (yield >98%).

The identity of the compound of formula **GD** was confirmed using ^{1}H NMR.

Compound **GD**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.40-7.34 (5H, m), 5.21 (2H, s), 2.06-1.71 (14H, m).

Alternatively, the compound of formula **GI** was prepared by the following route.



The compound of formula **GG** was prepared from the compounds of formula **GD** and **GF** in a manner similar to that described above (yield 38%).

The identity of the compound of formula **GG** was confirmed using ^{1}H NMR.

Compound **GG**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.38-7.36 (5H, m), 5.14 (2H, s), 2.92 (4H, t, J=5.62Hz), 2.39 (4H, t, J=5.79Hz), 2.00-1.59 (14H, m).

The compound of formula **GL** was prepared from the compound of formula **GG** in a manner similar to the preparation of the compound of formula **AB** in Example 1 except *tert*-butyl 2-aminophenylcarbamate (Sigma-Aldrich) was used in place of 1,2-phenylenediamine (yield 95%).

The identity of the compound of formula **GL**, benzyl 1-(4-(2-(*tert*-butoxycarbonylamino)phenylamino)piperidin-1-yl)cyclooctanecarboxylate,was confirmed using ^{1}H NMR.

Compound **GL**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.46-7.37 (5H, m), 7.07 (2H, dd, J=12.51, 6.13Hz), 6.78-6.71 (2H, m), 6.10 (1H, s), 5.16 (3H, s), 3.58 (1H, dd, J=9.65, 4.95Hz), 3.19-2.90 (4H, m), 2.41-1.34 (18H, m), 2.41 (9H, s).

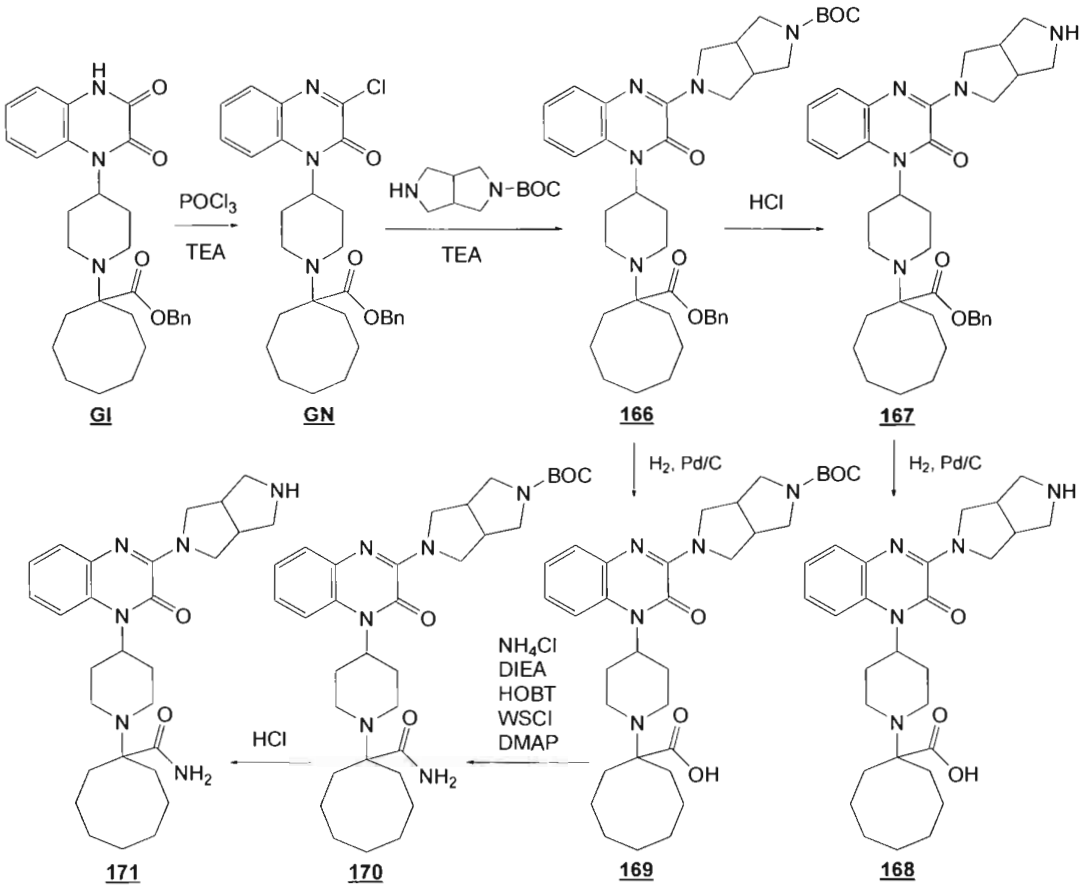
The compound of formula **GM** was prepared from the compound of formula **GL** and methyl 2-chloro-2-oxoacetate in a manner similar to the preparation of the compound of formula **CF** in Example 6 (yield >98%).

The identity of the compound of formula **GM**, benzyl 1-(4-(*N*-(2-(*tert*-butoxycarbonylamino)phenyl)-2-methoxy-2-oxoacetamido)piperidin-1-yl)cyclooctanecarboxylate,was confirmed using ^{1}H NMR.

Compound **GM**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.98 (1H, d, J=5.1Hz), 7.42-7.32 (5H, m), 7.06-7.04 (2H, m), 6.68 (1H, s), 5.10 (2H, s), 4.35 (1H, m), 3.49 (3H, s), 3.02 (2H, t, J=10.8Hz), 2.90 (1H, t, J=6.0Hz), 2.35 (1H, t, J=6.0Hz), 2.24 (2H, t, J=12.0Hz), 1.87-1.78 (6H, m), 1.51-1.27 (19H, m).

To the compound of formula **GM** (553mg, 0.89mmol) was added 4N HCl in EtOAc (5.5mL) at 0°C. Thereafter, the reaction mixture was stirred for 30min at a temperature of about 25°C. A white precipitate formed. Saturated aqueous $NaHCO_3$ (pH >8) was added and the reaction mixture was stirred for 30min at a temperature of about 25°C. Thereafter, the mixture was extracted twice with $CHCl_3$ (50mL for each extraction). The organic portions were combined, washed with water, dried ($MgSO_4$), and concentrated under reduced pressure to provide a colorless amorphous solid. The solid was recrystallized from a mixture of diethyl ether and *iso*-propyl ether to provide 333mg of the compound of formula **GI** as a white powder (yield 76%).

5.29 Example 29



In a manner similar to Example 3, the compound of formula **GN** was prepared from the compound of formula **GI** (yield 92%) then Substituted-Quinoxaline-Type Piperidine Compound **166** was prepared from *tert*-butyl hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate and the compound of formula **GN** (yield >98%).

The identity of the compound of formula **GN**, benzyl 1-(4-(3-chloro-2-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl)piperidin-1-yl)cyclooctanecarboxylate, was confirmed using ^{1}H NMR.

Compound **GN**: ^{1}H NMR: δ_H (300MHz, $CDCl_3$): 7.81 (1H, d, J=8.1Hz), 7.59-7.56 (2H, m), 7.39-7.35 (6H, m), 5.16 (2H, s), 4.83 (1H, br), 3.49 (3H, s), 3.25 (2H, d, J=11.7Hz), 2.91 (2H, m), 2.34 (2H, t, J=6.0Hz), 2.00-1.47 (16H, m).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **166**, *tert*-butyl 5-(4-(1-(1-(benzyloxycarbonyl)cyclooctyl)piperidin-4-yl)-3-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate, was confirmed using ^{1}H NMR.

Substituted-Quinoxaline-Type Piperidine Compound **166**: ^{1}H NMR: δ_H (300MHz, DMSO-d_6): 7.51-7.38 (7H, m), 7.18-7.15 (2H, m), 5.16 (2H, s), 4.45 (1H, br), 4.00 (2H, br), 3.71 (2H, br), 3.50 (2H, br), 3.24 (2H, d, J=11.1Hz), 2.76 (2H, d, J=9.3Hz), 2.33 (2H, t, J=10.8Hz), 2.01-1.47 (16H, m).

In a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **5** in Example 7, Substituted-Quinoxaline-Type Piperidine Compound **167**, benzyl 1-(4-(3-(hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)-2-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl)piperidin-1-yl)cyclooctanecarboxylate, was prepared from Substituted-Quinoxaline-Type Piperidine Compound **166** (yield 90%) then, in a manner similar to the removal of the benzyl group in Example 18, Substituted-Quinoxaline-Type Piperidine Compound **168** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **167** (yield 27%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **168**, 1-(4-(3-(hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)-2-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl)piperidin-1-yl)cyclooctanecarboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **168**: ^{1}H NMR: δ_H (300MHz, DCl/D_2O): 7.53 (2H, d, J=8.1Hz), 7.34 (1H, t, J=8.1Hz), 7.23 (1H, t, J=8.1Hz), 4.38 (5H, br), 3.57 (4H, d, J=5.7Hz), 3.35-3.22 (6H, m), 3.07-2.99 (2H, m), 2.23-2.00 (6H, m), 1.54 (6H, br), 1.24 (4H, br); LC/MS (100%, t_r=0.83min): *m/z*=494.2 $[M+H]^+$ (Calc: 493.3).

In a manner similar to the removal of the benzyl group in Example 18, Substituted-Quinoxaline-Type Piperidine Compound **169** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **166** (yield 81%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **169**, 1-(4-(3-(5-(*tert*-butoxycarbonyl)hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)-2-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl)piperidin-1-yl)cyclooctanecarboxylic acid, was confirmed using ^{1}H NMR.

Substituted-Quinoxaline-Type Piperidine Compound **169**: ^{1}H NMR: δ_H (300MHz, CD_3OD): 7.55-7.48 (2H, m), 7.23-7.19 (2H, m), 4.16 (2H, br), 3.90 (2H, br), 3.68-3.62 (4H, m), 3.30-3.22 (4H, m), 2.98 (2H, br), 2.24-2.00 (6H, m), 1.74-1.47 (21H, m).

At a temperature of about 25°C, a reaction mixture of Substituted-Quinoxaline-Type Piperidine Compound **169** (150mg, 0.25mmol, 1eq), NH_4Cl (16mg, 0.30mmol, 1.2eq), DIEA (51μL, 0.30mmol, 1.2eq), HOBT (38mg, 0.28mmol, 1.1eq, Acros Organics), WSCI (54mg, 0.28mmol, 1.1eq, Sigma-Aldrich), and DMAP (5.6mg, 0.05mmol, 0.2eq) in DMF (3mL) was stirred for 48 hr. Thereafter, the mixture was poured into water (20mL) and extracted twice with $CHCl_3$ (30mL for each extraction). The organic portions were combined, washed with saturated aqueous $NaHCO_3$, washed with water, dried ($MgSO_4$), and concentrated under reduced pressure to provide a pale yellow amorphous solid. The solid was chromatographed with a silica gel column eluted with a gradient of from 100%:0% $CHCl_3$:MeOH to 97%:3% $CHCl_3$:MeOH to provide 40mg of Substituted-Quinoxaline-Type Piperidine Compound **170** as a colorless amorphous solid (yield 27%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **170**, *tert*-butyl 5-(4-(1-(1-carbamoylcyclooctyl)piperidin-4-yl)-3-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate, was confirmed using ^{1}H NMR.

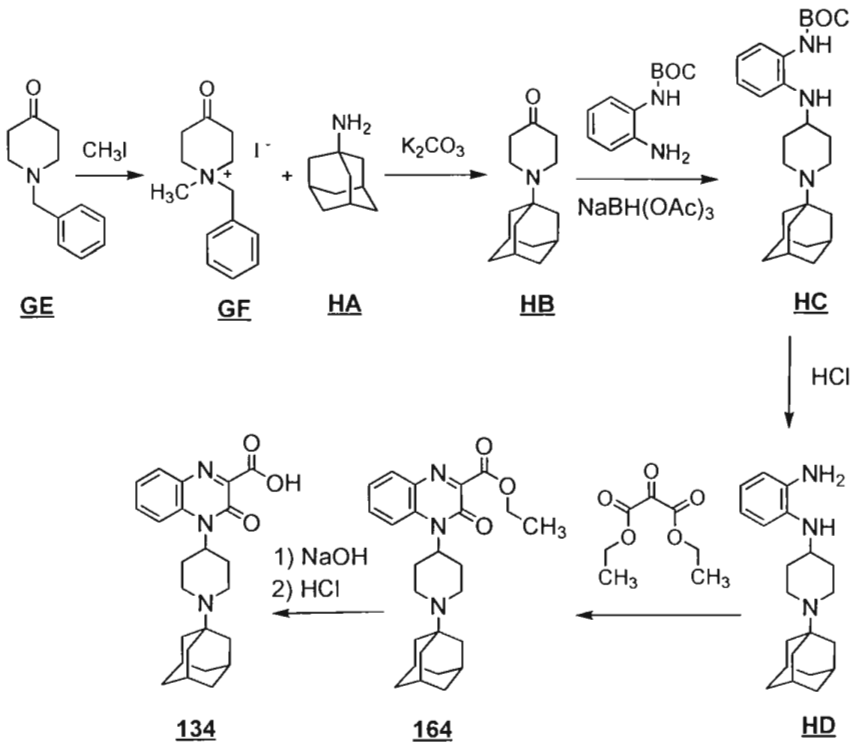
Substituted-Quinoxaline-Type Piperidine Compound **170**: ^{1}H NMR: δ_H (300MHz, DMSO-d_6): 7.71 (1H, br), 7.35-7.32 (1H, m), 7.16-7.12 (2H, m), 6.96 (1H, m), 3.99 (2H, br), 3.73 (1H, br), 3.50 (2H, br), 3.18-3.15 (2H, m), 2.99-2.89 (2H, m), 2.68-2.65 (2H, m), 2.38-2.31 (2H, m), 1.96-1.39 (28H, m).

In a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **5** in Example 7, Substituted-Quinoxaline-Type Piperidine Compound **171** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **170** (yield 41%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **171**, 1-(4-(3-(hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)-2-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl)piperidin-1-yl)cyclooctanecarboxamide, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **171**: ^{1}H NMR: δ_H (300MHz, DMSO-d_6): 7.70 (1H, br), 7.36-7.33 (1H, m), 7.16-7.13 (3H, m), 6.96 (1H, s), 4.65 (1H, br), 3.99 (2H, br), 3.50 (2H, br), 3.02-2.96 (4H, m), 2.80-2.66 (6H, m), 2.34 (2H, t, J=11.4Hz), 2.00-1.95 (2H, m), 1.83-1.78 (2H, m), 1.62-1.39 (12H, m); LC/MS (100%, t_r=0.78min): *m/z*=493.2 $[M+H]^+$ (Calc: 492.7).

5.30 Example 30



At a temperature of about 25°C, K_2CO_3 (228mg, 1.65mmol, 0.1eq) was added to a mixture of the compound of formula **HA** (1-adamantylamine, 5.02g, 33.2mmol), ethanol (12mL), and water (12mL). Then, a mixture of the compound of formula **GF** (5.47g, 16.5mmol), ethanol (13mL), and water (13mL) was added. The resulting reaction mixture was refluxed for 3h. Thereafter, the mixture was poured into water and extracted with EtOAc. The organic portion was dried (Na_2SO_4) then concentrated under reduced pressure to provide a residue. The residue was chromatographed with a silica gel column eluted with 97%:3% $CHCl_3$:MeOH to provide 1.97g of the compound of formula **HB** as a colorless solid (yield 51%).

The identity of the compound of formula **HB**, 1-adamantan-1-yl-piperidin-4-one, was confirmed using ^1H NMR.

Compound **HB**: ^1H NMR: δ_H (300MHz, $CDCl_3$): 2.96 (4H, s), 2.46 (4H, s), 2.14 (3H, s), 1.79-1.62 (14H, m).

The compound of formula **HC** was prepared in a manner similar to the preparation of the compound of formula **AB** in Example 1 except *tert*-butyl 2-aminophenylcarbamate was used in place of 1,2-phenylenediamine (yield 60%).

The identity of the compound of formula **HC**, [2-(1-adamantan-1-yl-piperidin-4-yl-amino)-phenyl]-carbamic acid *tert*-butyl ester, was confirmed using ^{1}H NMR and LC/MS.

Compound **HC**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 8.32 (1H, s), 7.13 (1H, d, J=7.6Hz), 6.96-6.92 (1H, m), 6.62 (1H, d, J=7.6Hz), 6.54-6.50 (1H, m), 4.52 (1H, d, J=7.1Hz), 3.18 (1H, dd, J=7.35, 3.30Hz), 2.99 (2H, d, J=11.15Hz), 2.25 (2H, t, J=10.14Hz), 2.03 (3H, s), 1.91 (2H, d, J=11.66Hz), 1.65-1.54 (12H, m), 1.43 (9H, s), 1.30 (2H, q, J=9.97Hz); LC/MS: *m/z*=426 $[M+H]^+$ (Calc: 425.3).

In a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **5** in Example 7, the compound of formula **HD** was prepared from the compound of formula **HC** (yield >98%).

The identity of the compound of formula **HD**, *N*-(1-adamantan-1-yl-piperidin-4-yl)benzene-1,2-diamine, was confirmed using ^{1}H NMR and LC/MS.

Compound **HD**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 6.54-6.35 (4H, m), 4.45 (2H, s), 4.05 (1H, d, J=7.6Hz), 3.10 (3H, m), 2.20 (2H, s), 2.04 (3H, s), 1.93 (2H, d, J=10.65Hz), 1.60 (12H, m), 1.31 (2H, br); LC/MS: *m/z*=325.8 $[M+H]^+$ (Calc: 325.3).

In a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **120** from Substituted-Quinoxaline-Type Piperidine Compound **74** in Example 21, Substituted-Quinoxaline-Type Piperidine Compound **164** was prepared from the compound of formula **HD** (yield 20%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **164**, 4-(1-adamantan-1-yl)-piperidin-4-yl)-3-oxo-3,4-dihydro-quinoxaline-2-carboxylic acid ethyl ester, was confirmed using ^{1}H NMR and LC/MS.

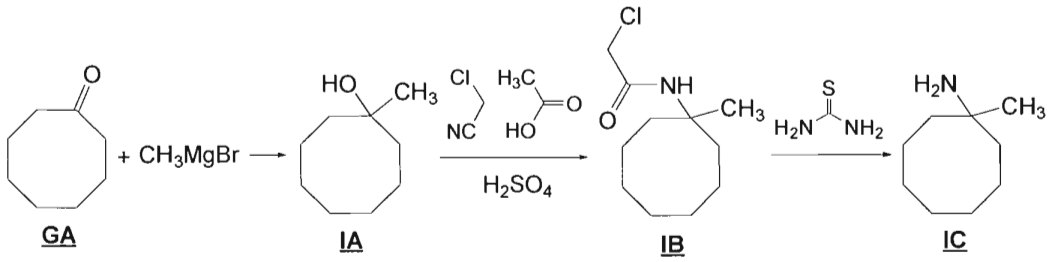
Substituted-Quinoxaline-Type Piperidine Compound **164**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 7.90 (2H, m), 7.76-7.71 (1H, m), 7.44 (1H, t, J=7.6Hz), 4.73 (1H, br), 4.37 (2H, q, J=7.1Hz), 3.25 (2H, m), 2.59 (2H, m), 2.28 (2H, t, J=10.9Hz), 2.06 (3H, s), 1.69-1.57 (14H, m), 1.32 (3H, t, J=7.1Hz); LC/MS: *m/z*=435.9 $[M+H]^+$ (Calc: 435.3).

Substituted-Quinoxaline-Type Piperidine Compound **134** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **164** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **111** in Example 5 (yield 91%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **134**, 4-(1-adamantan-1-yl-piperidin-4-yl)-3-oxo-3,4-dihydro-quinoxalin-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **134**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 8.11 (1H, br), 7.70 (1H, dd, J=8.11, 1.52Hz), 7.51 (1H, t, J=7.35Hz), 7.32 (1H, t, J=7.6Hz), 5.15 (1H, br), 3.67 (2H, s), 3.19-3.02 (6H, m), 2.17 (3H, s), 1.92 (7H, m), 1.65 (6H, s); LC/MS (100%, t_r=1.33min): *m/z*=408.3 $[M+H]^+$ (Calc: 407.5).

5.31 Example 31



Under a nitrogen atmosphere, to a mixture of the compound of formula **GA** (28g, 222mmol) and Et_2O (500mL) at a temperature of -40°C was added methylmagnesium bromide (89mL, 266mmol, Sigma-Aldrich). The resulting reaction mixture was stirred for 4h as its temperature warmed from -40°C to 0°C then stirred an additional 1.5h as its temperature warmed from 0°C to about 25°C. Thereafter, saturated aqueous NH_4Cl was added, the mixture was neutralized with 2N aqueous HCl to adjust the pH into the range between 5-6, and the mixture was extracted 3 times with Et_2O (400mL for each extraction). The organic portions were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to provide the compound of formula **IA**, 1-methylcyclooctanol, as a colorless oil. Acetic acid (29.3mL, 512mmol) was added to a mixture of the compound of formula **IA** (26g, 183mmol) and 2-chloroacetonitrile (23.20mL, 365mmol, Sigma-Aldrich) and the resulting reaction mixture was cooled to a temperature in the range of from 0°C to 3°C. H_2SO_4 (29.2mL, 548mmol) was added dropwise over 1h such that the temperature was kept below 10°C. Thereafter, the reaction mixture was warmed to a temperature of about 25°C and stirred for 1.5hrs. After quencing with ice-water (400mL), the mixture was neutralized with a 30% NaOH aqueous solution to adjust the pH into the range between 7-8; a white precipitate formed. The

precipitate was collected by filtration, washed twice with water (100mL for each wash), and dried under reduced pressure at 60°C for 6h to provide 27g of the compound of formula **IB** (yield 56%).

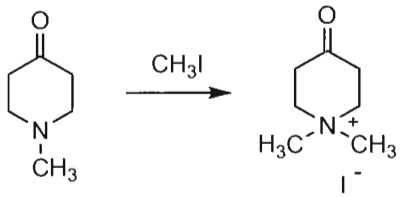
The identity of the compound of formula **IB**, 2-chloro-*N*-(1-methylcyclooctyl)acetamide, was confirmed using ^{1}H NMR.

Compound **IB**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 6.28 (1H, s), 3.95 (2H, s), 2.05-2.00 (2H, m), 1.72 (2H, td, J=10.01, 4.06Hz), 1.57 (11.2H, m), 1.41 (3H, s).

Under a nitrogen atmosphere, to a mixture of the compound of formula **IB** (27g, 124mmol) and ethanol (240mL) at a temperature of about 25°C was added thiourea (11.30g, 148mmol, Sigma-Aldrich) and acetic acid (45mL) The resulting reaction mixture was warmed to 110°C and stirred for 7h. After cooling the mixture to a temperature of about 25°C and quencing with water (700mL), the white precipitate that formed was filtered off. The filtrate was neutralized with a 30% NaOH aqueous solution, its pH was adjusted to pH14, it was washed twice with n-hexane:H_2O (400mL for each wash), dried (Na_2SO_4), and concentrated under reduced pressure to provide 17g of the compound of formula **IC** as a pale yellow oil (yield 97%).

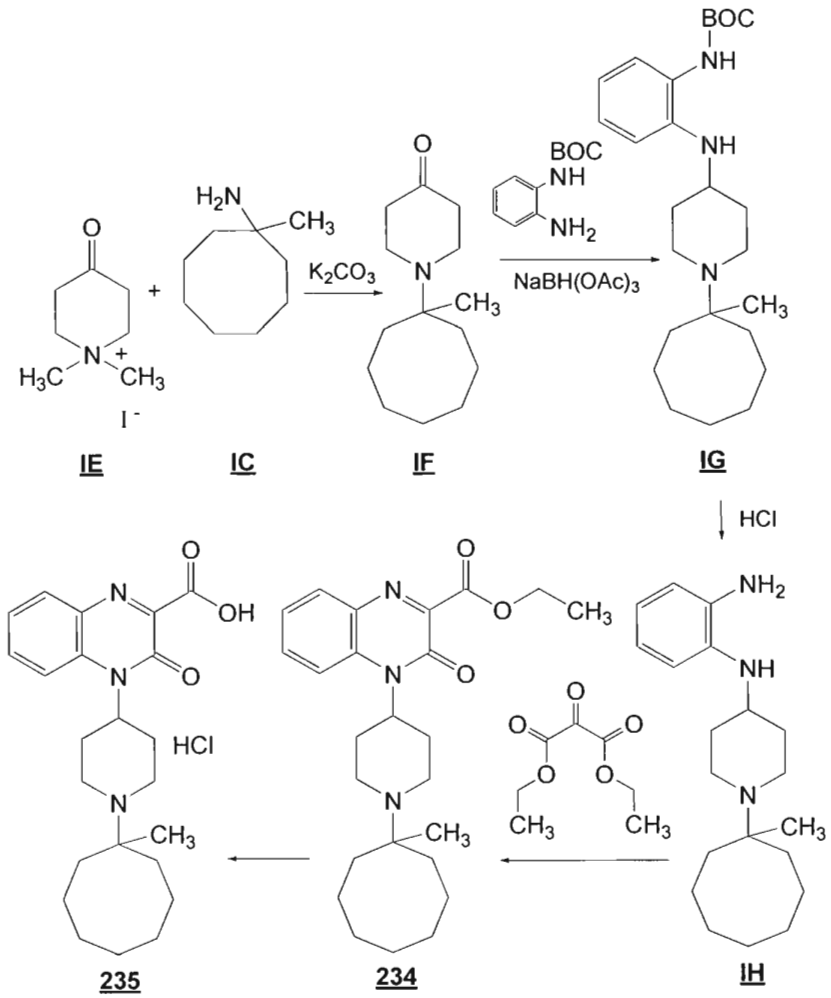
The identity of the compound of formula **IC**, 1-methylcyclooctanamine, was confirmed using ^{1}H NMR.

Compound **IC**: ^{1}H NMR: δ_H (300MHz, $CDCl_3$): 1.58-1.47 (14H, m), 1.26-1.21 (2H, m), 1.07 (3H, s).



ID **IE**

The compound of formula **IE** was prepared in a manner similar to the preparation of the compound of formula **DB** in Example 13 except 1-methylpiperidin-4-one (**ID**, Sigma-Aldrich) was used in place of tropinone and methyl iodide was used in place of dimethyl sulfate.



In a manner similar to Example 30, Substituted-Quinoxaline-Type Piperidine Compound **234** was prepared except that the compound of formula **IE** was used in place of the compound of formula **GF** and the compound of formula **IC** was used in place of the compound of formula **HA**.

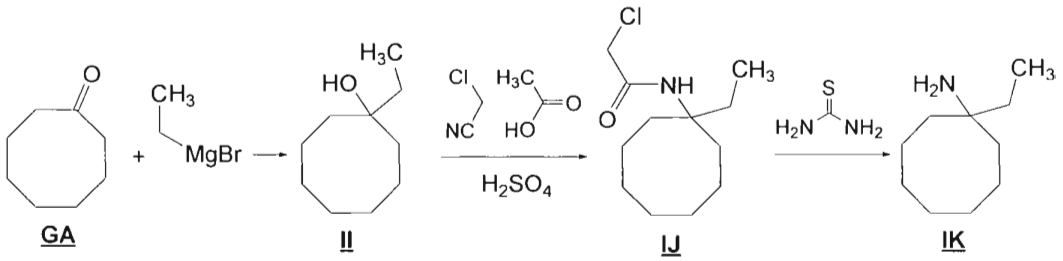
The identity of Substituted-Quinoxaline-Type Piperidine Compound **234**, ethyl 4-(1-(1-methylcyclooctyl)piperidin-4-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **234**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.93 (1H, dd, J=8.11, 1.01Hz), 7.76 (1H, d, J=4.56Hz), 7.61 (1H, dd, J=11.66, 4.06Hz), 7.36 (1H, t, J=7.6Hz), 4.90 (1H, br), 4.50 (2H, q, J=7.1Hz), 3.15 (2H, d, J=11.66Hz), 2.78 (2H, dd, J=5.07, 3.55Hz), 2.23 (2H, t, J=11.41Hz), 1.86-1.24 (20H, m), 0.84 (3H, d, J=10.65Hz); LC/MS: *m/z*=426 $[M+H]^+$ (Calc: 425).

At a temperature of about 25°C, to a mixture of Substituted-Quinoxaline-Type Piperidine Compound **234** (188mg, 0.442mmol) and ethanol (8mL) was added 2N aqueous NaOH (0.663mL, 1.325mmol) and the reaction mixture was stirred for 45min. Thereafter, the mixture was concentrated under reduced pressure to provide a residue. The residue was diluted with water, neutralized with 2N aqueous HCl (0.663mL), and extracted with $CHCl_3$:H_2O to provide an emulsion that was concentrated under reduced pressure to provide a second residue. The second residue was diluted with $CHCl_3$, dried ($MgSO_4$), and concentrated under reduced pressure to provide a pale yellow solid. The solid was washed with 1:1 EtOAc:Et_2O, filtrated, and dried under reduced pressure at 70°C for 12h to provide a third residue. The third residue was diluted with 2N aqueous HCl (2mL), heated, sonicated, and concentrated under reduced pressure to provide an oil. The oil was dried under reduced pressure at 70°C for 12h to provide the hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **235** as a yellow amorphous solid.

The identity of Substituted-Quinoxaline-Type Piperidine Compound **235**, 4-(1-(1-methylcyclooctyl)piperidin-4-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **235**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 8.28 (1H, br), 7.84 (1H, s), 7.65 (1H, s), 7.44 (1H, s), 5.32 (1H, s), 3.63 (4H, d, J=2.53Hz), 2.14-1.36 (21H, m); LC/MS (100%, t_r=1.40min): *m/z*=398 $[M+H]^+$ (Calc: 397).

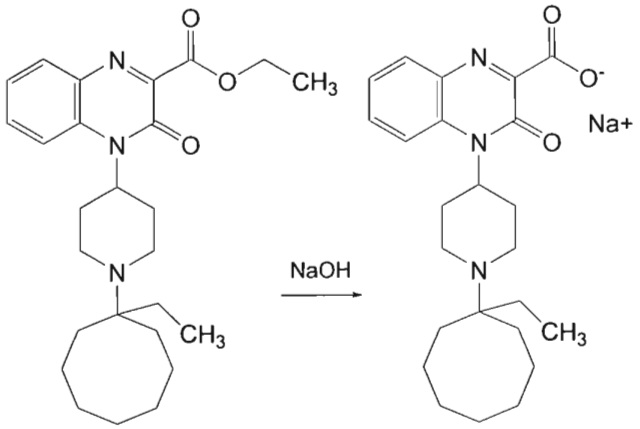


GA II IJ IK

In a manner similar to that described above, the compound of formula **IK** was prepared from the compound of formula **GA** except that ethylmagnesium bromide (Sigma-Aldrich) was used in place of methylmagnesium bromide (yield 20%).

The identity of the compound of formula **IK**, 1-ethylcyclooctanamine, was confirmed using ^{1}H NMR.

Compound **IK**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 1.63-1.34 (16H, m), 1.10 (2H, s), 0.86 (3H, t, J=7.6Hz).



236 **237**

In a manner similar to that described above, Substituted-Quinoxaline-Type Piperidine Compound **236** was prepared from the compound of formula **IE** except that the compound of formula **IK** was used in place of the compound of formula **IC**.

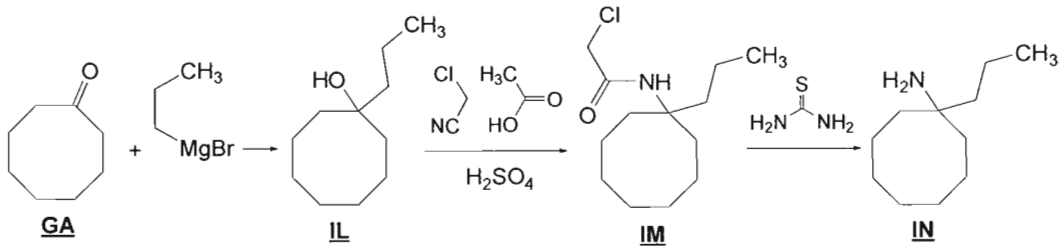
The identity of Substituted-Quinoxaline-Type Piperidine Compound **236**, ethyl 4-(1-(1-ethylcyclooctyl)piperidin-4-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **236**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.93 (1H, d, J=8.11Hz), 7.76 (1H, d, J=1.01Hz), 7.61 (1H, dd, J=7.86, 6.84Hz), 7.35 (1H, t, J=7.6Hz), 4.94 (1H, br), 4.50 (2H, ddd, J=14.19, 7.10, 1.52Hz), 3.15 (2H, d, J=10.65Hz), 2.71 (2H, br), 2.34 (2H, t, J=11.41Hz), 1.83-1.39 (18H, m), 0.86 (3H, t, J=7.35Hz); LC/MS: *m/z*=440 $[M+H]^+$ (Calc: 439).

2N aqueous NaOH (0.114mL, 0.227mmol) was added to a mixture of Substituted-Quinoxaline-Type Piperidine Compound **236** (100mg, 0.227mmol) and ethanol (2mL) at 25°C. The resulting reaction mixture was stirred at a temperature of about 25°C for 2h. After concentration under reduced pressure, the resulting solid was triturated with Et_2O, filtered, and dried under reduced pressure at 80°C to provide 98mg of the sodium salt of Substituted-Quinoxaline-Type Piperidine Compound **237** as a pale yellow solid (yield >98%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **237**, 4-(1-(1-ethylcyclooctyl)piperidin-4-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

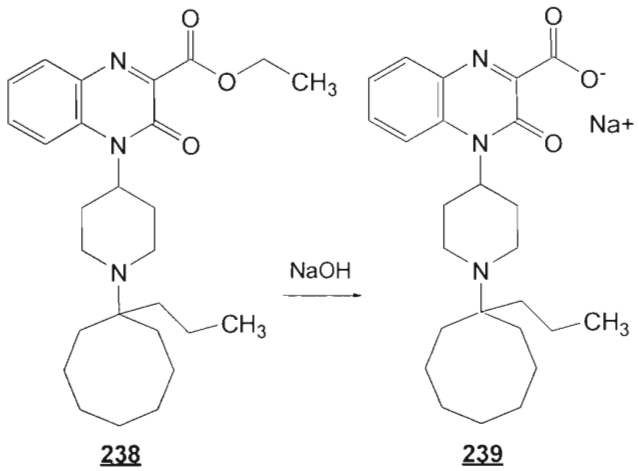
Substituted-Quinoxaline-Type Piperidine Compound **237**: ^{1}H NMR: δ_H (400MHz, CD_3OD): 7.82 (2H, dd, J=28.13, 7.86Hz), 7.58 (1H, dd, J=8.36, 7.35Hz), 7.34 (1H, t, J=7.6Hz), 3.19 (2H, d, J=10.65Hz), 2.80 (2H, d, J=10.65Hz), 2.40 (2H, t, J=11.41Hz), 1.89-1.46 (18H, m), 0.89 (3H, t, J=7.35Hz); LC/MS (100%, t_r=1.57min): *m/z*=411 $[M+H]^+$ (Calc: 410).



In a manner similar to that described above, the compound of formula **IN** was prepared from the compound of formula **GA** except that propylmagnesium bromide (Sigma-Aldrich) was used in place of methylmagnesium bromide (yield 26%).

The identity of the compound of formula **IN**, 1-propylcyclooctanamine, was confirmed using ^{1}H NMR.

Compound **IN**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 1.63-1.19 (20H, m), 0.92 (3H, t, J=5.83Hz).



In a manner similar to that described above, Substituted-Quinoxaline-Type Piperidine Compound **238** was prepared from the compound of formula **1E** except that the compound of formula **IN** was used in place of the compound of formula **IC**.

The identity of Substituted-Quinoxaline-Type Piperidine Compound **238**, ethyl 3-oxo-4-(1-(1-propylcyclooctyl)piperidin-4-yl)-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

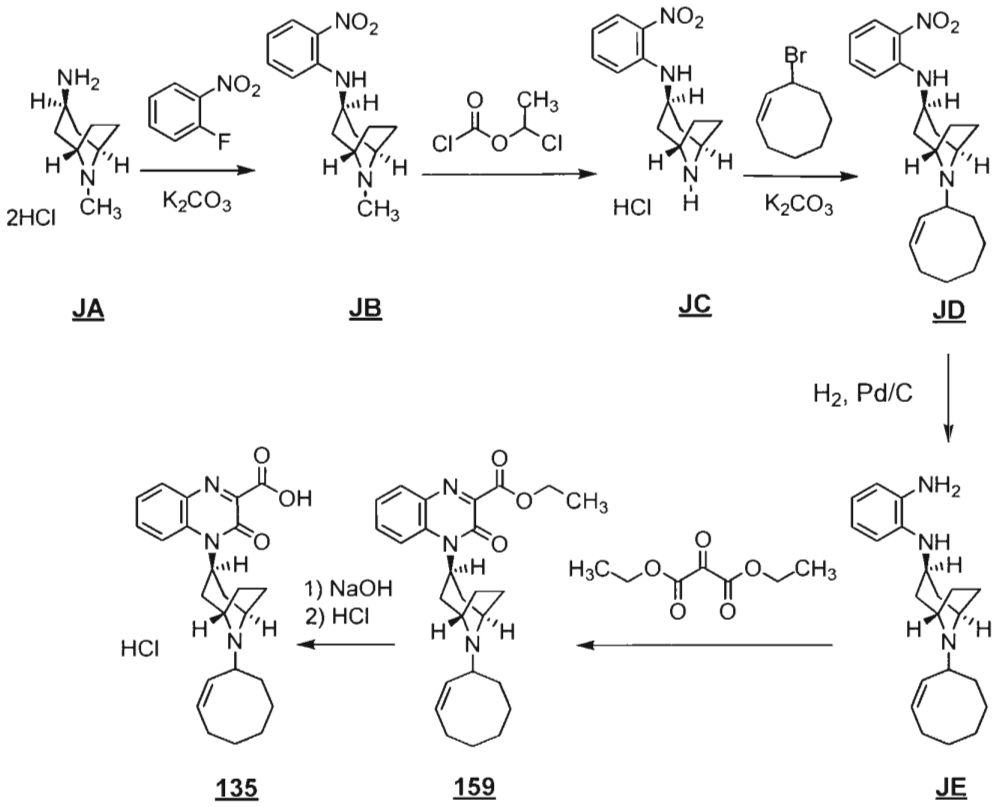
Substituted-Quinoxaline-Type Piperidine Compound **238**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.93 (1H, d, J=7.6Hz), 7.75 (1H, dd, J=3.80, 1.77Hz), 7.63-7.59 (1H, m), 7.35 (1H, t, J=7.6Hz), 4.93 (1H, br), 4.53-4.48 (2H, m), 3.54 (1H, br), 3.14 (2H, d, J=11.15Hz), 2.73 (2H, ddd, J=18.38, 11.03, 3.93Hz), 2.33 (2H, t, J=11.41Hz), 1.80-1.24 (20H, m), 0.91 (3H, d, J=12.67Hz); LC/MS: *m/z*=454 $[M+H]^+$ (Calc: 453).

In a manner similar to that described above, the sodium salt of Substituted-Quinoxaline-Type Piperidine Compound **239** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **238** (yield 88%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **239**, 3-oxo-4-(1-(1-propylcyclooctyl)piperidin-4-yl)-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **239**: ^{1}H NMR: δ_H (400MHz, CD_3OD): 7.86-7.77 (2H, m), 7.60-7.56 (1H, m), 7.34 (1H, t, J=7.6Hz), 3.18 (2H, d, J=11.15Hz), 2.79 (2H, d, J=9.63Hz), 2.39 (2H, t, J=11.41Hz), 1.90-1.29 (20H, m), 0.91 (3H, t, J=5.83Hz); LC/MS (96%, t_r=1.82min): *m/z*=425 $[M+H]^+$ (Calc: 424).

5.32 Example 32



The compound of formula **JA**, (*endo*)-8-methyl-8-azabicyclo[3.2.1]octan-3-amine, was prepared by a method known to those in the art, *e.g.*, M. Allegretti *et al.*, *Tetrahedron Let.*, 58:5669-5674 (2002). K_2CO_3 (9.12g, 66mmol) was added to a mixture of the dihydrochloride of the compound of formula **JA** (4.69g, 22mmol) and 1-fluoro-2-nitrobenzene (3.10g, 22mmol, Sigma-Aldrich) in THF (30mL) and water (10mL). The resulting reaction mixture was refluxed for 15h. After cooling to a temperature of about 25°C and quenching with water (50mL), the mixture was extracted twice with $CHCl_3$. The organic portions were combined, dried ($MgSO_4$), and concentrated under reduced pressure to provide a residue. The residue was chromatographed with an amino-silica gel column eluted with a gradient of from 30%:70% EtOAc:n-hexane to 100%:0% EtOAc:n-hexane to provide 5.5g of the compound of formula **JB** as an orange solid (yield 93%).

The identity of the compound of formula **JB**, (*endo*)-8-methyl-*N*-(2-nitrophenyl)-8-azabicyclo[3.2.1]octan-3-amine, was confirmed using ^{1}H NMR.

Compound **JB**: ^{1}H NMR: δ_H (300MHz, $CDCl_3$): 8.68 (1H, d, J=6.1Hz), 8.18 (1H, d, J=8.6Hz), 7.41 (1H, dd, J=8.4, 7.4Hz), 6.73 (1H, d, J=8.6Hz), 6.61 (1H, dd, J=8.4, 7.4Hz), 3.81

(1H, q, J=6.8Hz), 3.19 (2H, s), 2.30-2.27 (5H, m), 2.15-2.10 (2H, m), 1.96-1.94 (2H, m), 1.81 (2H, d, J=14.7Hz).

After cooling a mixture of the compound of formula **JB** (5.49g, 20.4mmol) and $CHCl_3$ (55mL) to a temperature of 0°C, 1-chloroethyl chloroformate (3.3mL, 30.6mmol, Sigma-Aldrich) was added and the reaction mixture was refluxed for 2.5h. After cooling to a temperature of about 25°C, the mixture was concentrated under reduced pressure to provide a residue. The residue was mixed with MeOH (55mL) to form a second reaction mixture which was refluxed for 5h. After cooling to a temperature of about 25°C, the mixture was diluted with EtOAc (100mL) and cooled further to 0°C where a precipitate formed. The precipitate was filtered, washed with EtOAc, and dried at 45°C under reduced pressure to provide 4.66g of the hydrochloride of the compound of formula **JC** as a yellow solid (yield 81%).

The identity of the compound of formula **JC**, (*endo*)-*N*-(2-nitrophenyl)-8-azabicyclo[3.2.1]octan-3-amine, was confirmed using ^{1}H NMR.

Compound **JC**: ^{1}H NMR: δ_H (300MHz, DMSO-d_6): 9.22 (2H, br s), 8.39 (1H, d, J=6.6Hz), 8.11 (1H, dd, J=8.6, 1.5Hz), 7.60-7.55 (1H, m), 7.02 (1H, d, J=8.6Hz), 6.75 (1H, t, J=7.9Hz), 4.08-3.98 (3H, m), 2.52-2.49 (4H, m), 2.47-2.40 (2H, m), 2.17-2.08 (4H, m), 2.01 (2H, d, J=15.7Hz).

A reaction mixture of the compound of formula **JC** (3.41g, 12.0mmol), (*Z*)-3-bromocyclooct-1-ene (3.40g, 18.0mmol, Sigma-Aldrich), K_2CO_3 (4.98g, 36.0mmol), and acetonitrile (120mL) was refluxed for 4.5h. After cooling to a temperature of about 25°C and quenching with water (100mL), the mixture was extracted twice with $CHCl_3$. The organic portions were combined, dried ($MgSO_4$), and concentrated under reduced pressure to provide a residue. The residue was recrystallized from EtOAc:n-hexane to provide 3.85g of the compound of formula **JD** as an orange solid (yield 97%).

The identity of the compound of formula **JD**, (*endo*)-8-((*Z*)-cyclooct-2-enyl)-*N*-(2-nitrophenyl)-8-azabicyclo[3.2.1]octan-3-amine, was confirmed using ^{1}H NMR.

Compound **JD**: ^{1}H NMR: δ_H (300MHz, $CDCl_3$): 8.73 (1H, d, J=6.6Hz), 8.19 (1H, dd, J=8.6, 1.5Hz), 7.42-7.39 (1H, m), 6.73 (1H, d, J=8.6Hz), 6.61 (1H, t, J=7.6Hz), 5.77 (1H, dd, J=18.8, 8.1Hz), 5.38 (1H, t, J=9.4Hz), 3.87 (1H, q, J=6.6Hz), 3.57-3.41 (3H, m), 2.33-1.26 (18H, m).

Under a hydrogen atmosphere, a mixture of the compound of formula **JD** (13.8g, 38.8mmol), 10% palladium on carbon (50mg, 0.047mmol), MeOH (10mL), and EtOAc (10mL) was stirred at a temperature of about 25°C for 5h. After the Pd/C was filtered off through cellulose powder, the mixture was washed with MeOH (50mL) and concentrated under reduced pressure to provide the compound of formula **JE**, N^1-((*endo*)-8-((*Z*)-cyclooct-2-enyl)-8-azabicyclo[3.2.1]octan-3-yl)benzene-1,2-diamine, as a brown solid. In a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **70** from the compound of formula **AB** in Example 12, Substituted-Quinoxaline-Type Piperidine Compound **159** was prepared from diethyl 2-oxomalonate and the compound of formula **JE** (yield 20% for two steps).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **159**, ethyl 4-((*endo*)-8-((*Z*)-cyclooct-2-enyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

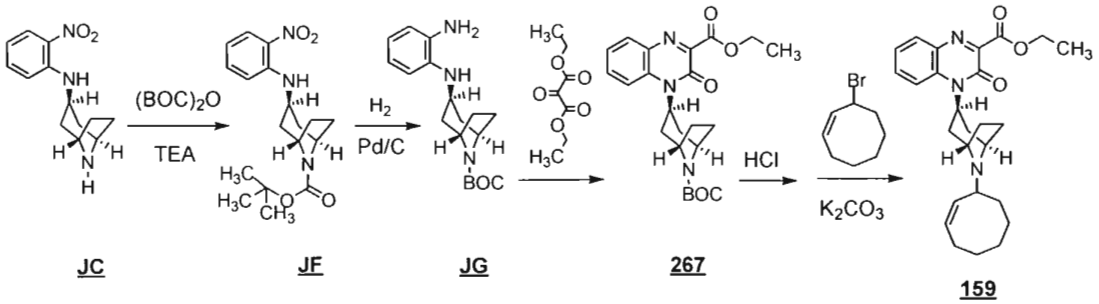
Substituted-Quinoxaline-Type Piperidine Compound **159**: ^{1}H NMR: δ_H (300MHz, $CDCl_3$): 7.88 (1H, dd, J=8.11, 1.52Hz), 7.79-7.75 (1H, m), 7.66 (1H, d, J=9.12Hz), 7.44 (1H, t, J=7.86Hz), 5.72 (1H, dd, J=18.25, 8.11Hz), 5.38 (2H, t, J=9.63Hz), 4.41-4.34 (2H, m), 3.71 (1H, t, J=7.6Hz), 3.51 (1H, t, J=7.86Hz), 3.19 (1H, dd, J=15.97, 8.36Hz), 2.30-2.22 (2H, m), 2.13-1.55 (14H, m), 1.39-1.18 (8H, m); LC/MS: *m/z*=435.9 $[M+H]^+$ (Calc: 435.3).

The hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **135** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **159** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **174** in Example 7 (yield 73%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **135**, 4-((*endo*)-8-((*Z*)-cyclooct-2-enyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **135**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 11.05 (1H, s), 8.09 (1H, d, J=8.11Hz), 7.90 (1H, dd, J=7.86, 1.27Hz), 7.76 (1H, t, J=7.35Hz), 7.47 (1H, t, J=7.6Hz), 6.05 (2H, dt, J=23.66, 7.98Hz), 5.85 (1H, t, J=9.63Hz), 4.37 (1H, t, J=7.1Hz), 4.01 (1H, s), 3.85 (1H, s), 2.63 (2H, dd, J=21.54, 9.38Hz), 2.36-1.91 (9H, m), 1.72 (3H, m), 1.31 (3H, m); LC/MS (98%, t_r=1.31min): *m/z*=408.2 $[M+H]^+$ (Calc: 407.5).

Alternatively, Substituted-Quinoxaline-Type Piperidine Compound **159** was prepared by the following route.



To a mixture of the compound of formula **JC** (2012mg, 7.09mmol) and CH_2Cl_2 (20mL) at 0°C was added TEA (2.95mL, 21.3mmol) and di-*tert*-butyl dicarbonate (1.81μL, 7.80mmol). The resulting reaction mixture was stirred at 0°C for 2h then concentrated under reduced pressure, diluted with water (20mL), and extracted three times with EtOAc (20mL for each extraction). The organic portions were combined, washed with saturated aqueous $NaHCO_3$ (10mL), washed with saturated aqueous NaCl (10mL), dried ($MgSO_4$), and concentrated under reduced pressure to provide an oil. The oil was chromatographed with a silica gel column eluted with 2:1 hexanes:EtOAc to provide 2421mg of the compound of formula **JF** as a yellow amorphous solid (yield 98%).

The identity of the compound of formula **JF**, (*endo*)-*tert*-butyl 3-(2-nitrophenylamino)-8-azabicyclo[3.2.1]octane-8-carboxylate, was confirmed using ^1H NMR and LC/MS.

Compound **JF**: ^1H NMR: δ_H (400MHz, DMSO): 8.60 (1H, d, J=8.0Hz), 8.10 (1H, d, J=8.0Hz), 7.55(1H, t, J=8.0Hz), 6.96 (1H, d, J=8.0Hz), 6.71 (1H, t, J=8.0Hz), 4.12 (2H, m), 4.03 (1H, m), 2.20 (2H, m), 2.06-1.90 (4H, m), 1.80 (2H, m), 1.43 (9H, s); LC/MS (100%, t_r=2.99min): *m/z*=348 $[M+H]^+$ (Calc: 347.2).

In a manner similar to the preparation of the compound of formula **CC** in Example 6, the compound of formula **JG** was prepared except that the compound of formula **JF** was used in place of the compound of formula **CB** (yield 85%).

The identity of the compound of formula **JG**, (*endo*)-*tert*-butyl 3-(2-aminophenylamino)-8-azabicyclo[3.2.1]octane-8-carboxylate, was confirmed using ^1H NMR and LC/MS.

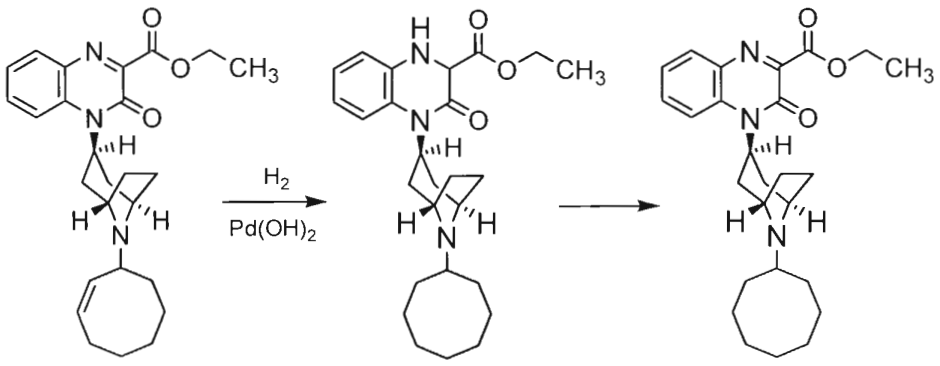
Compound **JG**: ^{1}H NMR: δ_H (400MHz, DMSO): 6.58 (1H, d, J=8.0Hz), 6.50 (2H, m), 6.34 (1H, d, J=8.0Hz), 4.49 (2H, s), 4.25 (1H, s), 4.03 (2H, m), 3.59 (1H, m), 2.13 (2H, d, J=8.0Hz), 2.04 (2H, m), 1.90-1.70 (4H, m), 1.42 (9H, s); LC/MS (100%, t_r=1.91min): *m/z*=318 $[M+H]^+$ (Calc: 317.2).

In a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **70** from the compound of formula **AB** in Example 12, Substituted-Quinoxaline-Type Piperidine Compound **267** was prepared from diethyl 2-oxomalonate and the compound of formula **JG** (yield 92%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **267**, ethyl 4-((*endo*)-8-(*tert*-butoxycarbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **267**: ^{1}H NMR: δ_H (400MHz, DMSO): 7.90 (1H, d, J=8.0Hz), 7.77 (1H, t, J=8.0Hz), 7.57 (1H, J=8.0Hz), 7.46 (1H, t, J=8.0Hz), 4.36 (2H, q, J=8.0Hz), 4.27 (2H, m), 2.37 (2H, m), 2.18 (2H, m), 2.02 (2H, m), 1.89 (2H, m), 1.48 (9H, s), 1.33 (3H, t, J=8.0Hz); LC/MS (100%, t_r=2.48min): *m/z*=428 $[M+H]^+$ (Calc: 427.2).

In a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **5** in Example 7, Substituted-Quinoxaline-Type Piperidine Compound **267** was treated with 4N HCl in dioxane to remove the BOC group; after concentration under reduced pressure, the resulting solid was reacted with (*Z*)-3-bromocyclooct-1-ene in a manner similar to the preparation of the compound of formula **JD** described above to provide Substituted-Quinoxaline-Type Piperidine Compound **159** (yield 68% for two steps).



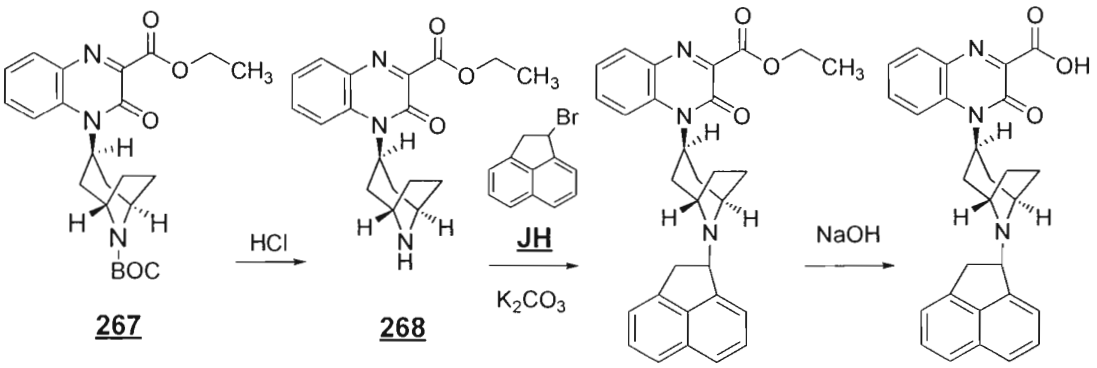
159 **389** **153**

Under a hydrogen atmosphere at a pressure of 4 Kgf/cm^2, a mixture of Substituted-Quinoxaline-Type Piperidine Compound **159** (124mg, 0.285mmol), 20% $Pd(OH)_2$ (24mg, Sigma-Aldrich), and MeOH (12mL) was stirred at 50°C for 8h. After the $Pd(OH)_2$ was filtered off, the filtrate was washed with EtOAc and concentrated under reduced pressure to provide Substituted-Quinoxaline-Type Piperidine Compound **389**, ethyl 4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-1,2,3,4-tetrahydroquinoxaline-2-carboxylate.

A mixture of the above Substituted-Quinoxaline-Type Piperidine Compound **389** and xylene (4mL) was stirred at 130°C for 5 days. After concentration under reduced pressure, the residue was chromatographed with a silica gel column eluted with 10:1 $CHCl_3$:MeOH to provide 113mg of Substituted-Quinoxaline-Type Piperidine Compound **153** as a yellow solid (yield 91% for two steps).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **153** was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **153**: ^{1}H NMR: δ_H (400MHz, DMSO): 7.88 (1H, d, J=8.0Hz), 7.77 (1H, t, J=8.0Hz), 7.63 (1H, d, J=8.0Hz), 7.44 (1H, t, J=8.0Hz), 5.20 (1H, br), 4.37 (2H, q, J=8.0Hz), 3.63 (2H, m), 2.36 (1H, m), 2.26 (2H, m), 2.06 (2H, m), 1.99 (2H, m), 1.85-1.20 (16H, m), 1.32 (3H, t, J=8.0Hz); LC/MS (100%, t_r=1.63min): *m/z*=438 $[M+H]^+$ (Calc: 437.3).



267 **268** **269** **270**

In a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **5** in Example 7, Substituted-Quinoxaline-Type Piperidine Compound **268** was prepared by treating Substituted-Quinoxaline-Type Piperidine Compound **267** with 4N HCl in dioxane to remove the BOC group (yield >98%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **268**, ethyl 4-((*endo*)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **268**: LC/MS: *m/z*=328 $[M+H]^+$ (Calc: 327).

In a manner similar to the preparation of the compound of formula **JD** described above, Substituted-Quinoxaline-Type Piperidine Compound **269** was prepared except that the compound of formula **JH** was used in place of (*Z*)-3-bromocyclooct-1-ene (yield 39%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **269**, ethyl 4-((*endo*)-8-(1,2-dihydroacenaphthylen-1-yl)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **269**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.90 (1H, d, J=7.6Hz), 7.68 (2H, dd, J=27.37, 8.11Hz), 7.58-7.47 (5H, m), 7.32 (2H, dd, J=11.91, 6.84Hz), 4.54-4.47 (3H, m), 4.08 (1H, br), 3.64-3.51 (2H, m), 3.27 (1H, d, J=16.73Hz), 2.33-1.98 (9H, m), 1.58 (3H, s), 1.44 (3H, t, J=7.1Hz); LC/MS: *m/z*=480 $[M+H]^+$ (Calc: 479).

Substituted-Quinoxaline-Type Piperidine Compound **270** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **269** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **111** in Example 5 (yield 84%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **270**, 4-((*endo*)-8-(1,2-dihydroacenaphthylen-1-yl)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

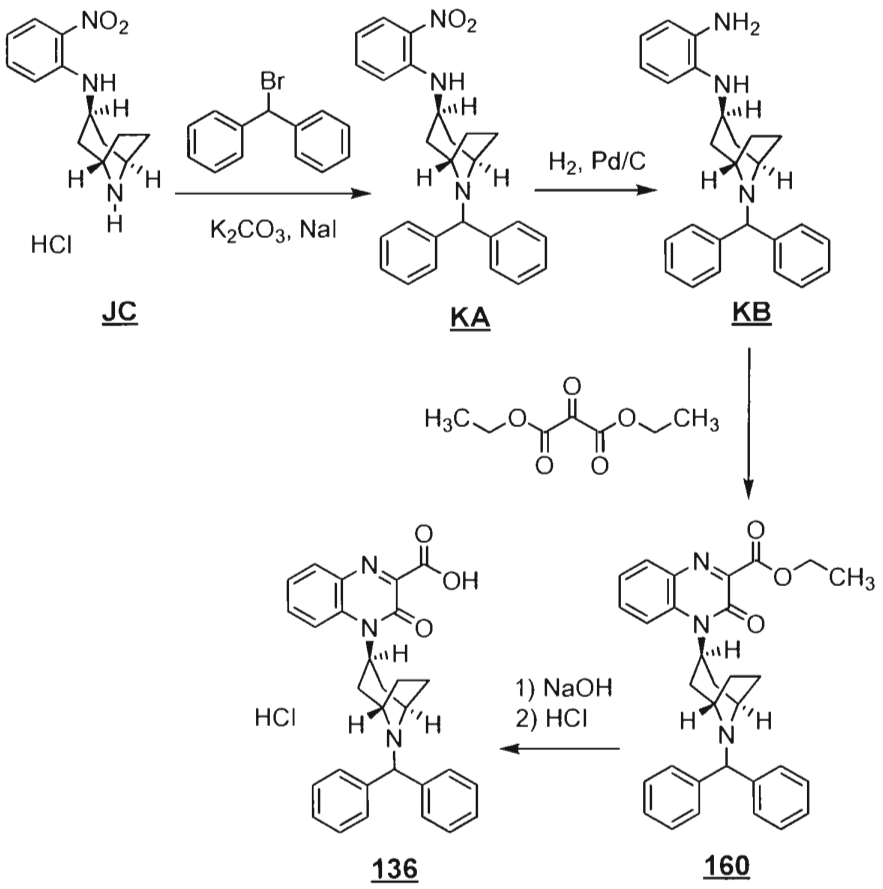
Substituted-Quinoxaline-Type Piperidine Compound **270**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 7.83-7.52 (8H, m), 7.42-7.37 (2H, m), 5.18 (1H, s), 4.73 (1H, brz), 4.21 (1H, br), 3.84-3.82 (1H, m), 3.65 (2H, br), 2.33-1.99 (8H, m); LC/MS (100%, t_r=1.45min): *m/z*=452 $[M+H]^+$ (Calc: 451).

The compound of formula **JH** was prepared as follows:

JH

Under a nitrogen atmosphere and at a temperature of about 25°C, a 1M solution of tribromophosphine in CH_2Cl_2 (2.350mL, 2.350mmol, Sigma-Aldrich) was added to a suspension of 1,2-dihydroacenaphthylen-1-ol (1000mg, 5.88mmol, Sigma-Aldrich) in diethyl ether (8mL). The resulting reaction mixture was stirred at a temperature of about 25°C for 30min; a yellow precipitate formed. After quenching with saturated aqueous $NaHCO_3$, the pH was adjusted to be within the range of from about 7 to about 8. Thereafter, the mixture was extracted twice with EtOAc:water (70mL for each extraction), dried ($MgSO_4$), concentrated under reduced pressure, and dried to provide 1350mg of the compound of formula **JH**, 1-bromo-1,2-dihydroacenaphthylene, as a pale yellow solid (yield 99%).

5.33 Example 33



JC KA KB

136 160

Under a nitrogen atmosphere at a temperature of about 25°C, K_2CO_3 (1218mg, 8.81mmol), sodium iodide (52.8mg, 0.352mmol), and (bromomethylene)dibenzene (523mg, 2.115mmol, Sigma-Aldrich) were added to a mixture of the compound of formula **JC** (500mg, 1.762mmol) and acetonitrile (10mL). The resulting reaction mixture was heated with stirring at 90°C for 1h. The reaction mixture was diluted with water (5mL), extracted twice with $CHCl_3$ (50mL for each extraction), washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to provide a yellow oil. The oil was chromatographed with an amino-silica gel column eluted with a gradient of from 0%:100% EtOAc:n-hexane to 20%:80% EtOAc:n-hexane to provide 464mg of the compound of formula **KA** as an orange solid (yield 64%).

The identity of the compound of formula **KA**, (*endo*)-8-benzhydryl-*N*-(2-nitrophenyl)-8-azabicyclo[3.2.1]octan-3-amine, was confirmed using ^{1}H NMR and LC/MS.

Compound **KA**: ^{1}H NMR: δ_H (300MHz, DMSO-d_6): 8.58 (1H, d, J=7.1Hz), 8.07 (1H, dd, J=8.62, 1.52Hz), 7.54 (5H, dd, J=9.89, 4.31Hz), 7.29 (4H, t, J=7.6Hz), 7.17 (2H, t, J=7.35Hz), 6.93 (1H, d, J=8.62Hz), 6.70-6.65 (1H, m), 4.62 (1H, s), 4.02 (1H, dd, J=6.84, 4.82Hz), 3.07 (2H, s), 2.25 (2H, m), 2.10 (2H, m), 1.83 (2H, dd, J=14.70, 6.59Hz), 1.65 (2H, d, J=13.69Hz); LC/MS: *m/z*=413.8 $[M+H]^+$ (Calc: 413.2).

In a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **135** from the compound of formula **KD** in Example 32, the compound of formula **KB** was prepared from the compound of formula **KA** (yield 90%), Substituted-Quinoxaline-Type Piperidine Compound **160** was prepared from the compound of formula **KB** and diethyl 2-oxomalonate (yield 49%), and the hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **136** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **160** (yield 70%).

The identity of the compound of formula **KB**, N^1-((*endo*)-8-benzhydryl-8-azabicyclo[3.2.1]octan-3-yl)benzene-1,2-diamine, was confirmed using ^{1}H NMR and LC/MS.

Compound **KB**: ^{1}H NMR: δ_H (300MHz, DMSO-d_6): 7.52 (2H, d, J=7.6Hz), 7.30-7.14 (8H, m), 6.58-6.29 (4H, m), 4.44 (2H, s), 4.12 (1H, s), 3.58 (1H, m), 2.99 (1H, s), 2.14-1.91 (5H, m), 1.65 (3H, m); LC/MS: *m/z*=383.9 $[M+H]^+$ (Calc: 383.2).

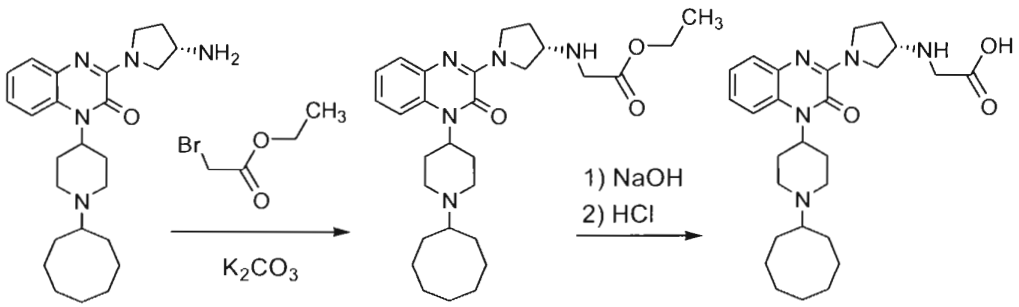
The identity of Substituted-Quinoxaline-Type Piperidine Compound **160**, ethyl 4-((*endo*)-8-benzhydryl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **160**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 7.91-7.16 (14H, m), 4.47 (1H, s), 4.36 (2H, q, J=6.9Hz), 2.52 (1H, m), 2.33-1.99 (6H, m), 1.75 (2H, m), 1.33 (3H, t, J=6.9Hz); LC/MS: *m/z*=494.0 $[M+H]^+$ (Calc: 493.2).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **136**, 4-((*endo*)-8-benzhydryl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **136**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 14.02 (0.7H, br), 10.95 (0.3H, br), 8.15-7.19 (14H, m), 6.19 (0.3H, br), 5.42 (0.7H, br), 4.47 (0.4H, s), 3.77 (0.6H, s), 2.69 (1H, m), 2.39-2.10 (6H, m), 1.77 (1H, s); LC/MS (96%, t_r=2.25min): *m/z*=466.2 $[M+H]^+$ (Calc: 465.5).

5.34 Example 34



165 **163** **112**

At a temperature of 0°C, ethyl 2-bromoacetate (20.2μL, 0.182mmol) and K_2CO_3 (25.2mg, 0.182mmol) were added to a mixture of Substituted-Quinoxaline-Type Piperidine Compound **165** (70mg, 0.165mmol) in THF (3mL). The resulting reaction mixture was stirred at 0°C for 2h. After warming it to 50°C, the reaction mixture was stirred at 50°C for 2h. After cooling to about 25°C, the mixture was diluted with water (10mL) and extracted twice with EtOAc (10mL for each extraction). The organic portions were combined, washed with brine (10mL), dried ($MgSO_4$), and concentrated under reduced pressure to provide a residue. The residue was chromatographed with a silica gel column eluted with 10:1 $CHCl_3$:MeOH to

provide 53mg of Substituted-Quinoxaline-Type Piperidine Compound **163** as a white solid (yield 63%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **163**, (*S*)-ethyl 2-(1-(4-(1-cyclooctylpiperidin-4-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)pyrrolidin-3-ylamino)acetate, was confirmed using ^{1}H NMR and LC/MS.

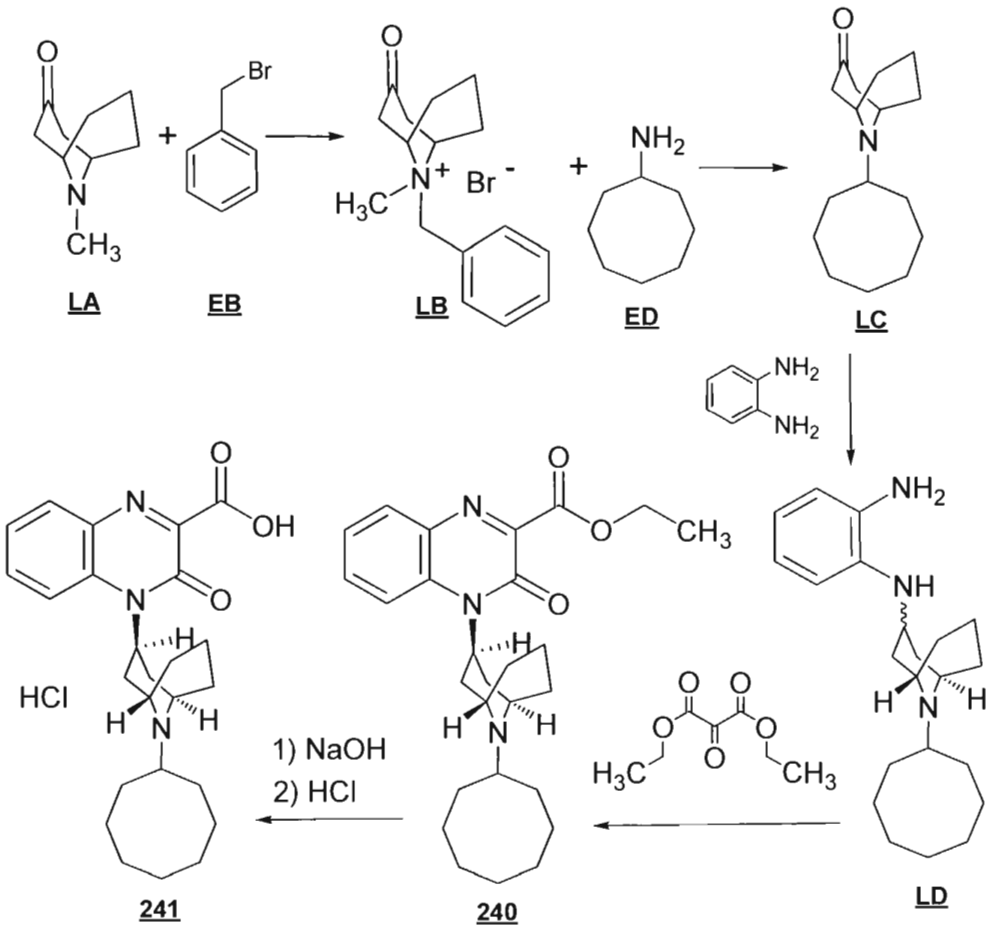
Substituted-Quinoxaline-Type Piperidine Compound **163**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.55 (1H, m), 7.45 (1H, d, J=8Hz), 7.10 (2H, m), 4.95 (1H, br), 4.20 (2H, q, J=8Hz), 4.30-3.90 (3H, m), 3.82 (1H, m), 3.46 (2H, s), 3.43 (1H, m), 2.98 (2H, m), 2.79 (2H, m), 2.68 (1H, m), 2.44 (2H, m), 2.10 (1H, m), 2.00-1.40 (18H, m), 1.60 (3H, t, J=8Hz); LC/MS (98%, t_r=1.08min): *m/z*=510.2 $[M+H]^+$ (Calc: 509.3).

Substituted-Quinoxaline-Type Piperidine Compound **112** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **163** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **111** in Example 5 (yield 96%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **112**, (*S*)-2-(1-(4-(1-cyclooctylpiperidin-4-yl)-3-oxo-3,4-dihydroquinoxalin-2-yl)pyrrolidin-3-ylamino)acetic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **112**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 7.97 (1H, br), 7.36 (1H, d, J=8Hz), 7.17 (2H, m), 5.00 (1H, br), 4.30-3.10 (9H, m), 2.20 (2H, m), 2.10 (3H, m), 1.92 (2H, d, J=4Hz), 1.90-1.40 (16H, m); LC/MS (100%, t_r=1.07min): *m/z*=482.2 $[M+H]^+$ (Calc: 481.3).

5.35 Example 35



A mixture of the compound of formula **LA** (10.00g, 65.4mmol, Trans World Chemicals, Inc., Rockville, MD) and the compound of formula **EB** (11.17g, 65.4mmol) was refluxed in acetone (150mL) for 3h, cooled, filtered, washed twice with diethyl ether (30mL for each wash), washed twice with hexanes (30mL for each wash), and dried under reduced pressure to provide 10g of the compound of formula **LB**, 9-methyl-9-benzyl-9-azabicyclo[3.3.1]nonan-3-one bromide, as white solid (yield 47%).

In a manner similar to Example 14, the *endo:exo* isomeric mixture of the compound of formula **LD**, N^1-(9-cyclooctyl-9-azabicyclo[3.3.1]nonan-3-yl)benzene-1,2-diamine, was prepared except that the compound of formula **LB** was used in place of the compound of formula **EC**. Thereafter, Substituted-Quinoxaline-Type Piperidine Compound **240** was prepared from diethyl 2-oxomalonate in a manner similar to Example 12 except that the

compound of formula **LD** was used in place of the compound of formula **AB** (overall yield 7%).

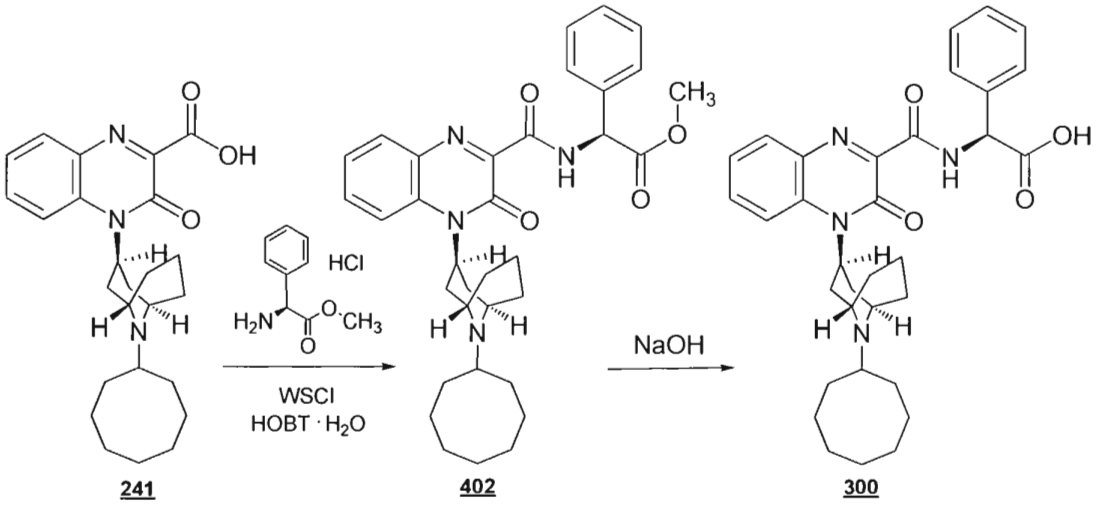
The identity of Substituted-Quinoxaline-Type Piperidine Compound **240**, ethyl 4-((*endo*)-9-cyclooctyl-9-azabicyclo[3.3.1]nonan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR, LC/MS and LC.

Substituted-Quinoxaline-Type Piperidine Compound **240**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.92 (d, 1H, J=8.2Hz), 7.58-7.66 (m, 2H), 7.36 (dd, 1H, J=8.1, 8.2Hz), 5.16 (br, 1H), 4.52 (t, 2H, J=7.0Hz), 3.48-3.53 (m, 2H), 3.02-3.06 (m, 1H), 2.72-2.74 (m, 2H), 2.38-2.44 (m, 1H), 1.98-2.04 (m, 2H), 1.4-1.8 (m, 25H), 1.12-1.15 (m, 2H); LC/MS (98.7%, t_r=7.534min): *m/z*=452.7 $[M+H]^+$ (Calc: 451.6); LC (SiO_2) 1:2 then 3:1 Et_2O:hexanes: Rf=0.5 with UV detection, Dragendorff's reagent.

In a manner similar to Example 7, the hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **241** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **240** (yield 40%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **241**, 4-((*endo*)-9-cyclooctyl-9-azabicyclo[3.3.1]nonan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **241**: ^{1}H NMR: δ_H (400MHz, 1:3 $CDCl_3$:CD_3OD): 8.45 (d, 1H, J=8.8Hz), 8.02 (dd, 1H, J=1.5, 8.1Hz), 7.82-7.86 (m, 1H), 7.5 (dd, 1H, 7.5, 7.9Hz), 5.96-6.04(m, 1H), 4.16-4.22 (m, 2H), 3.80-3.86 (m, 1H), 3.04-3.08 (m, 2H), 2.78-2.84 (m, 1H), 2.48-2.54 (m, 2H), 1.6-2.2 (m, 24H); LC/MS (98.7%, t_r=5.612min): *m/z*=424.6 $[M+H]^+$.



In a manner similar to Example 21, Substituted-Quinoxaline-Type Piperidine Compound **402** was prepared by using Substituted-Quinoxaline-Type Piperidine Compound **241** in place of Substituted-Quinoxaline-Type Piperidine Compound **74** and (*S*)-(+)-methyl 2-amino-2-phenylacetate hydrochloride in place of 4-methoxyaniline (yield 60%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **402**, (*S*)-methyl 2-(4-((*endo*)-9-cyclooctyl-9-azabicyclo[3.3.1]nonan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamido)-2-phenylacetate, was confirmed using LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **402**: LC/MS: *m/z*=571 $[M+H]^+$ (Calc: 570).

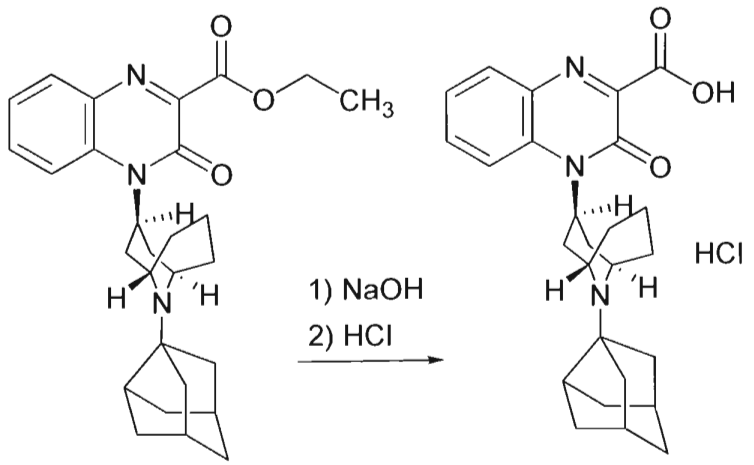
Substituted-Quinoxaline-Type Piperidine Compound **300** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **402** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **111** in Example 5 (yield 81%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **300**, (*S*)-2-(4-((*endo*)-9-cyclooctyl-9-azabicyclo[3.3.1]nonan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamido)-2-phenylacetic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **300**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 9.56 (d, 1H, J=7.0Hz), 8.35 (s, 1H), 7.89 (d, 1H, J=7.8Hz), 7.70-7.74 (m, 1H), 7.31-7.51 (m, 7H), 5.84 (s, 1H), 5.52 (d, 1H, J=7.0Hz)4.02 (s, 2H), 1.29-3.58 (m, 25H); LC/MS: *m/z*=557 $[M+H]^+$ (Calc: 556).

5.36 Example 36

In a manner similar to Example 35, the following Substituted-Quinoxaline-Type Piperidine Compounds were prepared from the compound of formula **LB**.



262 **263**

Substituted-Quinoxaline-Type Piperidine Compound **262** (yield 19% for three steps) and the hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **263** (yield 90%) were prepared by using 3-noradamantamine hydrochloride (Sigma-Aldrich) in place of the compound of formula **ED**.

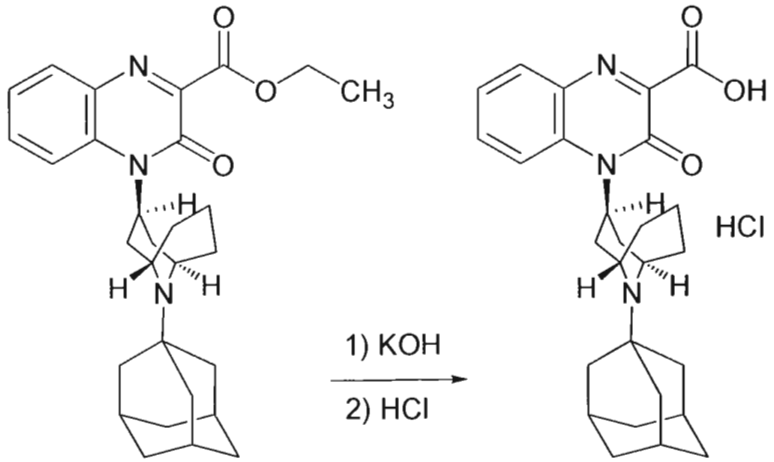
The identity of Substituted-Quinoxaline-Type Piperidine Compound **262**, *endo*-4-(9-(hexahydro-2,5-methano-pentalen-3a-yl)-9-aza-bicyclo[3.3.1]non-3-yl)-3-oxo-3,4-dihydro-quinoxaline-2-carboxylic acid ethyl ester, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **262**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.93 (1H, d, J=8Hz), 7.63 (1H, t, J=8Hz), 7.55 (1H, bs), 7.36 (1H, t, J=8Hz), 4.52 (2H, q, J=8.5Hz), 3.55 (2H, m), 2.73-2.38 (3H, m), 2.32 (2H, s), 2.22 (1H, t, J=8Hz), 2.03-1.50 (18H, m), 1.46 (3H, t, J=8Hz).1.36 (2H, m); LC/MS: m/z=462.6 $[M+H]^+$.

The identity of Substituted-Quinoxaline-Type Piperidine Compound **263**, 4-(9-(hexahydro-2,5-methano-pentalen-3a-yl)-9-aza-bicyclo[3.3.1]non-3-yl)-3-oxo-3,4-dihydro-quinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **263**: ^{1}H NMR: δ_H (600MHz, $(CD_3)_2SO$): 14.05 (1H, bs), 7.91 (1H, bd), 7.80 (1H, bt), 7.69 (1H, bs), 7.48 (1H, bt), 4.85 (1H, bs), 3.55 (2H, m), 2.50-2.20 (6H, m), 2.12-1.52 (15H, m), 1.36 (2H, m); LC/MS (100%): m/z=434.2 $[M+H]^+$.

In a manner similar to Example 35, the following Substituted-Quinoxaline-Type Piperidine Compounds were prepared from the compound of formula **LB** except that KOH replaced NaOH in the de-esterification step.



390 **333**

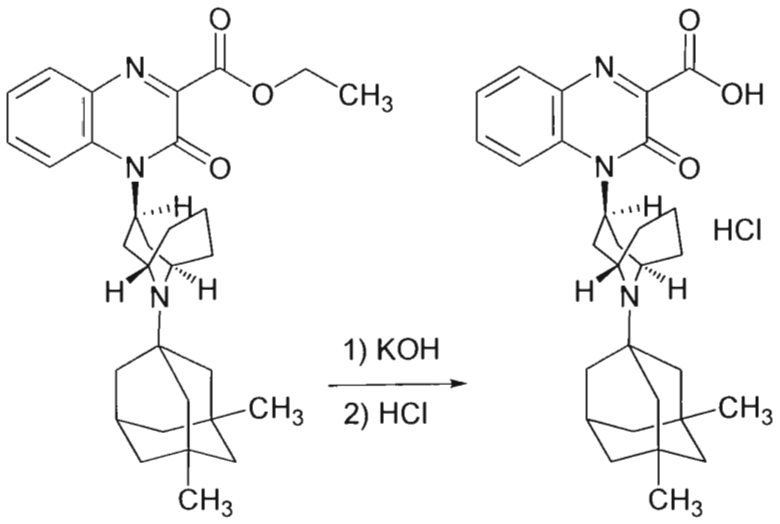
Substituted-Quinoxaline-Type Piperidine Compound **390** and the hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **333** were prepared by using 1-adamantylamine in place of the compound of formula **ED**.

The identity of Substituted-Quinoxaline-Type Piperidine Compound **390**, *endo*-4-(9-adamantan-1-yl)-9-aza-bicyclo[3.3.1]non-3-yl)-3-oxo-3,4-dihydro-quinoxaline-2-carboxylic acid ethyl ester, was confirmed using LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **390**: LC/MS (96.1%, t_r=2.374min): *m/z*=476.6 $[M+H]^+$ (Calc: 475.6).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **333**, *endo*-4-(9-adamantan-1-yl)-9-aza-bicyclo[3.3.1]non-3-yl)-3-oxo-3,4-dihydro-quinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **333**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 14.19 (1H, s), 9.21 (1H, m), 8.98 (1H, s), 8.21 (1H, m), 7.99 (1H, m), 7.59 (1H, m), 7.01 (1H, m), 4.31 (2H, s), 3.06 (1H, m), 2.79 (4H, m), 2.57 (6H, s), 2.31 (5H, m), 1.81 (9H, m); LC/MS (100%, t_r=5.604min): *m/z*=448.5 $[M+H]^+$ (Calc: 447.6).



391 **334**

Substituted-Quinoxaline-Type Piperidine Compound **391** (yield 9.1% for three steps) and the hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **333** (yield 38%) were prepared by using the hydrochloride of memantine (Sigma-Aldrich) in place of the compound of formula **ED**.

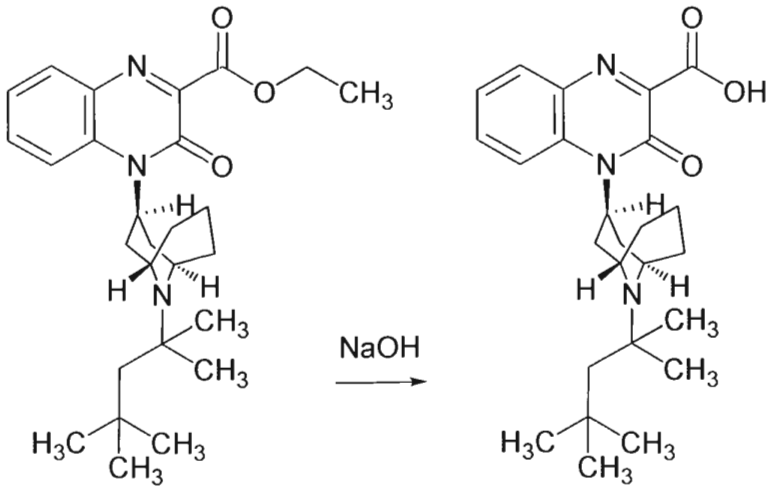
The identity of Substituted-Quinoxaline-Type Piperidine Compound **391**, *endo*-4-[9-(3,5-dimethyl-adamantan-1-yl)-9-aza-bicyclo[3.3.1]non-3-yl]-3-oxo-3,4-dihydro-quinoxaline-2-carboxylic acid ethyl ester, was confirmed using LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **391**: LC/MS (92.7%, t_r=2.453min): *m/z*=504.2 $[M+H]^+$ (Calc: 503.7).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **334**, *endo*-4-[9-(3,5-dimethyl-adamantan-1-yl)-9-aza-bicyclo[3.3.1]non-3-yl]-3-oxo-3,4-dihydro-quinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **334**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 14.09 (1H, s), 9.20 (1H, m), 9.08 (1H, s), 8.21 (1H, m), 8.00 (1H, m), 7.59 (1H, m), 7.01 (1H, m), 4.28 (2H, s), 3.17 (1H, m), 2.78 (4H, m), 2.39 (3H, s), 2.28 (2H, m), 2.20 (4H, s), 1.80 (3H, m), 1.60 (1H, s), 1.51 (2H, m), 1.18-1.45 (5H, m), 0.98 (3H, s); LC/MS (100%, t_r=7.12min): *m/z*=476.5 $[M+H]^+$ (Calc: 475.6).

In a manner similar to Example 35, the following Substituted-Quinoxaline-Type Piperidine Compounds were prepared from the compound of formula **LB** except that the final HCl treatment was omitted.



285 **286**

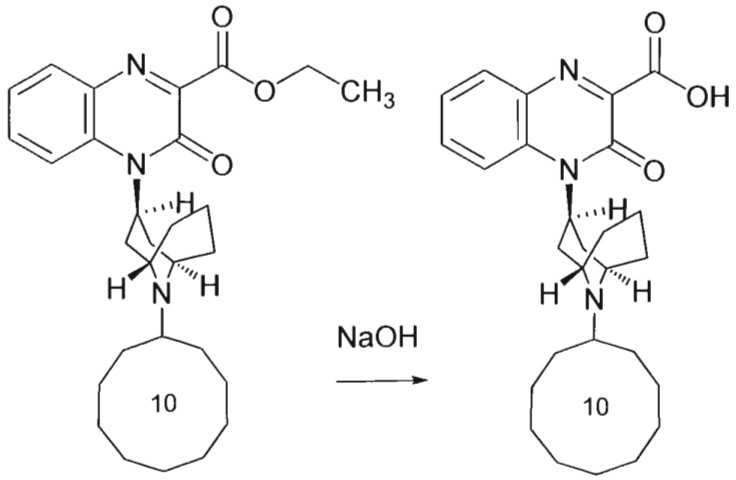
Substituted-Quinoxaline-Type Piperidine Compounds **285** (yield 0.42% for three steps) and **286** (yield 92%) were prepared by using 2,4,4-trimethylpentan-2-amine (Sigma-Aldrich) in place of the compound of formula **ED**.

The identity of Substituted-Quinoxaline-Type Piperidine Compound **285**, ethyl 3-oxo-4-((*endo*)-9-(2,4,4-trimethylpentan-2-yl)-9-azabicyclo[3.3.1]nonan-3-yl)-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **285**: ^{1}H NMR: δ_H ($CDCl_3$): 7.92 (1H, d, J=7.6Hz), 7.60 (2H, m), 7.35 (1H, t, J=7.6Hz), 4.80 (1H, m), 4.51 (2H, q, J=7.2Hz), 3.71 (2H, m), 2.58 (3H, m), 1.94 (2H, m), 1.70 (3H, m), 1.57 (3H, s), 1.45 (3H, t, J=7.2Hz), 1.32 (2H, m), 1.31 (6H, s), 1.04 (9H, s); LC/MS: *m/z*=454 $[M+H]^+$ (Calc: 453.6).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **286**, 3-oxo-4-((*endo*)-9-(2,4,4-trimethylpentan-2-yl)-9-azabicyclo[3.3.1]nonan-3-yl)-3,4-dihydroquinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **286**: ^{1}H NMR: δ_H ($DMSO-d_6$): 7.87 (1H, d, J=7.6Hz), 7.74 (1H, t, J=7.6Hz), 7.62 (1H, br), 7.44 (1H, t, J=7.6Hz), 4.80 (1H, br), 3.68 (2H, m), 2.40 (3H, m), 1.95 (2H, m), 1.65 (3H, m), 1.55 (2H, s), 1.27 (6H, s), 1.25 (2H, m), 1.05 (9H, s); LC/MS (98%, t_r=2.09min): *m/z*=426 $[M+H]^+$ (Calc: 425.6).



287 **288**

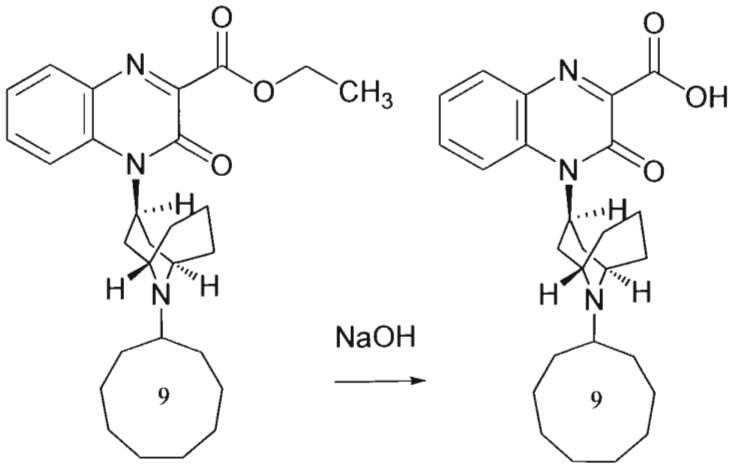
Substituted-Quinoxaline-Type Piperidine Compounds **287** and **288** were prepared by using cyclodecanamine (Sigma-Aldrich) in place of the compound of formula **ED**.

The identity of Substituted-Quinoxaline-Type Piperidine Compound **287**, ethyl 4-((*endo*)-9-cyclodecyl-9-azabicyclo[3.3.1]nonan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **287**: ^{1}H NMR: δ_H ($CDCl_3$): 7.93 (1H, d, J=8.0Hz), 7.66-7.52 (2H, m), 7.36 (1H, m), 5.11 (1H, br), 4.51 (2H, q, J=7.2Hz), 3.51 (2H, d, J=11.15Hz), 3.05 (1H, m), 2.71 (2H, m), 2.39 (1H, m), 2.01 (2H, m), 1.82-1.40 (29H, m), 1.15 (2H, m); LC/MS: *m/z*=480 $[M+H]^+$ (Calc: 479.6).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **288**, 4-((*endo*)-9-cyclodecyl-9-azabicyclo[3.3.1]nonan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **288**: ^{1}H NMR: δ_H ($CDCl_3$, DCl): 8.70 (0.2H, m), 8.17 (0.8H, m), 7.93 (1H, m), 7.69 (1H, m), 7.29 (1H, m), 6.10 (1H, br), 4.18 (2H, m), 3.60 (2H, br), 3.05 (2H, m), 2.89 (1H, m), 2.60 (2H, m), 2.20 (4H, m), 1.90-1.40 (18H, m); LC/MS (100%, t_r=1.87min): *m/z*=452 $[M+H]^+$ (Calc: 454.6).



289 **290**

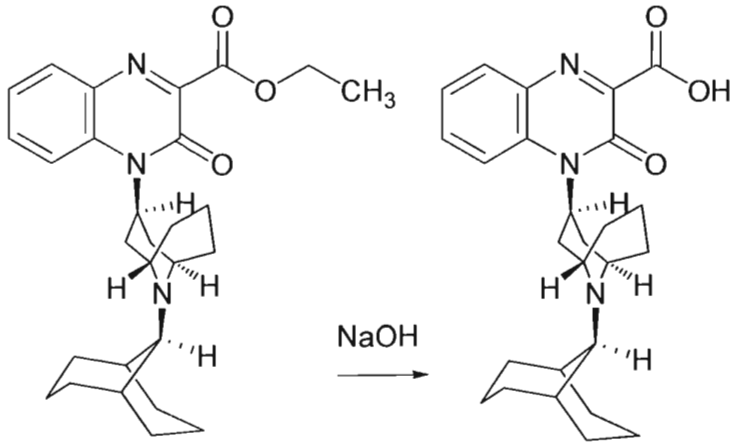
Substituted-Quinoxaline-Type Piperidine Compounds **289** and **290** were prepared by using cyclononanamine (Sigma-Aldrich) in place of the compound of formula **ED**.

The identity of Substituted-Quinoxaline-Type Piperidine Compound **289**, ethyl 4-((*endo*)-9-cyclononyl-9-azabicyclo[3.3.1]nonan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **289**: ^{1}H NMR: δ_H ($CDCl_3$): 7.93 (1H, d, J=8.11Hz), 7.63 (2H, m), 7.36 (1H, t, J=8.11Hz), 5.18 (1H, br), 4.51 (2H, q, J=7.1Hz), 3.51 (2H, d, J=10.65Hz), 3.04 (1H, m), 2.73 (2H, m), 2.40 (1H, m), 2.00 (2H, m), 1.82-1.43 (22H, m), 1.14 (2H, m); LC/MS: *m/z*=466 $[M+H]^+$ (Calc: 465.6).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **290**, 4-((*endo*)-9-cyclononyl-9-azabicyclo[3.3.1]nonan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **290**: ^{1}H NMR: δ_H ($CDCl_3$): 8.11 (1H, m), 7.87 (1H, d, J=8.11Hz), 7.57 (1H, m), 7.25 (1H, m), 6.03 (1H, br), 4.16 (2H, s), 3.69 (1H, s), 3.08-2.89 (3H, m), 2.57 (2H, m), 2.23-1.38 (21H, m); LC/MS (100%, t_r=1.67min): *m/z*=438 $[M+H]^+$ (Calc: 437.6).



291 **292**

Substituted-Quinoxaline-Type Piperidine Compounds **291** and **292** were prepared by using (*exo*)-bicyclo[3.3.1]nonan-9-amine (Sigma-Aldrich) in place of the compound of formula **ED**.

The identity of Substituted-Quinoxaline-Type Piperidine Compound **291**, ethyl 4-((*endo*)-9-((*exo*)-bicyclo[3.3.1]nonan-9-yl)-9-azabicyclo[3.3.1]nonan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

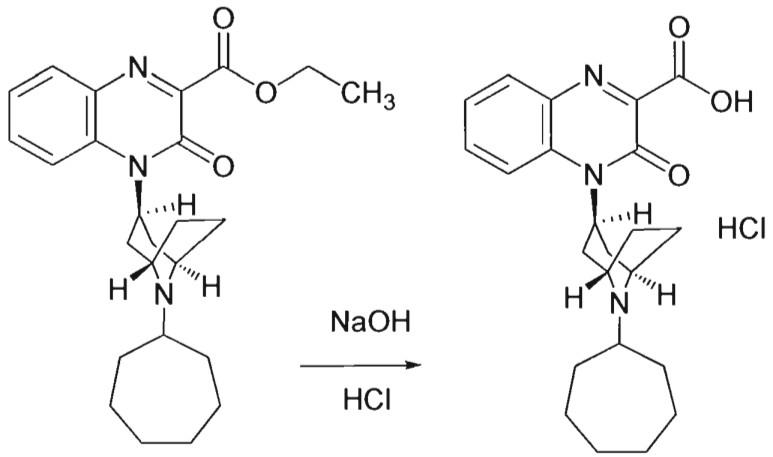
Substituted-Quinoxaline-Type Piperidine Compound **291**: ^{1}H NMR: δ_H ($CDCl_3$): 7.93 (1H, d, J=8.11Hz), m), 7.36 (1.1H, t, J=7.35Hz), 5.28 (1H, m), 4.51 (2H, q, J=7.1Hz), 3.55 (2H, m), 2.81 (3H, m), 2.36 (1H, m), 2.09-1.41 (22H, m), 1.07 (2H, d, J=12.67Hz); LC/MS: *m/z*=464 $[M+H]^+$ (Calc: 463.6).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **292**, 4-((*endo*)-9-((*exo*)-bicyclo[3.3.1]nonan-9-yl)-9-azabicyclo[3.3.1]nonan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **292**: ^{1}H NMR: δ_H ($CDCl_3$): 8.26 (1H, d, J=8.11Hz), 7.81 (1H, t, J=7.6Hz), 7.70 (1H, m), 7.55 (1H, m), 5.40 (1H, m), 3.61 (2H, d, J=10.14Hz), 2.85 (1H, s), 2.81 (2H, m), 2.35 (1H, m), 2.13-1.46 (19H, m), 1.12 (2H, m); LC/MS (100%, t_r=1.67min): *m/z*=436 $[M+H]^+$ (Calc: 435.6).

5.37 Example 37

In a manner similar to Example 35, the following Substituted-Quinoxaline-Type Piperidine Compounds were prepared except that the compound of formula **EC** was used in place of the compound of formula **LB**.

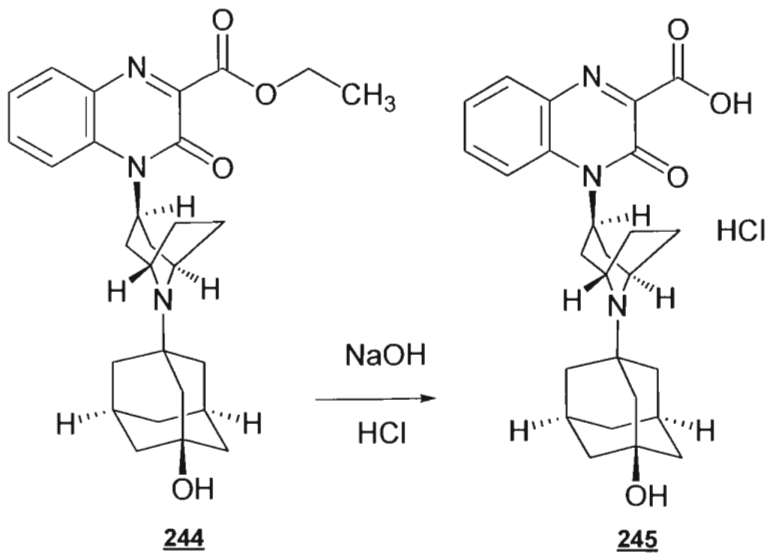


242 **243**

Substituted-Quinoxaline-Type Piperidine Compound **242**, ethyl 4-((*endo*)-8-cycloheptyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, and the hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **243** were prepared by using cycloheptanamine (Sigma-Aldrich) in place of the compound of formula **ED**.

The identity of Substituted-Quinoxaline-Type Piperidine Compound **243**, 4-((*endo*)-8-cycloheptyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **243**: ^{1}H NMR: δ_H (400MHz, 1:3 $CDCl_3$:CD_3OD): 8.01-8.04 (m, 1H), 7.94-7.96 (m, 1H), 7.82-7.86 (m, 1H), 7.51-7.55 (m, 1H), 5.7-5.8 (m, 1H), 4.26-4.38 (m, 2H), 3.02-3.12 (m, 1H), 2.72-2.85 (m, 2H), 2.20-2.64 (m, 8H), 1.60-1.92 (m, 10H); LC/MS (100%, t_r=4.981min): m/z=396.6 $[M+H]^+$.

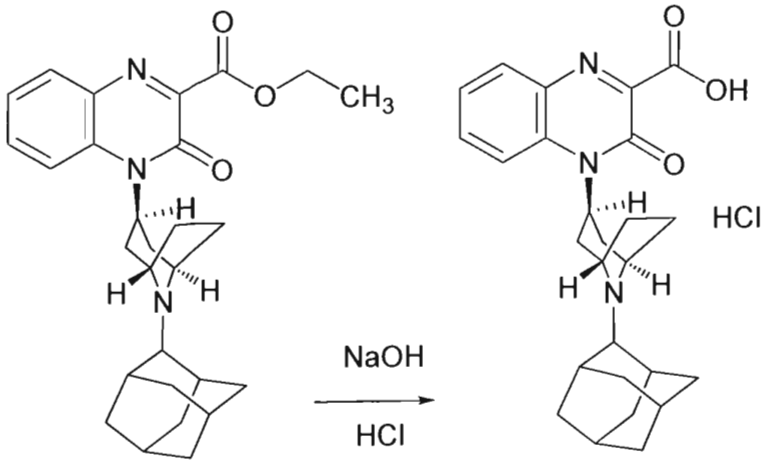


244 **245**

Substituted-Quinoxaline-Type Piperidine Compound **245**, *endo*-4-[8-(3-hydroxy-adamantan-1-yl)-8-aza-bicyclo[3.2.1]oct-3-yl]-3-oxo-3,4-dihydro-quinoxaline-2-carboxylic acid ethyl ester, and the hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **245** were prepared by using 3-amino-adamantan-1-ol (Sigma-Aldrich) in place of the compound of formula **ED**.

The identity of Substituted-Quinoxaline-Type Piperidine Compound **245**, *endo*-4-[8-(3-hydroxy-adamantan-1-yl)-8-aza-bicyclo[3.2.1]oct-3-yl]-3-oxo-3,4-dihydro-quinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **245**: ^{1}H NMR: δ_H (400MHz, 1:3 $CDCl_3$:CD_3OD): 8.1 (d, 1H, J=8.8Hz), 8.02 (dd, 1H, J=1.2, 7.8Hz), 7.83 (ddd, 1H, J=1.5, 7.2, 8.3Hz), 7.51-7.55 (m, 1H), 6.04-6.18 (m, 1H), 4.48-4.52 (m, 2H), 2.94-3.02 (m, 2H), 2.60-3.64 (m, 2H), 2.32-2.68 (m, 6H), 2.08-2.24 (m, 6H), 1.6-1.8 (m, 6H); LC/MS (100%, t_r=4.338min): *m/z*=450.6 $[M+H]^+$.

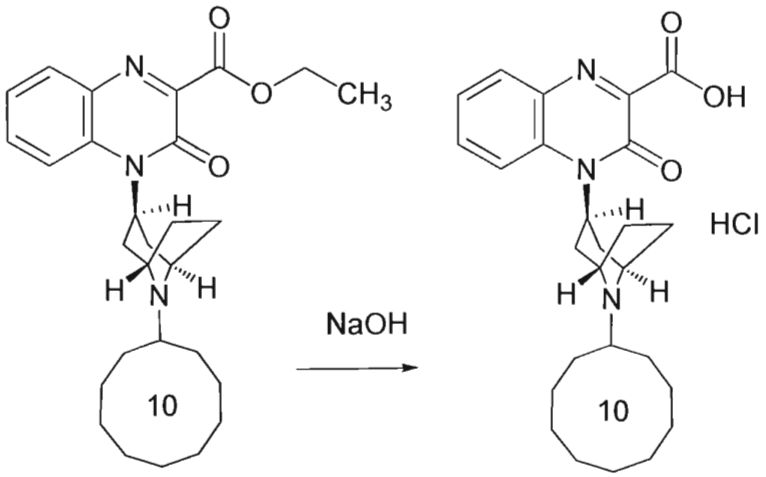


246 **247**

Substituted-Quinoxaline-Type Piperidine Compound **246**, *endo*-4-(8-adamantan-2-yl-8-aza-bicyclo[3.2.1]oct-3-yl)-3-oxo-3,4-dihydro-quinoxaline-2-carboxylic acid ethyl ester (yield 35%), and the hydrochloride of Substituted-Quinoxaline-Type Piperidine Compoundand **247** (yield 58%) were prepared by using 2-amino-adamantane (Sigma-Aldrich) in place of the compound of formula **ED**.

The identity of Substituted-Quinoxaline-Type Piperidine Compound **247**, *endo*-4-(8-adamantan-2-yl-8-aza-bicyclo[3.2.1]oct-3-yl)-3-oxo-3,4-dihydro-quinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **247**: ^{1}H NMR: δ_H (400MHz, 1:3 $CDCl_3$:CD_3OD): 8.1 (d, 1H, J=8.7Hz), 8.03 (d, 1H, J=8.1Hz), 7.82-7.86 (m, 1H), 7.51-7.55 (m, 1H), 6.14-6.21(m, 1H), 4.28-4.42 (m, 2H), 3.18-3.26 (m, 1H), 2.97-3.04 (m, 2H), 2.58-2.64 (m, 4H), 2.28-2.44 (m, 6H), 1.6-2.2 (m, 10H); LC/MS (97.9%, t_r=5.362min): *m/z*=434.5 $[M+H]^+$.



293 **294**

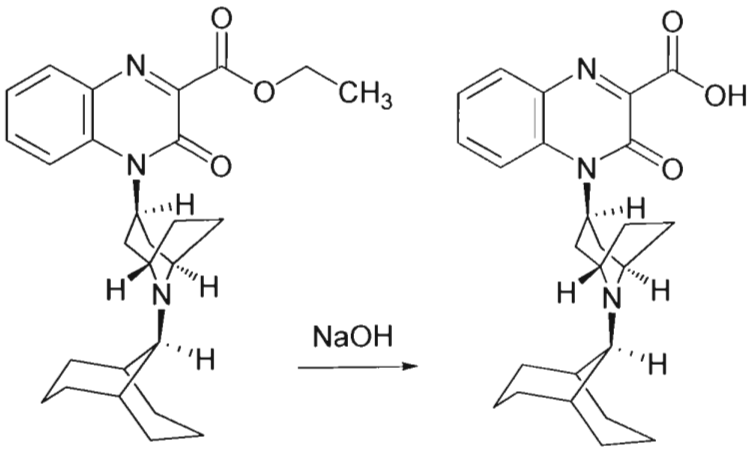
Substituted-Quinoxaline-Type Piperidine Compounds **293** and **294** were prepared by using cyclodecanamine in place of the compound of formula **ED** and omitting the final HCl treatment.

The identity of Substituted-Quinoxaline-Type Piperidine Compound **293**, ethyl 4-((*endo*)-8-cyclodecyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **293**: ^{1}H NMR: δ_H ($CDCl_3$): 7.91 (1H, m), 7.64-7.54 (2H, m), 7.34 (1H, m), 5.20 (1H, br), 4.49 (2H, q, J=7.1Hz), 3.68 (2H, s), 2.45-2.20 (5H, m), 2.02 (2H, m), 1.81 (2H, m), 1.72-1.42 (22H, m); LC/MS: *m/z*=466 $[M+H]^+$ (Calc: 465.6).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **294**, 4-((*endo*)-8-cyclodecyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **294**: ^{1}H NMR: δ_H ($CDCl_3$): 7.88 (2H, m), 7.42 (1H, m), 7.24 (1H, m), 5.80 (1H, m), 4.13 (2H, m), 3.10 (1H, m), 2.85 (1H, m), 2.60-1.40 (24H, m); LC/MS (99%, t_r=1.76min): *m/z*=438 $[M+H]^+$ (Calc: 437.6).



295 **296**

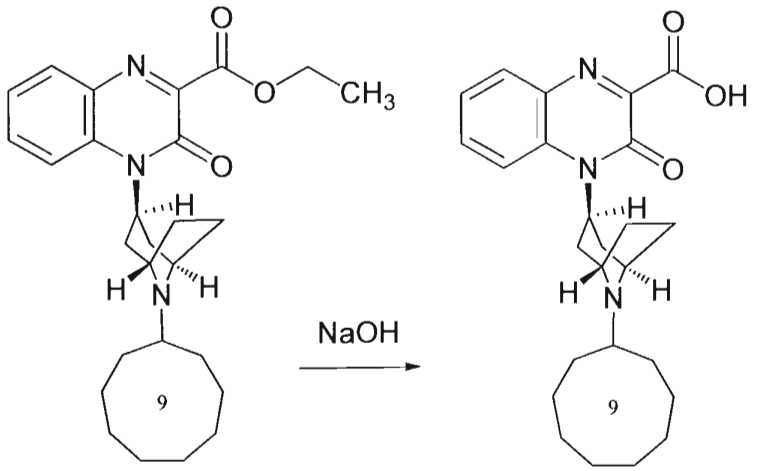
Substituted-Quinoxaline-Type Piperidine Compounds **295** and **296** were prepared by using (*exo*)-bicyclo[3.3.1]nonan-9-amine in place of the compound of formula **ED** and omitting the final HCl treatment.

The identity of Substituted-Quinoxaline-Type Piperidine Compound **295**, ethyl 4-((*endo*)-8-((*exo*)-bicyclo[3.3.1]nonan-9-yl)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **295**: ^{1}H NMR: δ_H ($CDCl_3$): 7.92 (1H, d, J=8.11Hz), 7.62 (1H, t, J=7.86Hz), 7.52 (1H, d, J=8.62Hz), 7.35 (1.1H, t, J=7.6Hz), 5.20 (1H, br), 4.49 (2H, q, J=7.1Hz), 3.68 (2H, s), 2.45-2.20 (5H, m), 2.02 (2H, m), 1.81 (2H, m), 1.72-1.42 (24H, m); LC/MS: *m/z*=450 $[M+H]^+$ (Calc: 449.6).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **296**, 4-((*endo*)-8-((*exo*)-bicyclo[3.3.1]nonan-9-yl)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **296**: ^{1}H NMR: δ_H ($CDCl_3$): 8.42 (1H, m), 8.21 (1H, m), 7.92 (1H, m), 7.58 (1H, m), 6.60 (1H, m), 4.27 (2H, m), 3.10 (3H, m), 2.60-1.30 (22H, m); LC/MS (100%, t_r=1.54min): *m/z*=424 $[M+H]^+$ (Calc: 423.6).



297 **298**

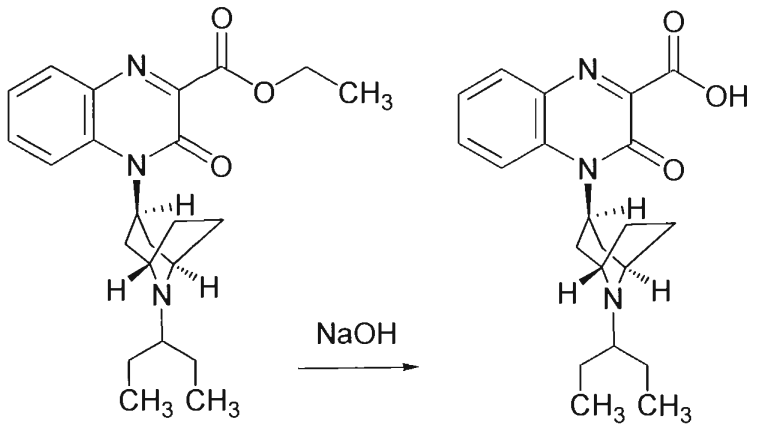
Substituted-Quinoxaline-Type Piperidine Compounds **297** and **298** were prepared by using cyclononanamine in place of the compound of formula **ED** and omitting the final HCl treatment.

The identity of Substituted-Quinoxaline-Type Piperidine Compound **297**, ethyl 4-((*endo*)-8-cyclononyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **297**: ^{1}H NMR: δ_H ($CDCl_3$): 7.92 (1H, d, J=8.0Hz), 7.62 (1H, t, J=8.0Hz), 7.52 (1H, d, J=8.0Hz), 7.35 (1H, t, J=8.0Hz), 5.40 (1H, br), 4.50 (2H, q, J=7.1Hz), 3.68 (2H, s), 2.28-1.40 (26H, m); LC/MS: *m/z*=450 $[M+H]^+$ (Calc: 449.6).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **298**, 4-((*endo*)-8-cyclononyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **298**: ^{1}H NMR: δ_H ($CDCl_3$): 8.23 (1H, d, J=8.11Hz), 7.74 (2H, m), 7.53 (1H, t, J=7.6Hz), 5.60 (1H, br), 3.75 (2H, s), 3.49 (1H, s), 2.40-1.47 (22H, m); LC/MS (100%, t_r=1.40min): *m/z*=422 $[M+H]^+$ (Calc: 421.6).



392 **365**

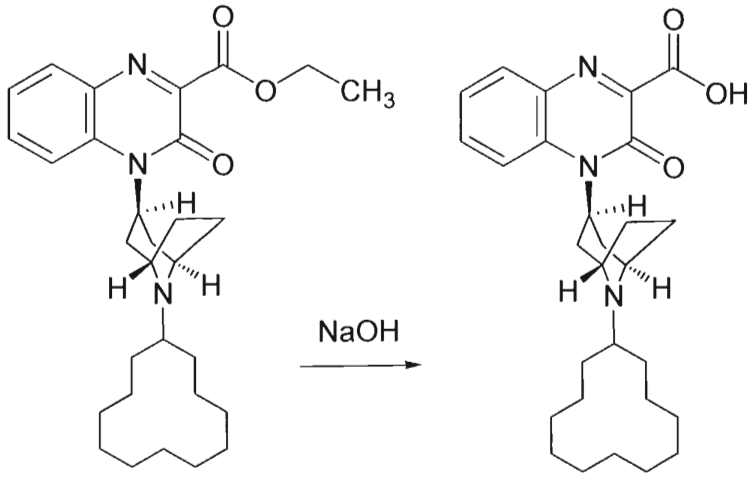
Substituted-Quinoxaline-Type Piperidine Compounds **392** and **365** were prepared by using pentan-3-amine (Sigma-Aldrich) in place of the compound of formula **ED** and omitting the final HCl treatment.

The identity of Substituted-Quinoxaline-Type Piperidine Compound **392**, ethyl 3-oxo-4-((*endo*)-8-(pentan-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR.

Substituted-Quinoxaline-Type Piperidine Compound **392**: ^{1}H NMR: δ_H ($CDCl_3$): 0.95 (t, J=7.39Hz, 6H), 1.40-1.60 (m, 7H), 1.85 (m, 2H), 2.05 (m, 2H), 2.15-2.38 (m, 5H), 3.67 (m, 2H), 4.54 (q, J=7.11Hz, 2H), 5.30 (br, 1H), 7.38 (t, J=8.0Hz, 1H), 7.57 (d, J=8.0Hz, 1H), 7.68 (t, J=8.0Hz, 1H), 7.96 (d, J=8.0Hz, 1H).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **365**, 3-oxo-4-((*endo*)-8-(pentan-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)-3,4-dihydroquinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **365**: ^{1}H NMR: δ_H (DMSO-d_6): 0.96 (t, J=7.4Hz, 6H), 1.86 (m, 4H), 2.16-2.27 (m, 6H), 2.66 (m, 2H), 2.84 (m, 1H), 4.20 (m, 2H), 6.14 (m, 1H), 7.44 (t, J=8.0Hz, 1H), 7.73 (t, J=8.0Hz, 1H), 7.87 (d, J=8.0Hz, 1H), 8.11 (d, J=8.0Hz, 1H); LC/MS (99%, t_r=0.81min): *m/z*=370 $[M+H]^+$ (Calc: 369.6).



393 **356**

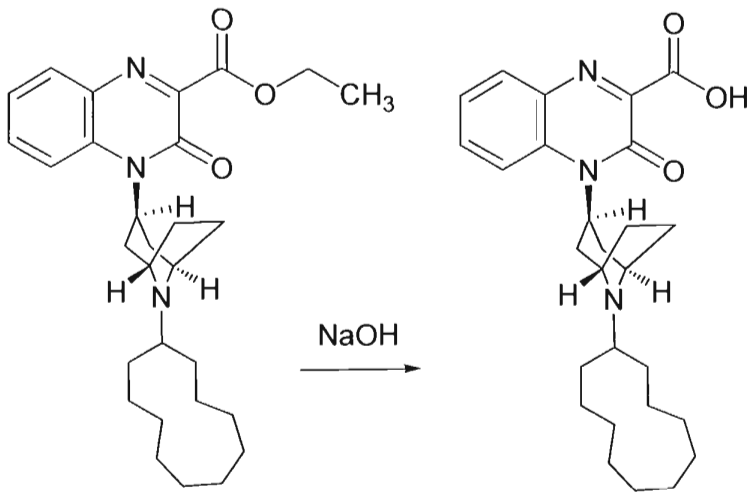
Substituted-Quinoxaline-Type Piperidine Compounds **393** and **356** were prepared by using cyclododecanamine (Sigma-Aldrich) in place of the compound of formula **ED** and omitting the final HCl treatment.

The identity of Substituted-Quinoxaline-Type Piperidine Compound **393**, ethyl 4-((*endo*)-8-cyclododecyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **393**: ^{1}H NMR: δ_H ($CDCl_3$): 1.35 (m, 25H), 1.82 (m, 2H), 2.02 (m, 2H), 2.26 (m, 5H), 3.68 (m, 2H), 4.49 (q, J=7.1Hz, 2H), 5.20 (br, 1H), 7.34 (t, J=7.6Hz, 1H), 7.54 (d, J=7.6Hz, 1H), 7.62 (t, J=7.6Hz, 1H), 7.91 (d, J=7.6Hz, 1H); LC/MS: *m/z*=494 $[M+H]^+$ (Calc: 493.6).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **356**, 4-((*endo*)-8-cyclododecyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **356**: ^{1}H NMR: δ_H ($CDCl_3$): 1.42 (m, 16H), 1.60-2.60 (m, 12H), 2.72 (s, 1H), 3.06 (m, 2H), 4.16 (s, 2H), 6.00 (br, 1H), 7.32 (t, J=7.35Hz, 1H), 7.60 (m, 1H), 7.93 (d, J=8.11Hz, 1H).8.10 (m, 1H); LC/MS (100%, t_r=2.20min): *m/z*=466 $[M+H]^+$ (Calc: 465.6).



394 **358**

Substituted-Quinoxaline-Type Piperidine Compounds **394** and **358** were prepared by using cycloundecanamine (Sigma-Aldrich) in place of the compound of formula **ED** and omitting the final HCl treatment.

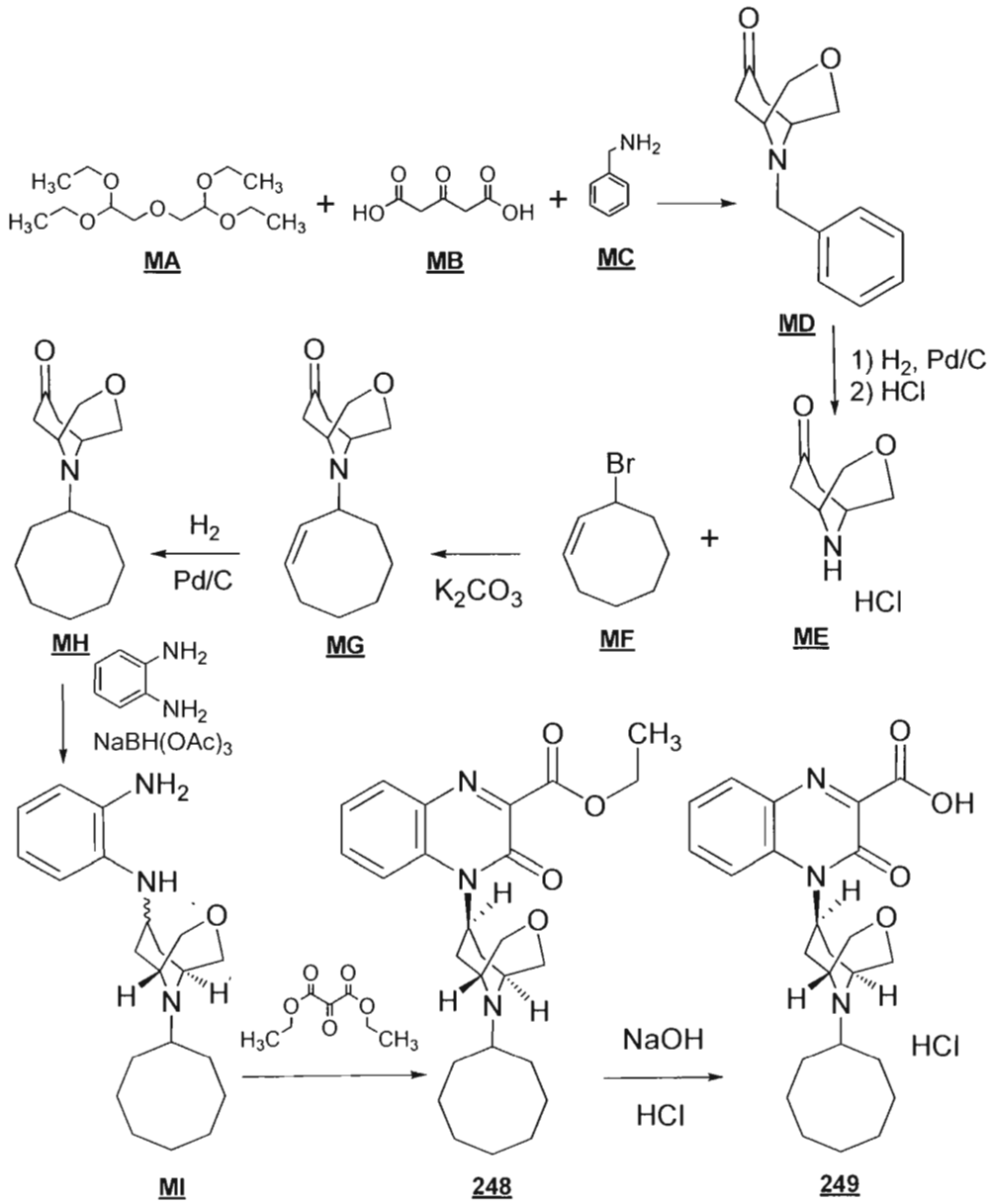
The identity of Substituted-Quinoxaline-Type Piperidine Compound **394**, ethyl 4-((*endo*)-8-cycloundecyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **394**: ^{1}H NMR: δ_H ($CDCl_3$): 1.30-1.70 (m, 24H), 1.83 (m, 2H), 2.00 (m, 2H), 2.25 (m, 5H,), 3.66 (m, 2H), 4.50 (d, J=7.14Hz, 2H), 5.20 (br, 1H), 7.36 (t, J=7.6Hz, 1H), 7.56 (d, J=7.6Hz, 1H), 7.60 (t, J=7.6Hz, 1H), 7.91 (d, J=7.6Hz, 1H); LC/MS: *m/z*=480 $[M+H]^+$ (Calc: 479.6).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **358**, 4-((*endo*)-8-cycloundecyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **358**: ^{1}H NMR: δ_H ($CDCl_3$): 1.30-1.60 (m, 14H), 1.75 (m, 2H), 2.13 (m, 6H), 2.39 (m, 4H), 2.61 (m, 1H), 3.04 (m, 2H), 4.12 (m, 2H), 5.83 (m, 1H), 7.25 (m, 1H), 7.44 (m, 1H), 7.85-7.94 (m, 2H); LC/MS (99%, t_r=2.06min): *m/z*=452 $[M+H]^+$ (Calc: 451.6).

5.38 Example 38



The compound of formula **MA**, 2-(2,2-diethoxyethoxy)-1,1-diethoxyethane, was prepared according the procedure described in C.L. Zirkle *et al.*, *J. Org. Chem.* 26:395 (1961).

A mixture of the compound of formula **MA** (25g, 0.14mmol), AcOH (7mL), and water (25mL) was warmed to 100°C and stirred for 2h. After cooling to about 25°C, the resulting colorless solution was added to 350mL of a buffer solution containing 36g of $Na_2HPO_4 \cdot 7\ H_2O$ and 25g citric acid. Under an argon atmosphere, 400mL of water and the compounds of formula **MB** (3-oxopentanedioic acid, 40g, 0.27mol, Sigma-Aldrich) and **MC** (phenylmethanamine, 27g,

0.25mol) were added. After holding the reaction mixture at 26-28°C for 24h, it was saturated with NaCl, neutralized with about 50g of NaOH to a pH of about 11, and extracted four times with DCM (250mL for each extraction). The organic portions were combined and concentrated under reduced pressure to provide a brown oil which was diluted with acetone (200mL), concentrated under reduced pressure, and dried to provide about 7g of the compound of formula **MD**, 9-benzyl-3-oxa-9-azabicyclo[3.3.1]nonan-7-one, as white solid. In a manner similar to Example 18, the benzyl group of the compound of formula **MD** was removed to provide 3.8g of the hydrochloride of the compound of formula **ME**, 3-oxa-9-azabicyclo[3.3.1]nonan-7-one, as a white solid.

In a manner similar to Example 32, the compound of formula **MG**, 9-((Z)-cyclooct-2-enyl)-3-oxa-9-azabicyclo[3.3.1]nonan-7-one, was prepared from the compound of formula **MF** except that the compound of formula **ME** was used in place of the compound of formula **JC** (yield 90%). Under a hydrogen atmosphere, a mixture of the compound of formula **MG**, 5% palladium on carbon (1.0g, Sigma-Aldrich), and EtOH (20mL) was stirred at a temperature of about 25°C for 4h. After the Pd/C was filtered off, the filtrate was concentrated under reduced pressure to provide the compound of formula **MH**, 9-cyclooctyl-3-oxa-9-azabicyclo[3.3.1]nonan-7-one.

In a manner similar to Example 1, a mixture of the *endo* and *exo* isomers of the compound of formula **MI**, N^1-9-cyclooctyl-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)benzene-1,2-diamine, was prepared except that the compound of formula **MH** was used in place of the compound of formula **AA**. Substituted-Quinoxaline-Type Piperidine Compound **248** was prepared from diethyl 2-oxomalonate in a manner similar to Example 12 except that the compound of formula **MI** was used in place of the compound of formula **AB** (yield 15% from **MH**).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **248**, ethyl 4-((*endo*)-9-cyclooctyl-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

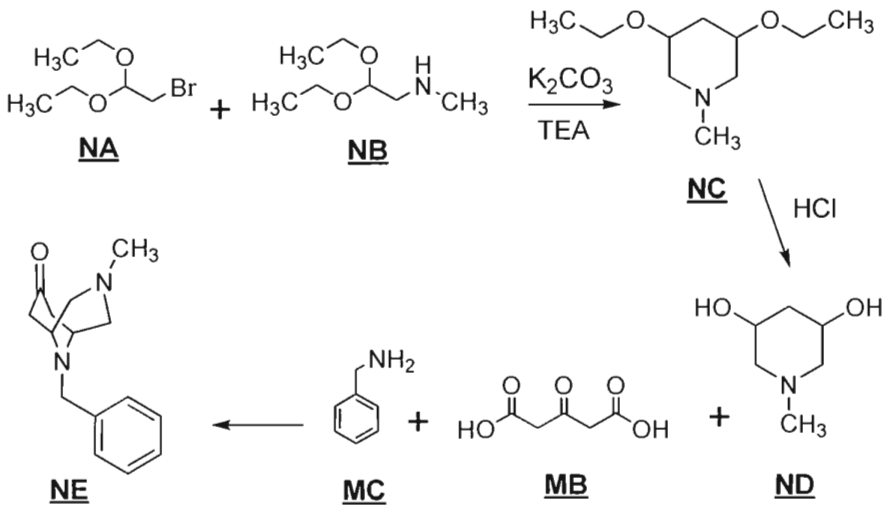
Substituted-Quinoxaline-Type Piperidine Compound **248**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 8.30 (br, 1H), 7.95 (dd, 1H, J=1.5, 8.1Hz), 7.64 (ddd, 1H, J=1.5, 7.2, 8.2Hz), 7.35 (ddd, 1H, J=1.1, 7.1, 8.3Hz), 6.05 (br, 1H), 4.52 (t, 2H, J=7.2Hz), 3.80-3.83 (m, 2H), 3.66-3.71 (m, 2H), 3.30-3.34 (m, 2H), 3.04-3.08 (m, 1H), 2.20-2.24 (m, 2H), 1.4-1.8 (m, 19H); LC/MS (100%, t_r=6.056min): *m/z*=454.6 $[M+H]^+$ (Calc: 453.6).

The hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **249** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **248** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **174** in Example 7 (yield 78%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **249**, 4-((*endo*)-9-cyclooctyl-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

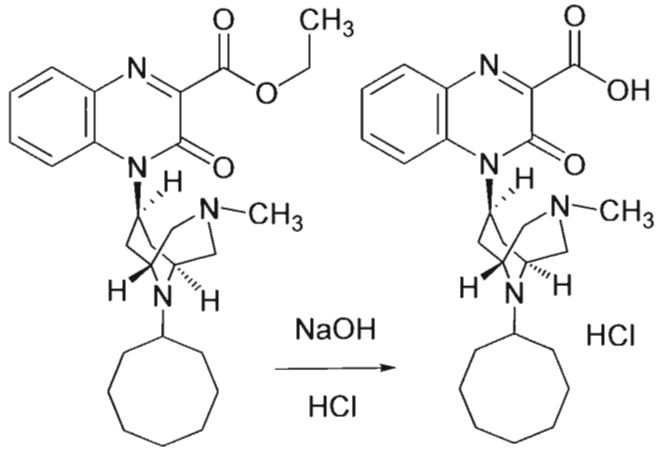
Substituted-Quinoxaline-Type Piperidine Compound **249**: ^{1}H NMR: δ_H (400MHz, 1:3 $CDCl_3$:CD_3OD): 8.25-8.42 (m, 1H), 8.02-8.06 (m, 1H), 7.83-7.86 (m, 1H), 7.53 (dd, 1H, J=7.4, 7.9Hz), 6.24 (br, 1H), 3.80-4.32 (m, 7H), 3.20-3.26 (m, 1H), 2.60-3.78 (m, 3H), 1.60-2.24 (m, 14H); LC/MS (99.1%, t_r=2.067min): *m/z*=426.5 $[M+H]^+$.

5.39 Example 39



A reaction mixture of 2-bromo-1,1-diethoxyethane (**NA**, 25g, Sigma-Aldrich), 2,2-diethoxy-*N*-methylethanamine (**NB**, 1.0eq, Sigma-Aldrich), TEA (1.0eq), and K_2CO_3 (1.0eq) in CH_3CN (200mL) was warmed to 60°C and stirred for 20h. After cooling to about 25°C, the reaction mixture was diluted with water, extracted with Et_2O, concentrated under reduced pressure, and distilled (at 56-60°C and 0.5mmHg) to provide 30g of the compound of formula **NC**, 3,5-diethoxy-1-methylpiperidine, as a colorless oil (yield 87%). The compound of formula **NC** was treated with 1N HCl (150mL) at a temperature of 100°C for 2h to provide the compound of formula **ND**, 1-methylpiperidine-3,5-diol. Thereafter, the compound of

formula **NE**, 9-benzyl-3-methyl-3,9-diazabicyclo[3.3.1]nonan-7-one, was prepared in a manner similar to the preparation of the compound of formula **MD** in Example 38 except that the compound of formula **ND** was used in place of the compound of formula **MA**.



250 **251**

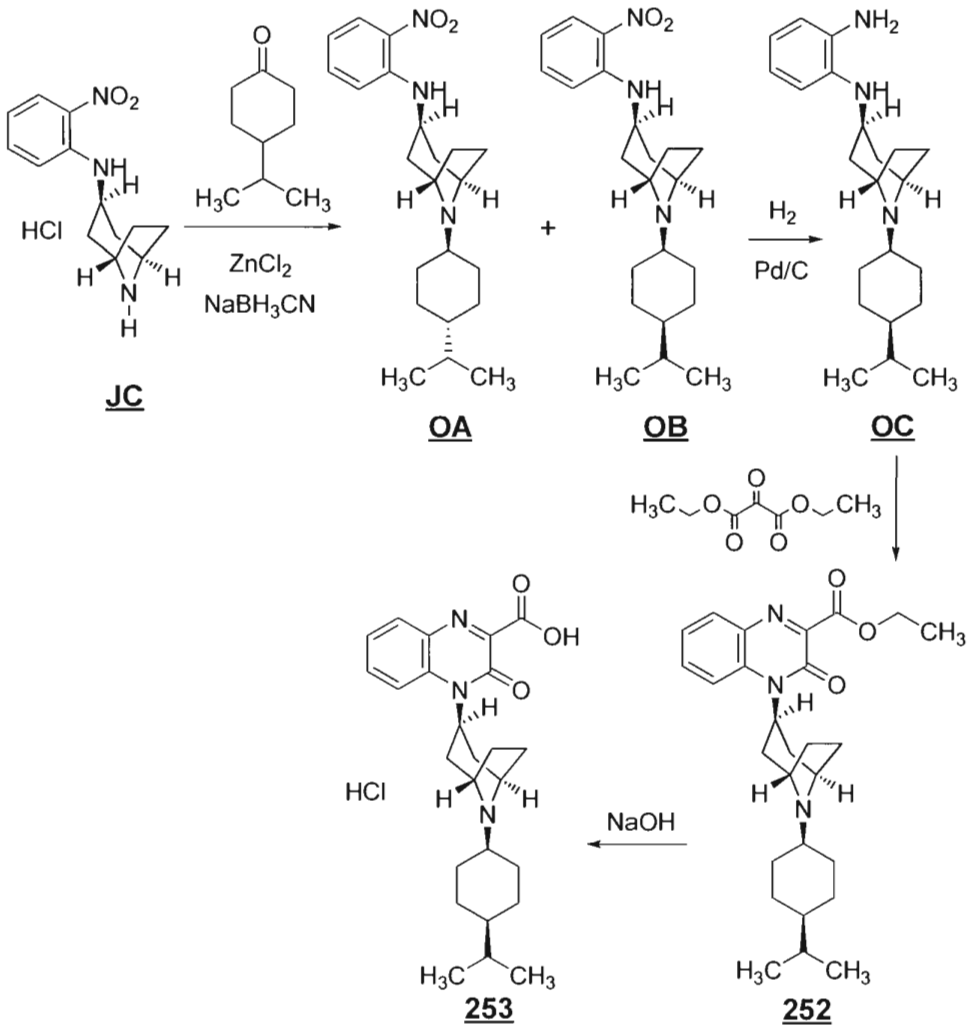
In a manner similar to Example 38, Substituted-Quinoxaline-Type Piperidine Compound **250**, ethyl 4-((*endo*)-9-cyclooctyl-3-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was prepared except that the compound of formula **NE** was used in place of the compound of formula **MD**.

The hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **251** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **250** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **174** in Example 7 (yield 36%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **251**, 4-((*endo*)-9-cyclooctyl-3-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **251**: ^{1}H NMR: δ_H (400MHz, 1:3 $CDCl_3$:CD_3OD): 8.08-8.11 (m, 1H), 7.86-7.93 (m, 2H), 7.59-7.63 (m, 1H), 5.64 (br, 1H), 4.08 (br, 2H), 3.44-3.60 (m, 4H), 3.16 (s, 3H, Nme), 2.66-2.78 (m, 3H), 1.6-2.24 (m, 16H); LC/MS (99.1%, t_r=4.586min): *m/z*=439.2 $[M+H]^+$ (Calc: 438.6).

5.40 Example 40



At a temperature of about 25°C, a 28% aqueous ammonia solution was added to a mixture of the compound of formula **JC** (1.0g, 3.52mmol) and $CHCl_3$ (30mL) and the reaction mixture was stirred for 10min. The mixture was extracted three times with $CHCl_3$:H_2O (30mL for each extraction), dried ($MgSO_4$), and concentrated under reduced pressure to provide a yellow oil. Under a nitrogen atmosphere, to a mixture of the resulting oil and MeOH (300mL) at a temperature of about 25°C was added 4-isopropylcyclohexanone (0.593g, 4.23mmol, Sigma-Aldrich), $NaBH_3CN$ (1.107g, 17.62mmol, Sigma-Aldrich) and zinc chloride (4.804g, 35.2mmol, Sigma-Aldrich). The resulting reaction mixture was stirred at a temperature of about 25°C for 72h. Thereafter, the mixture was concentrated under reduced pressure, neutralized with 28% aqueous ammonia to adjust the pH to about 14, and extracted twice with $CHCl_3$:H_2O (100mL for each extraction). The organic portions were combined, dried

($MgSO_4$), and concentrated under reduced pressure to provide a yellow oil. The oil was chromatographed with an amino-silica gel column (Yamazen Corp. W091-01) eluted with a gradient of from 5%:95% EtOAc:n-hexane to 15%:85% EtOAc:n-hexane to 50%:50% EtOAc:n-hexane to provide 320mg of the compound of formula **OA** (yield 24%) and 989mg of the compound of formula **OB** (yield 75%), each as a yellow solid.

The identity of the compound of formula **OA**, (*endo*)-8-((*trans*)-4-isopropylcyclohexyl)-*N*-(2-nitrophenyl)-8-azabicyclo[3.2.1]octan-3-amine, was confirmed using ^{1}H NMR and LC/MS.

Compound **OA**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 8.73 (1H, d, J=6.08Hz), 8.18 (1H, t, J=4.31Hz), 7.40 (1H, dd, J=8.36, 7.35Hz), 6.71 (1H, d, J=9.12Hz), 6.61 (1H, dd, J=8.36, 7.35Hz), 3.86 (1H, q, J=6.59Hz), 3.56 (2H, s), 2.27 (3H, dd, J=8.36, 4.31Hz), 2.02-1.94 (6.3H, m), 1.70 (6H, m), 1.44-1.40 (1H, m), 1.07 (5H, m), 0.85 (6H, dd, J=11.66, 7.10Hz); LC/MS: *m/z*=372 $[M+H]^+$ (Calc: 371).

The identity of the compound of formula **OB**, (*endo*)-8-((*cis*)-4-isopropylcyclohexyl)-*N*-(2-nitrophenyl)-8-azabicyclo[3.2.1]octan-3-amine, was confirmed using ^{1}H NMR and LC/MS.

Compound **OB**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 8.74 (1H, d, J=6.08Hz), 8.18 (1H, d, J=8.62Hz), 7.40 (1H, dd, J=8.11, 7.10Hz), 6.72 (1H, d, J=8.62Hz), 6.60 (1H, dd, J=8.36, 7.35Hz), 3.85 (1H, q, J=6.42Hz), 3.47 (2H, s), 2.52 (1H, s), 2.25 (2H, m), 1.95 (5H, m), 1.75-1.02 (17.6H, m), 0.87 (7H, dd, J=5.58, 4.56Hz); LC/MS: *m/z*=372 $[M+H]^+$ (Calc: 371).

In a manner similar to the preparation of the compound of formula **CC** in Example 6, the compound of formula **OC** was prepared except that the compound of formula **OB** was used in place of the compound of formula **CB** (yield 98%).

The identity of the compound of formula **OC**, N^1-((*endo*)-8-((*cis*)-4-isopropylcyclohexyl)-8-azabicyclo[3.2.1]octan-3-yl)benzene-1,2-diamine, was confirmed using LC/MS.

Compound **OC**: LC/MS: *m/z*=342 $[M+H]^+$ (Calc: 341).

In a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **70** in Example 12, Substituted-Quinoxaline-Type Piperidine Compound **252** was

prepared except that the compound of formula **OC** was used in place of the compound of formula **AB** (yield 19%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **252**, ethyl 4-((*endo*)-8-((*cis*)-4-isopropylcyclohexyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

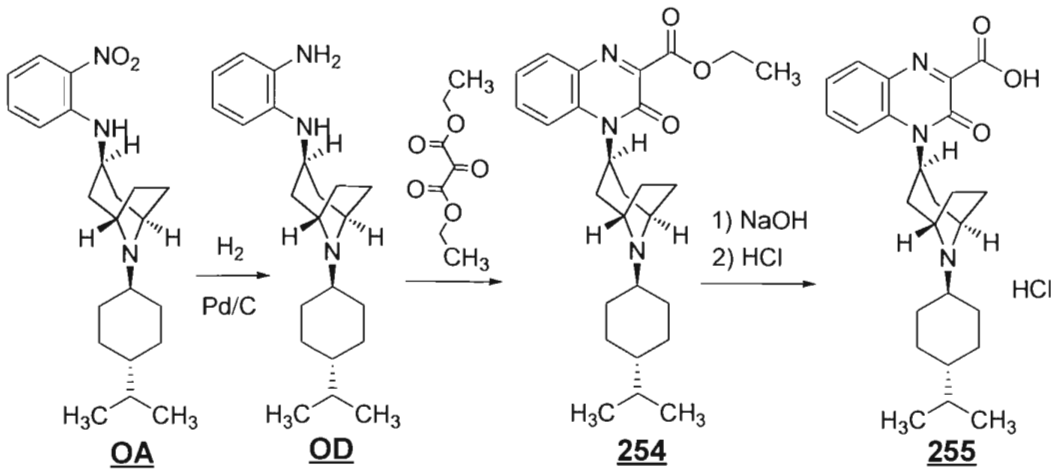
Substituted-Quinoxaline-Type Piperidine Compound **252**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 7.89 (1H, d, J=8.11Hz), 7.73 (1H, t, J=7.86Hz), 7.58 (1H, d, J=8.62Hz), 7.44 (1H, t, J=7.6Hz), 5.20 (1H, br), 4.37 (2H, q, J=7.1Hz), 3.61 (2H, br), 2.34-1.16 (30H, m), 0.92 (7H, d, J=6.59Hz); LC/MS: *m/z*=452 $[M+H]^+$ (Calc: 451).

The hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **253** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **252** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **174** in Example 7 (yield 64%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **253**, 4-((*endo*)-8-((*cis*)-4-isopropylcyclohexyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **253**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 10.30 (0.8H, s), 9.73 (0.2H, s), 8.12 (1H, d, J=8.62Hz), 7.89 (1H, d, J=7.6Hz), 7.75 (1H, t, J=7.86Hz), 7.47 (1H, t, J=7.35Hz), 6.00 (0.8H, t, J=9.63Hz), 5.24 (0.2H, s), 4.22 (2H, m), 2.91 (1H, m), 2.65 (2H, m), 2.34-2.09 (6H, m), 1.90-1.60 (8H, m), 1.37-1.14 (3H, m), 0.90 (6H, d, J=6.08Hz); LC/MS (100%, t_r=1.66min): *m/z*=424 $[M+H]^+$ (Calc: 423).

In a manner similar to the above preparation of Substituted-Quinoxaline-Type Piperidine Compounds **252** and **253**, the following Substituted-Quinoxaline-Type Piperidine Compounds were prepared except that the compound of formula **OA** was used in place of from the compound of formula **OB**.



OA OD 254 255

The identity of Substituted-Quinoxaline-Type Piperidine Compound **254**, ethyl 4-((*endo*)-8-((*trans*)-4-isopropylcyclohexyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

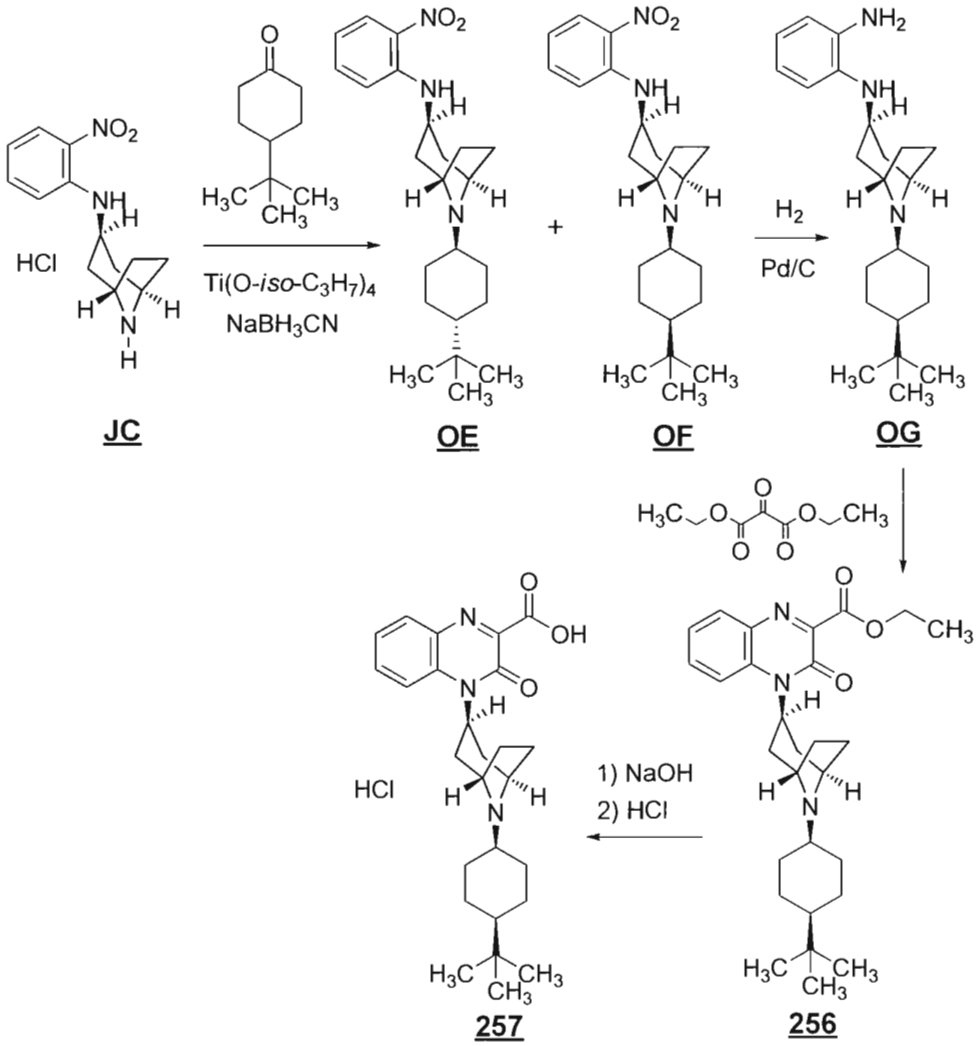
Substituted-Quinoxaline-Type Piperidine Compound **254**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 7.88 (1H, d, J=7.6Hz), 7.77 (1H, t, J=7.1Hz), 7.65 (1H, d, J=6.59Hz), 7.44 (1H, t, J=7.35Hz), 5.17 (1H, br), 4.36 (2H, t, J=7.1Hz), 3.69 (2H, d, J=16.22Hz), 2.23 (2H, q, J=9.97Hz), 2.02-1.71 (14H, m), 1.41-1.30 (5H, m), 1.08-0.84 (15H, m); LC/MS: *m/z*=452 $[M+H]^+$ (Calc: 451).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **255**, 4-((*endo*)-8-((*trans*)-4-isopropylcyclohexyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **255**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 10.22 (0.8H, s), 9.72 (0.2H, s), 8.09 (1H, d, J=8.62Hz), 7.89 (1H, d, J=8.11Hz), 7.76 (1H, t, J=7.86Hz), 7.47 (1H, t, J=7.6Hz), 5.97 (0.8H, t, J=9.38Hz), 5.23 (0.2H, s), 4.31 (1.5H, s), 4.13 (0.5H, s), 2.83 (1H, s), 2.63-2.55 (2H, m), 2.24 (8H, tt, J=30.92, 8.28Hz), 1.95-1.22 (7H, m), 1.04 (3H, s), 0.86 (6H, d, J=6.59Hz); LC/MS (98%, t_r=1.77min): *m/z*=424 $[M+H]^+$ (Calc: 423).

In a manner similar to the above preparation of Substituted-Quinoxaline-Type Piperidine Compounds **252** and **253**, the following Substituted-Quinoxaline-Type Piperidine Compounds were prepared except that 4-*tert*-butylcyclohexanone (Sigma-Aldrich) was used in

place of 4-*iso*-propylcyclohexanone and titanium(IV) *iso*-propoxide (Sigma-Aldrich) was used in place of zinc chloride.



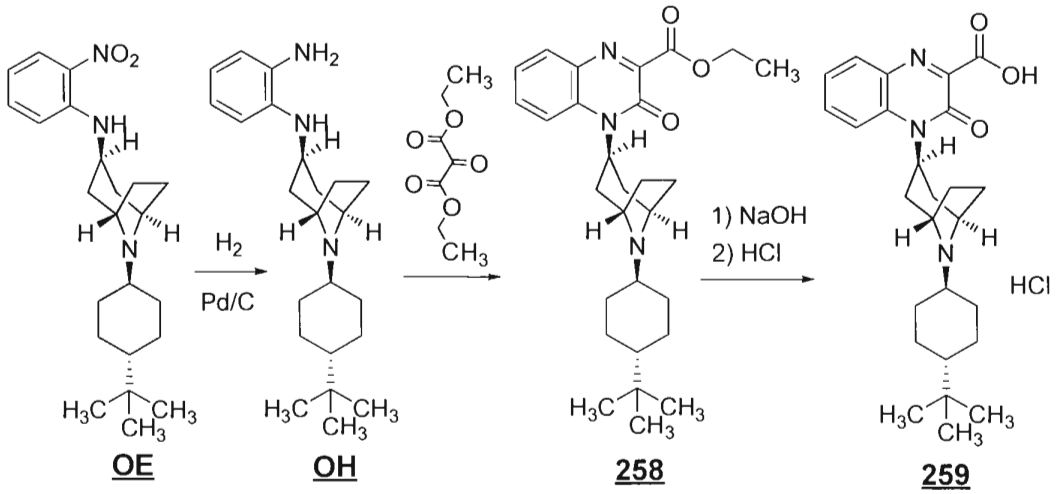
The identity of Substituted-Quinoxaline-Type Piperidine Compound **256**, ethyl 4-((*endo*)-8-((*cis*)-4-*tert*-butylcyclohexyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **256**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 7.89 (1H, d, J=8.11Hz), 7.69 (1H, t, J=7.6Hz), 7.54 (1H, d, J=8.62Hz), 7.44 (1H, t, J=7.6Hz), 5.22 (1H, s), 4.37 (2H, q, J=7.1Hz), 3.62 (2H, s), 2.36 (1H, s), 2.19 (4H, m), 1.93 (4H, m), 1.62 (4H, m), 1.36 (8H, m), 1.09 (1H, m), 0.94 (9H, d, J=19.77Hz); LC/MS: *m/z*=466 $[M+H]^+$ (Calc: 465).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **257**, 4-((*endo*)-8-((*cis*)-4-*tert*-butylcyclohexyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **257**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 10.06 (0.7H, br), 8.85 (0.3H, s), 8.13 (1H, d, J=9.12Hz), 7.89 (1H, d, J=8.11Hz), 7.75 (1H, t, J=7.35Hz), 7.47 (1H, t, J=7.1Hz), 6.17 (0.7H, br), 5.26 (0.3H, s), 4.22 (2H, s), 3.63 (0.3H, br), 3.04 (0.7H, br), 2.69 (2H, dd, J=20.53, 11.41Hz), 2.41-1.50 (15H, m), 1.17 (1H, m), 0.90-0.82 (9H, m); LC/MS (100%, t_r=1.87min): *m/z*=438 $[M+H]^+$ (Calc: 437).

In a manner similar to the above preparation of Substituted-Quinoxaline-Type Piperidine Compounds **256** and **257**, the following Substituted-Quinoxaline-Type Piperidine Compounds were prepared except that the compound of formula **OE** was used in place of from the compound of formula **OF**.



OE **OH** **258** **259**

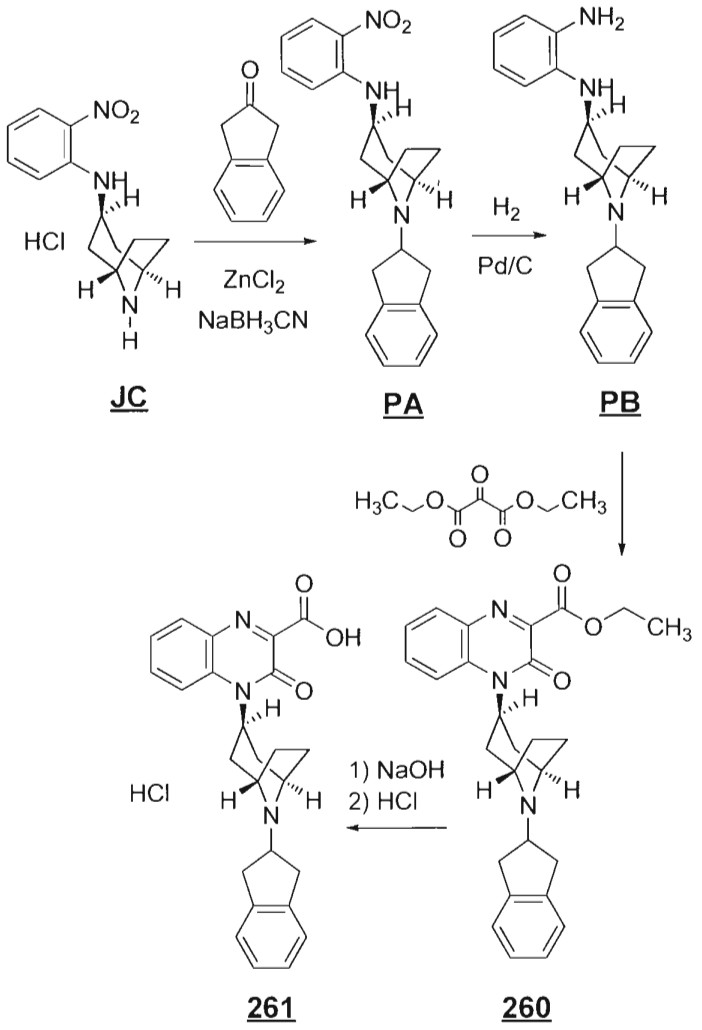
The identity of Substituted-Quinoxaline-Type Piperidine Compound **258**, ethyl 4-((*endo*)-8-((*trans*)-4-*tert*-butylcyclohexyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **258**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 7.88 (1H, d, J=7.6Hz), 7.76 (1H, d, J=8.11Hz), 7.66 (1H, s), 7.44 (1H, m), 4.37 (2H, q, J=6.93Hz), 3.69 (2H, m), 2.23 (2H, d, J=12.17Hz), 1.87 (15H, m), 1.32 (3H, m), 1.02 (6H, m), 0.84 (9H, s); LC/MS: *m/z*=466 $[M+H]^+$ (Calc: 465).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **259**, 4-((*endo*)-8-((*trans*)-4-*tert*-butylcyclohexyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **259**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 10.22 (0.8H, s), 9.69 (0.2H, s), 8.09 (1H, d, J=8.11Hz), 7.89 (1H, d, J=8.11Hz), 7.76 (1H, t, J=7.1Hz), 7.47 (1H, t, J=7.35Hz), 5.96 (0.8H, dd, J=13.18, 5.58Hz), 5.24 (0.2H, s), 4.23 (2H, m), 2.85 (1H, br), 2.58 (2H, br), 2.25 (7H, m), 1.95-1.56 (4H, m), 1.27 (1H, m), 1.11-0.86 (12H, m); LC/MS (100%, t_r=1.92min): *m/z*=438 $[M+H]^+$ (Calc: 437).

5.41 Example 41



Substituted-Quinoxaline-Type Piperidine Compound **260** was prepared in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **252** in Example 40 except that 1*H*-inden-2(3*H*)-one (Sigma-Aldrich) was used in place of 4-*iso*-propylcyclohexanone (yield 23%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **260**, ethyl 4-((*endo*)-8-(2,3-dihydro-1*H*-inden-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

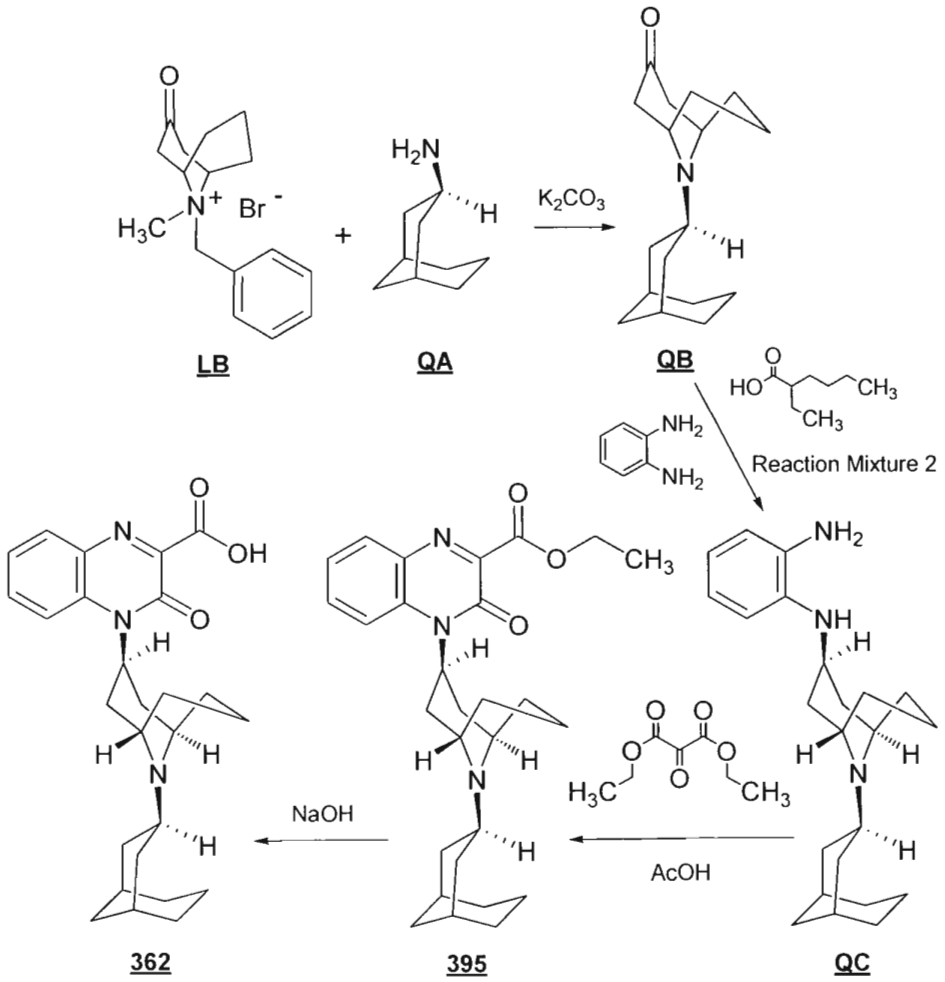
Substituted-Quinoxaline-Type Piperidine Compound **260**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 7.88 (1H, d, J=7.6Hz), 7.74 (2H, d, J=7.1Hz), 7.44 (1H, t, J=7.6Hz), 7.15 (4H, dt, J=25.52, 4.31Hz), 5.23 (1H, br), 4.38 (2H, q, J=7.1Hz), 3.59 (2H, s), 3.25-3.07 (3H, m), 2.78 (2H, m), 2.33 (2H, dd, J=21.54, 8.87Hz), 2.05 (4H, dd, J=28.39, 16.73Hz), 1.76 (2H, d, J=7.1Hz), 1.32 (3H, t, J=6.84Hz); LC/MS: *m/z*=444 $[M+H]^+$ (Calc: 443).

The hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **261** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **260** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **174** in Example 7 (yield >98%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **261**, 4-((*endo*)-8-(2,3-dihydro-1*H*-inden-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **261**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 11.42 (0.7H, s), 10.78 (0.2H, s), 8.09 (1H, d, J=8.11Hz), 7.90 (1H, d, J=7.6Hz), 7.76 (1H, t, J=7.1Hz), 7.47 (1H, t, J=7.6Hz), 7.25 (4H, d, J=13.18Hz), 6.04-6.00 (0.8H, m), 5.32 (0.2H, s), 4.11 (3H, m), 3.58 (2H, m), 2.76-2.68 (2H, m), 2.55-2.20 (11H, m); LC/MS (100%, t_r=1.2min): *m/z*=416 $[M+H]^+$ (Calc: 415).

5.42 Example 42



To a solution of the compound of formula **QA** ((*exo*)-bicyclo[3.3.1]nonan-3-amine, , 10.44mmol) in EtOH (3.1mL) and water (0.7mL), K_2CO_3 (144mg, 1.04mmol), at a temperature of about 25°C was added a mixture of the compound of formula **LB** (4060mg, 12.53mmol) in EtOH (29mL), and water (18mL). After the addition, the resulting reaction mixture was warmed to a temperature of 90°C and stirred for 5h. Thereafter, the reaction mixture was cooled to a temperature of about 0°C to provide a white precipitate. The precipitate was filtrated, washed twice with water (8mL for each wash), and dried to provide 1580mg of the compound of formula **QB** as a white solid (yield 57.9%).

The identity of the compound of formula **QB**, 9-((*exo*)-bicyclo[3.3.1]nonan-3-yl)-9-azabicyclo[3.3.1]nonan-3-one, was confirmed using ^{1}H NMR and LC/MS.

Compound **QB**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 1.40-1.70 (m, 12H), 1.75-1.90 (m, 2H), 1.90-2.10 (m, 4H), 2.20 (d, J =.20Hz, 2H), 2.60 (m, 2H), 3.35 (m, 1H), 3.66 (m, 2H); LC/MS: m/z=262.1 $[M+H]^+$ (Calc: 261).

Under a nitrogen atmosphere, to a solution of the compound of formula **QB** (1020mg, 3.90mmol) in CH_2Cl_2 (15mL) at a temperature of about 25°C was added 1,2-phenylenediamine (1266mg, 11.71mmol) and 2-ethylhexanoic acid (0.938mL, 5.85mmol). The mixture was stirred at a temperature of about 25°C for 30min to provide reaction mixture 1.

Under a nitrogen atmosphere, to a solution of sodium tetrahydroborate (590mg, 15.61mmol) in CH_2Cl_2 (10mL) at a temperature of about 25°C was added 2-ethylhexanoic acid (8.75mL, 54.6mmol). The mixture was stirred at a temperature of about 25°C for 30min to provide reaction mixture 2.

Under a nitrogen atmosphere, to reaction mixture 1 at 0°C was added reaction mixture 2 dropwise over a 15min period. After the addition, the resulting reaction mixture was warmed to a temperature of about 25°C and stirred for 30min. Thereafter, the reaction mixture was warmed to a temperature of 60°C and stirred for 16h. After cooling the reaction mixture to a temperature of about 25°C, saturated aqueous $NaHCO_3$ (20mL) was added, the mixture stirred for 10min, then extracted twice with 1M aqueous K_2CO_3/EtOAc (200mL for each extraction). The organic portions were combined, dried (Na_2SO_4), and concentrated under reduced pressure to provide a brown solid. The solid was chromatographed with an amino-silica gel column (Yamazen Corp. W091-01) eluted with a gradient of from 0%:100% EtOAc:n-hexane to 30%:70% EtOAc:n-hexane to provide 815mg of the compound of formula **QC** as a colorless solid (yield 59%).

The identity of the compound of formula **QC**, *N*^{1}-((*endo*)-9-((*exo*)-bicyclo[3.3.1]nonan-3-yl)-9-azabicyclo[3.3.1]nonan-3-yl)benzene-1,2-diamine, was confirmed using ^{1}H NMR and LC/MS.

Compound **QC**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 1.02-1.83 (m, 17H), 2.01 (m, 5H), 2.40-2.48 (m, 2H), 3.06-3.45 (m, 6H), 3.76 (br, 1H), 6.61-6.82 (m, 4H); LC/MS: m/z=354.1 $[M+H]^+$ (Calc: 353).

Under a nitrogen atmosphere, to a solution of the compound of formula **QC** (815mg, 2.305mmol) in toluene (16mL) at a temperature of about 25°C was added diethyl 2-oxomalonate (0.407mL, 2.54mmol) and AcOH (0.145mL, 2.54mmol). After the addition, the

resulting reaction mixture was warmed to a temperature of 130°C and stirred for 1h. Thereafter, the reaction mixture was cooled to a temperature of about 25°C and concentrated under reduced pressure to provide a sticky oil. The oil was diluted with saturated aqueous $NaHCO_3$, extracted twice with $CHCl_3$/water (100mL for each extraction), dried (Na_2SO_4), and concentrated under reduced pressure to provide an orange solid. The solid was chromatographed with an amino-silica gel column (Yamazen Corp. W091-01) eluted with a gradient of from 0%:100% EtOAc:n-hexane to 20%:80% EtOAc:n-hexane to provide 560mg of Substituted-Quinoxaline-Type Piperidine Compound **395** as a colorless solid (yield 52%).

Alternatively, compound **395** can be prepared as follows:

Under a nitrogen atmosphere, to a solution of the compound of formula **QC** (11.04g, 31.2mmol) in toluene (202mL) at a temperature of about 25°C was added diethyl 2-ketomalonate (6.02mL, 37.5mmol) and AcOH (2.143mL, 37.5mmol). After the addition, the resulting reaction mixture was warmed to a temperature of 130°C and stirred for 1h. Thereafter, the reaction mixture was cooled to a temperature of about 25°C and concentrated under reduced pressure to provide a sticky oil. The oil was diluted with saturated aqueous $NaHCO_3$, extracted twice with $CHCl_3$ (600mL for each extraction), dried (Na_2SO_4), and concentrated under reduced pressure to provide an orange solid. The resulting orange solid was sonicated by n-hexane/Et_2O (4/1), collected by filtration and dried under reduced pressure at 65°C for 8hr to give 1-(exo-9-bicyclo[3.3.1]-endo-9-aza-bicyclo[3.3.1]non-3-yl)-2-oxo-1,2-dihydro-quinoxaline-3-carboxylic acid ethyl ester **395** as a pale yellow solid. The remaining filtrate was purified by column chromatography (silica-gel; $CHCl_3$/MeOH=100/0~95/5) to give further **395** as a pale yellow solid. (Combined Yield; 9.83g, 67%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **395**, ethyl 4-((*endo*)-9-((*exo*)-bicyclo[3.3.1]nonan-3-yl)-9-azabicyclo[3.3.1]nonan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^1H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **395**: ^1H NMR: δ_H (400MHz, $CDCl_3$): 1.04-1.11 (m, 2H), 1.35-1.86 (m, 17H), 1.92-2.02 (m, 6H), 2.37-2.47 (m, 1H), 2.67-

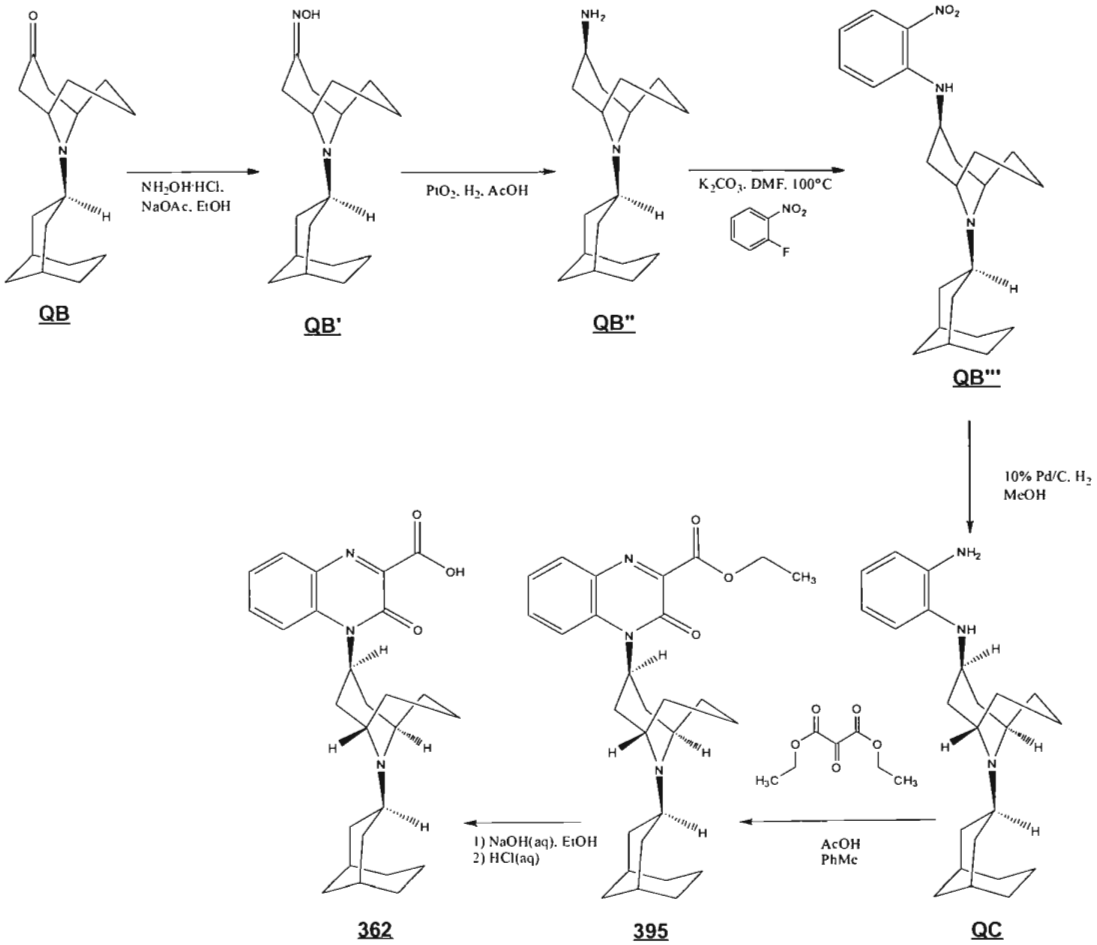
2.79 (m, 1H), 3.46-3.56 (m, 3H), 4.51 (q, J=7.07Hz, 2H), 5.20 (m, 1H), 7.34-7.37 (m, 1H), 7.63 (t, J=6.57Hz, 2H), 7.92 (d, J=8.08Hz, 1H); LC/MS: *m/z*=464.2 $[M+H]^+$ (Calc: 463).

To a suspension of Substituted-Quinoxaline-Type Piperidine Compound **395** (561mg, 1.21mmol) in ethanol (15mL) at a temperature of about 25°C was added 2N aqueous NaOH (1.812mL, 3.62mmol). The resulting reaction mixture was stirred at a temperature of about 25°C for 1h. Thereafter, the reaction mixture was concentrated under reduced pressure to provide a residue. The residue was diluted with water (10mL) to form a colorless solution, neutralized with 2N aqueous HCl (2.3mL), and sonicated to provide a white precipitate. The precipitate was collected by filtration, washed with water, and dried for 5h under reduced pressure at 75°C to provide 396mg of Substituted-Quinoxaline-Type Piperidine Compound **362** as a colorless solid (yield 75%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **362**, 4-((*endo*)-9-((*exo*)-bicyclo[3.3.1]nonan-3-yl)-9-azabicyclo[3.3.1]nonan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **362**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 0.83 (dq, J=8.72, 2.78Hz, 1H), 1.22 (s, 1H), 1.38 (br, 1H), 1.54 (d, J=12.63Hz, 1H), 1.69 (s, 6H), 1.87 (m, 4H), 2.05 (t, J=13.89Hz, 2H), 2.22 (s, 2H), 2.51 (dd, J=19.71, 11.12Hz, 2H), 2.70 (m, 3H), 2.98 (t, J=12.38Hz, 2H), 4.11-4.22 (m, 3H), 6.65 (br, 1H), 7.51-7.62 (m, 4H), 7.93 (t, J=7.83Hz, 1H), 8.16 (d, J=8.08Hz, 1H), 8.96 (dd, J=7.83, 6.32Hz, 1H), 10.89 (s, 1H); LC/MS (100%, t_r=1.55min): *m/z*=436.2 $[M+H]^-$ (Calc: 436).

Alternatively the compound **QC** and Substituted-Quinoxaline-Type Piperidine Compound **362** can be synthesized via an different route, which is shown below:



Compound **QB'** was prepared as follows:

Under a nitrogen atmosphere, to a suspension of the compound of formual **QB** (10.77g, 41.2mmol) in ethanol (215mL) at a temperature of about 25°C was added hydroxylamine hydrochloride (4.29g, 61.8mmol) and sodium acetate (5.07g, 61.8mmol). After the addition, the mixture was stirred at this temperature for 1.5hr. After quenching with water (50mL), the mixture was separated by $CHCl_3$/saturated $NaHCO_3$ (200mL for each extraction). The organic portions were combined, dried over Na_2SO_4, and concentrated to under reduced pressure to give 9-bicyclo[3.3.1]non-3-yl-9-aza-bicyclo[3.3.1]nonan-3-one oxime (**QB'**) as a pale yellow solid which was used in the next reaction without further purification (Yield; 11.39g, 100%).

The identity of the compound of formula **QB'**, 9-bicyclo[3.3.1]non-3-yl-9-aza-bicyclo[3.3.1]nonan-3-one oxime, was confirmed by LC/MS.

Compound **QB'**: LC/MS: m/z=277.45 $[M+H]^+$ (Calc: 276.42)

Compound **QB''** was prepared as follows:

To a solution of **QB'** (11.39g, 41.2mmol) in AcOH (203mL) at a temperature of about 25°C was added platinum(IV) oxide (1.871g, 8.24mmol). The mixture was stirred at a temperature of about 25°C. for 24hr under a hydrogen atmosphere at 5atm pressure. After filtration and washing with AcOEt (100mL), the filtrate was concentrated under reduced pressure to give a sticky yellow oil. To this oil water was added, and the resulting mixture was neutralized by 28% aqueous ammonia solution to give a white gel like precipitate. The mixture was extracted twice using $CHCl_3$/MeOH/H_2O (700mL for each extraction). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo to give the desired product, 9- exo- bicyclo[3.3.1]non-3-yl-9-endo-aza-bicyclo[3.3.1]non-3-ylamine **QB''** only in the *endo*-form, as a colorless solid, which was used in the next reaction without purification. (Yield; 9.07g, 84%)

The identity of the compound of formula **QB''**, 9- exo- bicyclo[3.3.1]non-3-yl-9-endo-aza-bicyclo[3.3.1]non-3-ylamine, was confirmed using ^{1}H NMR and LC/MS.

Compound **QB''**: ^{1}H-NMR (400MHz, DMSO-d_6) δ: 0.92-0.99 (m, 4H), 1.23-1.65 (m, 16H), 1.98 (m, 7H), 3.12 (s, 1H), 3.28 (s, 2H); LC/MS: m/z=263.15 $[M+H]^+$ (Calc: 262.43).

Compound **QB'''** was prepared as follows:

Under a nitrogen atmosphere, to a solution of **QB''** (9.07g, 34.6mmol) in DMF (136mL) at a temperture of about 25°C was added potassium carbonate (7.16g, 51.8mmol) and 1-fluoro-2-nitrobenzene (3.65mL, 34.6mmol). The mixture was stirred at 100°C for 2hr. The reaction mixture was cooled and quenched with ice-water (100mL) and saturated $NaHCO_3$ (10mL) to give a yellow precipitate which was collected by filtration. The precipitate was subsequently washed twice with water (50mL each), dried under reduced pressure at 70°C for 8hr to give the desired product (9-bicyclo[3.3.1]non-3-yl-9-aza-bicyclo[3.3.1]non-3-yl-(2-nitro-phenyl)-amine **QB'''** as a yellow solid (Yield; 11.98g, 90%).

The identity of the compound of formula **QB'''**, (9-bicyclo[3.3.1]non-3-yl-9-aza-bicyclo[3.3.1]non-3-yl-(2-nitro-phenyl)-amine, was confirmed using ^{1}H NMR and LC/MS.

Compound **QB'''**: ^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.85-2.02 (m, 26H), 2.45 (m, 2H), 3.49 (m, 3H), 4.03 (t, J=3.79Hz, 1H), 6.58 (t, J=7.58Hz, 1H), 6.93 (d, J=8.08Hz, 1H), 7.40 (t, J=7.33Hz, 1H), 8.09 (dd, J=48.50, 7.58Hz, 2H); LC/MS: m/z=384.2 $[M+H]^+$ (Calc: 383.53).

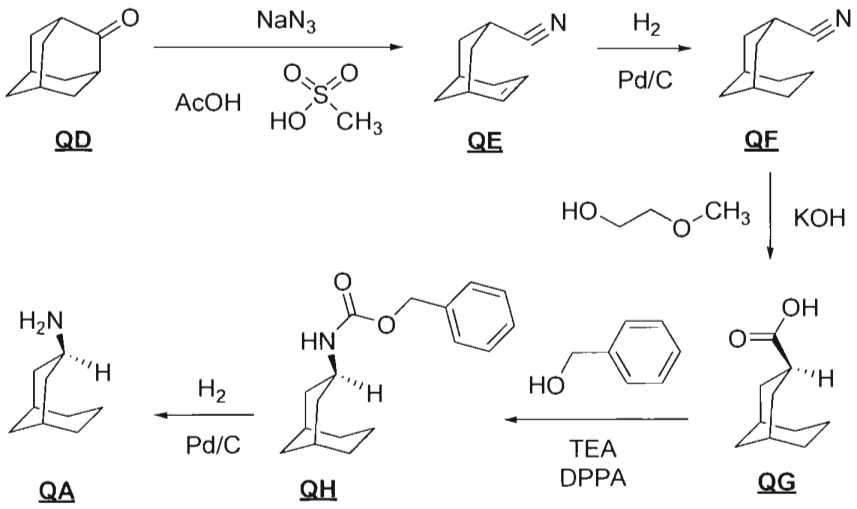
Compound **QC** was prepared as follows:

Under a hydrogen atmosphere, to a suspension of **QB'''** (11.98g, 31.2mmol) in MeOH (240mL) at a temperature of about 25°C was added 10%Pd-C (1.330g, 1.249mmol), and the mixture was stirred at this temperature for 1.5h. After the addition of $CHCl_3$ (150mL), the mixture was filtrated, washed with $CHCl_3$ and concentrated in vacuo to give N-(9-bicyclo[3.3.1]non-3-yl-9-aza-bicyclo[3.3.1]non-3-yl)benzene-1,2-diamine (**QC**) as a pale green solid which was very pure by NMR and therefore used in the next step without purification (Yield; 11.04g, 100%).

The identity of the compound of formula **QC**, N-(9-bicyclo[3.3.1]non-3-yl-9-aza-bicyclo[3.3.1]non-3-yl)benzene-1,2-diamine, was confirmed using ^{1}H NMR and LC/MS.

Compound **QC**: ^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.02-1.83 (m, 17H), 2.01 (m, 5H), 2.40-2.48 (m, 2H), 3.06-3.45 (m, 6H), 3.76 (br, 1H), 6.61-6.82 (m, 4H); LC/MS: m/z=354.14 $[M+H]^+$ (Calc: 353)

The compound of formula **QA** was prepared as follows:



Under a nitrogen atmosphere, to a solution of the compound of formula **QD** (adamantane-2-one, 60g, 399mmol, Sigma-Aldrich) in AcOH (251mL, 4394mmol) and methanesulfonic acid (182.00mL, 2803mmol, Sigma-Aldrich) at a temperature of 20°C was

added sodium azide (29.9g, 459mmol) portionwise over 45min. After the addition, the resulting reaction mixture was stirred for 30min at a temperature of from 20°C to 25°C. Thereafter, ice water (1L) was poured into the reaction mixture to provide a white precipitate that was collected by filtration, washed with water (400mL), and dried for 4h under reduced pressure at 60°C to provide 40.78g of the compound of formula **QE** as a colorless solid (yield 69%).

The identity of the compound of formula **QE**, bicyclo[3.3.1]non-6-ene-3-carbonitrile, was confirmed using ^{1}H NMR.

Compound **QE**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 1.53 (d, J=12.67Hz, 1H), 1.72-2.05 (m, 5H), 2.23 (dt, J=17.91, 8.11Hz, 2H), 2.41-2.50 (m, 2H), 2.96 (dd, J=9.63, 4.06Hz, 1H), 5.85-5.95 (m, 2H).

Under a hydrogen atmosphere, a mixture of the compound of formula **QE** (5260mg, 35.7mmol), 10% palladium on carbon (570mg, 0.536mmol), and MeOH (150mL) was stirred at a temperature of about 25°C for 4h. After the Pd/C was filtered off, the mixture was concentrated under reduced pressure to provide a colorless oil. The oil was chromatographed with a silica gel column eluted with a gradient of from 3%:97% EtOAc:n-hexane to 20%:80% EtOAc:n-hexane to provide 3500mg of the compound of formula **QF** as a colorless solid (yield 66%).

The identity of the compound of formula **QF**, bicyclo[3.3.1]nonane-3-carbonitrile, was confirmed using ^{1}H NMR.

Compound **QF**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 1.22 (m, 1H), 1.38-1.59 (m, 8H), 1.72-1.82 (m, 1H), 2.04-2.08 (m, 2H), 2.20-2.28 (m, 2H), 2.60-2.69 (m, 1H).

Under a nitrogen atmosphere, to a solution of the compound of formula **QF** (2530mg, 16.95mmol) in 2-methoxyethanol (26.9mL, 339mmol) at a temperature of about 25°C was added KOH (4280mg, 76mmol). After the addition, the resulting reaction mixture was warmed to a temperature of 120°C and stirred for 16h. Thereafter, the reaction mixture was cooled to a temperature of about 25°C, 2N aqueous HCl was added to adjust the pH within the range of from about 3 to about 4, and a pale brown precipitate formed. The precipitate was collected by filtration, washed with water, and dried for 3h under reduced pressure at 70°C to provide a pale brown solid, which ^{1}H NMR showed to be a 1:9 mixture of *endo*:*exo* isomers.

Under a nitrogen atmosphere, to a solution of the above *endo*:*exo* isomer mixture in 2-methoxyethanol (73.5mL, 932mmol) at a temperature of about 25°C was added KOH (4756mg, 85mmol). After the addition, the resulting reaction mixture was warmed to a temperature of 120°C and stirred for 16h. Thereafter, the reaction mixture was cooled to a temperature of about 25°C, 2N aqueous HCl was added to adjust the pH within the range of from about 3 to about 4, and a pale brown precipitate formed. The precipitate was collected by filtration, washed with water, and dried for 3h under reduced pressure at 70°C to provide 2187mg of the compound of formula **QG** as a pale brown solid, with a melting point of 126-128°C and present only as the *exo* isomer (yield 77%).

The identity of the compound of formula **QG**, (*exo*)-bicyclo[3.3.1]nonane-3-carboxylic acid, was confirmed using ^{1}H NMR.

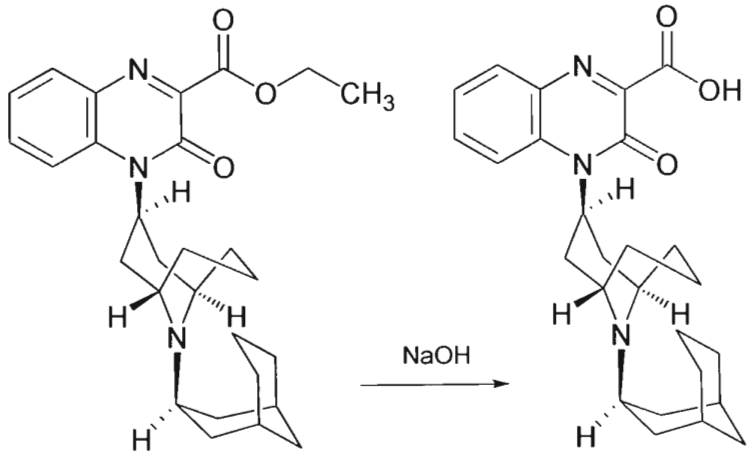
Compound **QG**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 1.52-1.85 (m, 10H), 1.96 (t, J=6.59Hz, 4H), 3.10-3.19 (m, 1H).

Under a nitrogen atmosphere, to a solution of the compound of formula **QG** (2680mg, 15.93mmol) in toluene (25mL) at a temperature of about 25°C was added TEA (2.65mL, 19.12mmol) and DPPA (4.51mL, 19.12mmol). After the addition, the resulting reaction mixture was warmed to a temperature of 70°C and stirred for 1h. Thereafter, the reaction mixture was cooled to a temperature of about 25°C and concentrated under reduced pressure to provide a pale yellow oil, which was dried under reduced pressure at a temperature of about 25°C. To the oil was added phenylmethanol (4.77mL, 45.9mmol, Sigma-Aldrich). After the addition, the resulting reaction mixture was warmed to a temperature of 90°C and stirred for 1.5h. Thereafter, the reaction mixture was cooled to a temperature of about 25°C and chromatographed with a silica gel column eluted with a gradient of from 2%:98% EtOAc:n-hexane to 10%:90% EtOAc:n-hexane to provide 4270mg of the compound of formula **QH** as a colorless solid (yield 98%).

The identity of the compound of formula **QH**, benzyl (*exo*)-bicyclo[3.3.1]nonan-3-ylcarbamate, was confirmed using ^{1}H NMR and LC/MS.

Compound **QH**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 1.32 (td, J=12.25, 3.71Hz, 2H), 1.44-1.80 (m, 8H), 1.97-2.09 (m, 4H), 4.28-4.46 (m, 2H), 5.08 (s, 2H), 7.26-7.35 (m, 5H); LC/MS: *m/z*=274.2 $[M+H]^+$ (Calc: 273).

Under a hydrogen atmosphere, a mixture of the compound of formula **QH** (4456mg, 16.30mmol), 10% palladium on carbon (694mg, 0.652mmol), and EtOH (50mL) was stirred at a temperature of about 25°C for 3h. After filtering off the Pd/C and washing with EtOH, the mixture was concentrated under reduced pressure to a volume of 20mL. The ethanol solution contained 2270mg (16.30mmol) of the compound of formula **QA**.



396 **369**

In a manner similar to that described above, Substituted-Quinoxaline-Type Piperidine Compounds **396** (yield 8% for three steps) and **369** (yield 91%) were prepared from the compound of formula **LB** by using (*endo*)-bicyclo[3.3.1]nonan-3-amine (**QI**) in place of the compound of formula **QA**.

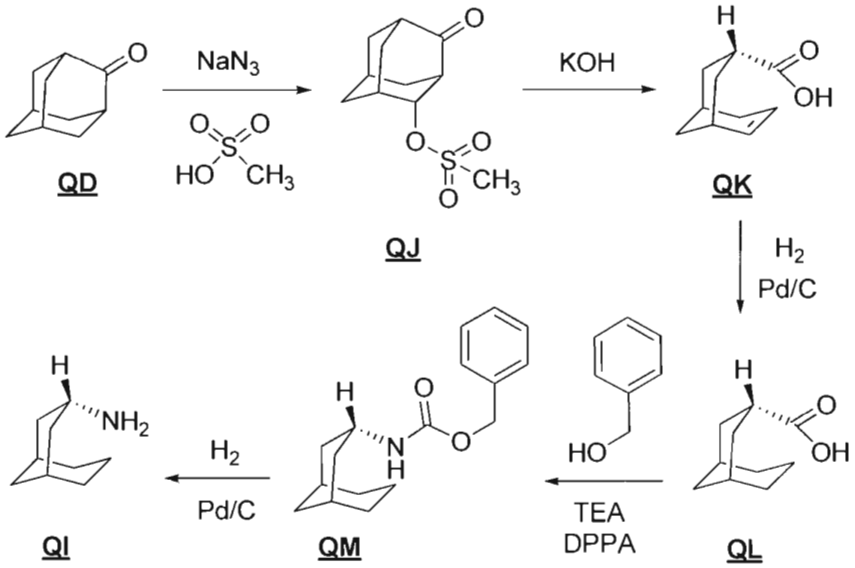
The identity of Substituted-Quinoxaline-Type Piperidine Compound **396**, ethyl 4-((*endo*)-9-((*endo*)-bicyclo[3.3.1]nonan-3-yl)-9-azabicyclo[3.3.1]nonan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **396**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 0.98-1.12 (m, 5H), 1.26 (s, 1H), 1.43 (m, 7H), 1.57 (m, 1H), 1.75-1.85 (m, 5H), 2.10 (m, 5H), 2.40-2.45 (m, 1H), 2.72 (br, 2H), 3.00-3.07 (m, 1H), 3.53 (d, J=10.11Hz, 2H), 4.51 (q, J=7.07Hz, 2H), 5.20 (br, 1H), 7.36 (t, J=3.54Hz, 1H), 7.65 (s, 2H), 7.93 (d, J=8.08Hz, 1H); LC/MS: *m/z*=464.1 $[M+H]^+$ (Calc: 463).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **369**, 4-((*endo*)-9-((*endo*)-bicyclo[3.3.1]nonan-3-yl)-9-azabicyclo[3.3.1]nonan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **369**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 0.84-0.89 (m, 1H), 1.27 (m, 4H), 1.40-1.52 (m, 2H), 1.66 (m, 5H), 1.85 (m, 1H), 2.11 (m, 2H), 2.28 (s, 4H), 2.50 (m, 2H), 2.76 (m, 1H), 3.00 (t, J=12.63Hz, 2H), 3.69-3.74 (m, 1H), 4.16 (d, J=10.11Hz, 2H), 6.78 (s, 1H), 7.56 (t, J=7.58Hz, 1H), 7.93 (t, J=7.83Hz, 1H), 8.19 (d, J=8.08Hz, 1H), 9.07 (t, J=7.58Hz, 1H), 11.08 (s, 1H); LC/MS (100%, t_r=1.55min): *m/z*=436.2 $[M+H]^+$ (Calc: 436).

The compound of formula **QI** was prepared as follows:



Under a nitrogen atmosphere, to a solution of the compound of formula **QD** (6.0g, 39.9mmol) in methanesulfonic acid (33.7mL, 519mmol) at a temperature of 20°C was added sodium azide (2.726g, 41.9mmol) portionwise over 2.5h. After the addition, the resulting reaction mixture was stirred for 3 days at 20°C. Thereafter, ice water (300mL) was poured into the reaction mixture to provide a white precipitate that was collected by filtration, washed with water, and dried for 6h under reduced pressure at 40°C to provide 5.63g of the compound of formula **QJ** as a colorless solid with a melting point of 69-72°C (yield 58%).

The identity of the compound of formula **QJ**, methanesulfonic acid 4-oxo-adamantan-2-yl ester, was confirmed using ^{1}H NMR.

Compound **QJ**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 1.75-2.12 (m, 9H), 2.31 (m, 1H), 2.41-2.50 (m, 2H), 2.58 (s, 1H), 2.88 (s, 1H), 3.05 (d, J=6.59Hz, 3H), 4.80 (t, J=3.55Hz, 1H).

To a solution of the compound of formula **QJ** (5.63g, 23.04mmol) in EtOH (100mL) at a temperature of about 25°C was added a KOH (8.469g, 151mmol) in water (67mL) solution. After the addition, the resulting reaction mixture was warmed to a temperature of 110°C and stirred for 12h. Thereafter, the reaction mixture was cooled to a temperature of about 25°C, 10% aqueous HCl was added to adjust the pH within the range of from about 3 to about 4, and a colorless precipitate formed. The precipitate was collected by filtration, washed with water, concentrated under reduce pressure, and dried for 8h under reduced pressure at 50°C to provide 3.61g of the compound of formula **QK** as a colorless solid with a melting point of 189-192°C (yield 94%).

The identity of the compound of formula **QK**, (*endo*)-bicyclo[3.3.1]non-6-ene-3-carboxylic acid, was confirmed using ^{1}H NMR.

Compound **QK**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 1.64 (m, 4H), 2.07-2.42 (m, 6H), 2.58 (t, J=6.32Hz, 1H), 5.57-5.68 (m, 2H).

In a manner similar to the preparation of the compound of formula **QF** above, the compound of formula **QL** was prepared from the compound of formula **QK** (yield 99%).

The identity of the compound of formula **QL**, (*endo*)-bicyclo[3.3.1]nonane-3-carboxylic acid, was confirmed using ^{1}H NMR.

Compound **QL**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 1.17 (d, J=13.18Hz, 1H), 1.37-1.82 (m, 10H), 2.12 (m, 4H), 2.51-2.60 (m, 1H).

In a manner similar to the preparation of the compound of formula **QH** above, the compound of formula **QM** was prepared from the compound of formula **QL** (yield 90%).

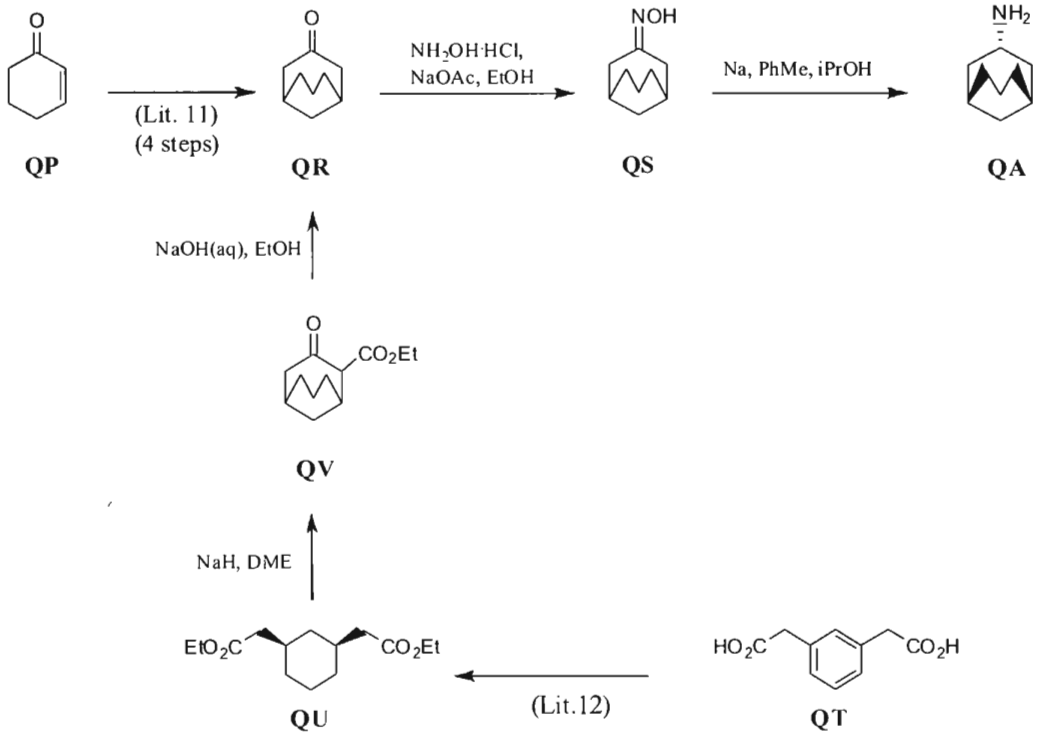
The identity of the compound of formula **QM**, benzyl (*endo*)-bicyclo[3.3.1]nonan-3-ylcarbamate, was confirmed using ^{1}H NMR and LC/MS.

Compound **QM**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 1.31 (m, 2H), 1.44-1.76 (m, 9H), 2.04 (s, 2H), 2.09 (s, 2H), 4.31-4.40 (m, 2H), 5.08 (s, 2H), 7.28-7.39 (m, 5H); LC/MS: *m/z*=274.2 $[M+H]^+$ (Calc: 273).

Under a hydrogen atmosphere, a mixture of the compound of formula **QM** (4.11g, 15.03mmol), 10% palladium on carbon (0.64g, 0.601mmol), and EtOH (45mL) was stirred at a temperature of about 25°C for 3h. After filtering off the Pd/C and washing with EtOH, the

mixture was concentrated under reduced pressure to a volume of 10mL. The ethanol solution contained 2.093g (15.03mmol) of the compound of formula **QI**.

Alternatively the compound of formula **QA** can be prepared by the two further synthetic routes shown below:



The compound of formula **QR** can be prepared according to a literature procedure described in "Improved synthetic methods for bicyclo[3.3.1]nonan-3-one". Mososе,Takefumi; Muraoka, Osamu, *Chemical and Pharmaceutical Bulletin* 26(1):288-295 (1978) (Lit. 11) starting from cyclohexen-2-one, **QP**. The compound of formula **QR** can also be prepared starting from cis-cyclohexane-1,3-diacetic acid diethyl ester, as described in H. K. Hall, *J. Org. Chem.* 28:3213-3214 (1963) (Lit. 12).

The compound of formula **QU** can be prepared as follows (Lit. 12):

Concentrated sulfuric acid (2mL) was added at a temperature of about 25°C to a solution of phenyl-1,3-diacetic acid (**QT**, 50g, 0.26 mol, TCI US) in ethanol (500mL). The resulting mixture was heated under reflux for 24h. After cooling to a temperature of about

25°C, the mixture was concentrated to about 200mL under reduced pressure, and diluted with toluene (400mL). The toluene solution was washed with water (100mL), and brine (100mL) and concentrated to dryness in vacuo to give intermediate phenyl-1,3-diacetic acid diethyl ester as a colorless oil (63g, 98%).

The identity of the intermediate phenyl-1,3-diacetic acid diethyl ester was confirmed using ^{1}H NMR.

Intermediate phenyl-1,3-diacetic acid diethyl ester: ^{1}HNR ($CDCl_3$, 400MHz): 7.26-7.3 (m, 1H), 7.18-7.21 (m, 3H), 4.15 (q, J=7.1Hz, 4H), 3.6 (s, 4H), 1.25 (t, J=7.2Hz, 6H).

A mixture of phenyl-1,3-diacetic acid diethyl ester (63g, 0.25 mol) and platinum dioxide (2g, 0.09 mol) in acetic acid (250mL) was degassed and stirred under an hydrogen atmosphere at 30°C for 15h. The reaction mixture was flushed with argon, and diluted with water (40mL). Subsequently, the catalyst was removed by filtration and the solution was concentrated to about 200mL. The resulting mixture was then diluted with toluene (400mL). The mixture was washed with water twice (100mL each), $NaHCO_3$ (100mL each) and brine (100mL). The solvent was removed under reduced pressure to give crude cis-cyclohexane-1,3-diacetic acid diethyl ester **QU** as a colorless oil (Lit. 12).

The identity of the compound of formula **QU** was confirmed using ^{1}H NMR.

Compound **QU**: ^{1}H NMR ($CDCl_3$, 400MHz): 4.15 (q, J=7.2Hz, 4H), 2.17 (d, J=7.0Hz, 4H), 1.4-1.9 (m, 7H), 1.25 (t, J=7.1Hz, 6H), 0.83-0.92 (m, 2H), 0.71 (dd, J=11.8, 11.9Hz).

The compound of formula **QV** can be prepared as follows:

Cis-cyclohexane-1,3-diacetic acid diethyl ester **QU** was dissolved in dry DME (300mL). To this solution, sodium hydride (15g) was added and the suspension stirred at 94°C for 16h. After cooling, the reaction mixture was slowly poured into ice-water (500mL) and extracted four times with EtOAc (200mL each). The combined organic layer was washed with brine, and concentrated to give 3-oxo-bicyclo[3.3.1]nonane-2-carboxylic acid ethyl ester **QV** which was used without purification in the next step.

Alternative preparation of bicyclo[3.3.1]nonan-3-one (**QR**):

Compound **QV** from the previous reaction was dissolved in ethanol (150mL). To this solution, sodium hydroxide (30g, 750mmol) in water (150mL) was added and the mixture

heated to 70°C for 8h. The reaction mixture was concentrated in vacuo, diluted with brine (150mL) and extracted three times with ether (150mL each). The combined organic extracts were concentrated to dryness in vacuo to give bicyclo[3.3.1]nonan-3-one **QR** as a white solid (Yield: 18g, 51% from 1,3-phenyl-diacetic acid).

The identity of the compound of formula **QR** was confirmed using ^{1}H NMR.

Compound **QR**: ^{1}H-NMR ($CDCl_3$) δ: 2.52-1.31 (m, 6H), 1.82 (m, 2H), 1.70-1.56 (m, 5H), 1.54-1.32 (m, 2H).

Preparation of bicyclo[3.3.1]nonan-3-one oxime (**QS**)

Under a nitrogen atmosphere, to a solution of **QR** (975mg, 7.05mmol) in ethanol (40mL) at a temperature of about 25°C was added sodium acetate (1,157mg, 14.11mmol) and hydroxylamine hydrochloride (980mg, 14.11mmol). The mixture was stirred at a temperature of about 25°C for 2 hr. The reaction mixture was diluted with saturated $NaHCO_3$, then extracted thrice with EtOAc (30mL each). The organic layers were combined and washed with saturated NaCl. The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo to give **QS** (800mg, 76%) as a yellow solid. The oxime was used for the next reaction without purification.

The identity of the compound of formula **QS** was confirmed using ^{1}H NMR.

Compound **QS**: ^{1}H-NMR ($CDCl_3$) δ: 1.40 (m, 1H), 1.50-1.80 (m, 8H), 1.99-2.17 (m, 3H), 2.40 (d, J=8.0Hz, 2H), 3.20 (d, J=16.0Hz, 1H).

Alternative preparation of bicyclo[3.3.1]non-3-ylamine (**QA**) (Ref.: *J. Med. Chem.* 49:1781-1791 (2006)):

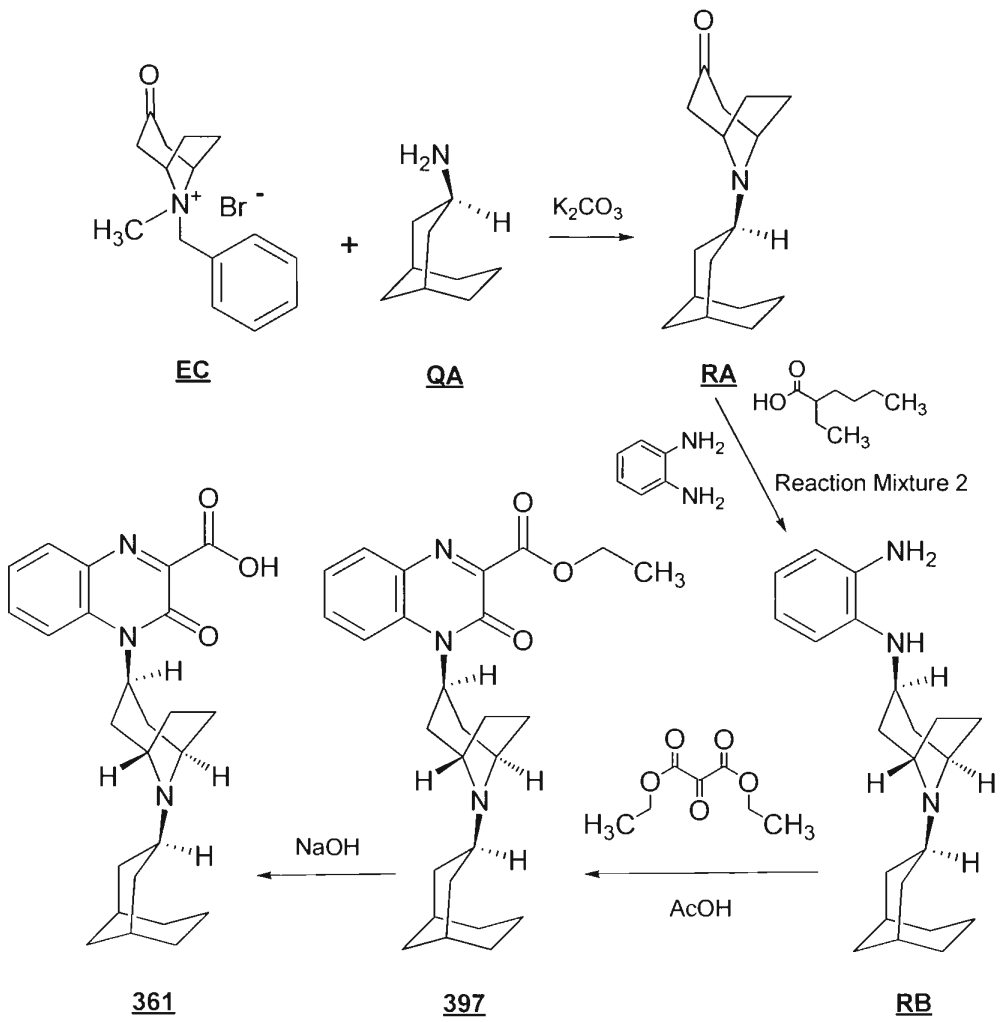
Under a nitrogen atmosphere, to a refluxing suspension of sodium (2.401g, 104mmol) in toluene (20mL) at a temperature of about 115°C was added dropwise over 30min bicyclo[3.3.1]nonan-3-one oxime (**QS**, 1.60g, 10.44mmol) in 2-propanol (8mL). The mixture was stirred at reflux for 2 hr. After addition of the oxime solution is completed, 2-propanol (3mL) was added dropwise. The reaction mixture was heated to reflux until all of the Na was consumed followed by cooling to a temperature of about 25°C. The reaction mixture was then quenched by the addition of H_2O (20mL). The organic layer was separated, and washed twice with 1N HCl (30mL each). The acidic solution was made alkaline by the addition of 2N NaOH (50mL), and extracted thrice with Et_2O (50mL each). The organic layers were combined and

washed with saturated NaCl (50mL). The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo to give of bicyclo[3.3.1]non-3-ylamine **QA**. This compound was used in the next step without purification in 2-propanol solution.

The identity of the compound of formula **QA** was confirmed using ^1H NMR.

Compound **QA**: ^1H-NMR ($CDCl_3$) δ: 1.20-1.70 (m, 10H), 1.90 (m, 4H), 3.38 (m, 1H).

5.43 Example 43



To a mixture of the compound of formula **QA** (2270mg, 16.30mmol), K_2CO_3 (225.3mg, 1.63mmol), EtOH (20mL), and water (5mL) at a temperature of about 25°C was added dropwise a mixture of the compound of formula **EC** (5058mg, 16.30mmol), EtOH (20mL), and water (27mL). After the addition, the resulting reaction mixture was warmed to a

temperature of 90°C and stirred for 4h. Thereafter, the reaction mixture was cooled to a temperature of about 25°C, diluted with saturated aqueous $NaHCO_3$, then extracted twice with EtOAc/water (100mL for each extraction). The organic portions were combined, dried (Na_2SO_4), and concentrated under reduced pressure to provide an oil. The oil was chromatographed with a silica gel column eluted with a gradient of from 20%:80% EtOAc:n-hexane to 80%:20% EtOAc:n-hexane to provide 2030mg of the compound of formula **RA** as a colorless solid (yield 50%).

The identity of the compound of formula **RA**, 8-((*exo*)-bicyclo[3.3.1]nonan-3-yl)-8-azabicyclo[3.2.1]octan-3-one, was confirmed using ^{1}H NMR and LC/MS.

Compound **RA**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 1.79 (m, 12H), 2.26 (m, 8H), 2.87 (d, J=13.64Hz, 2H), 3.52 (td, J=11.12, 5.56Hz, 1H), 3.99 (s, 2H); LC/MS: *m/z*=248.5 $[M+H]^+$ (Calc: 247).

Under a nitrogen atmosphere, to a solution of the compound of formula **RA** (2029mg, 8.20mmol) in CH_2Cl_2 (25mL) at a temperature of about 25°C was added 1,2-phenylenediamine (2661mg, 24.61mmol) and 2-ethylhexanoic acid (1.971mL, 12.30mmol). The mixture was stirred at a temperature of about 25°C for 30min to provide reaction mixture 1.

Under a nitrogen atmosphere, to a solution of sodium tetrahydroborate (1241mg, 32.8mmol) in CH_2Cl_2 (17mL) at a temperature of about 25°C was added 2-ethylhexanoic acid (18.40mL, 115mmol). The mixture was stirred at a temperature of about 25°C for 30min to provide reaction mixture 2.

Under a nitrogen atmosphere, to reaction mixture 1 at 0°C was added reaction mixture 2 dropwise over a 15min period. After the addition, the resulting reaction mixture was warmed to a temperature of about 25°C and stirred for 30min. Thereafter, the reaction mixture was warmed to a temperature of 60°C and stirred for 16h. After cooling the reaction mixture to a temperature of about 25°C, saturated aqueous $NaHCO_3$ (20mL) was added, the mixture stirred for 10min, then extracted twice with 1M aqueous K_2CO_3/EtOAc (150mL for each extraction). The organic portions were combined, dried (Na_2SO_4), and concentrated under reduced pressure to provide a yellow oil. The oil was chromatographed with a silica gel column eluted with a gradient of from 97%:3% $CHCl_3$:(10% NH_3 in MeOH) to 80%:20% $CHCl_3$:(10% NH_3 in MeOH) to provide 874mg of the compound of formula **RB** as a pale yellow amorphous solid (yield 31%).

The identity of the compound of formula **RB**, *N*^{1}-((*endo*)-8-((*exo*)-bicyclo[3.3.1]nonan-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)benzene-1,2-diamine, was confirmed using ^{1}H NMR and LC/MS.

Compound **RB**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 0.91 (m, 3H), 1.26-2.10 (m, 20H), 2.35 (m, 2H), 3.28-3.33 (m, 1H), 3.69 (m, 3H), 6.57 (d, J=7.58Hz, 1H), 6.75 (m, 3H); LC/MS: *m/z*=340.6 $[M+H]^+$ (Calc: 339).

Under a nitrogen atmosphere, to a solution of the compound of formula **RB** (870mg, 2.56mmol) in xylene (15mL) at a temperature of about 25°C was added diethyl 2-oxomalonate (0.494mL, 3.07mmol) and AcOH (0.176mL, 3.07mmol). After the addition, the resulting reaction mixture was warmed to a temperature of 130°C and stirred for 1h. Thereafter, the reaction mixture was cooled to a temperature of about 25°C, diluted with saturated aqueous $NaHCO_3$, extracted twice with EtOAc (100mL for each extraction), dried (Na_2SO_4), and concentrated under reduced pressure to provide an orange oil. The oil was chromatographed with an amino-silica gel column (Yamazen Corp. W091-01) eluted with a gradient of from 5%:95% EtOAc:n-hexane to 30%:70% EtOAc:n-hexane to provide a pale yellow solid. The solid was triturated with 1:4 Et_2O:n-hexane and dried under reduced pressure at 70°C to provide 343mg of Substituted-Quinoxaline-Type Piperidine Compound **397** as a colorless solid (yield 30%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **397**, ethyl 4-((*endo*)-8-((*exo*)-bicyclo[3.3.1]nonan-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

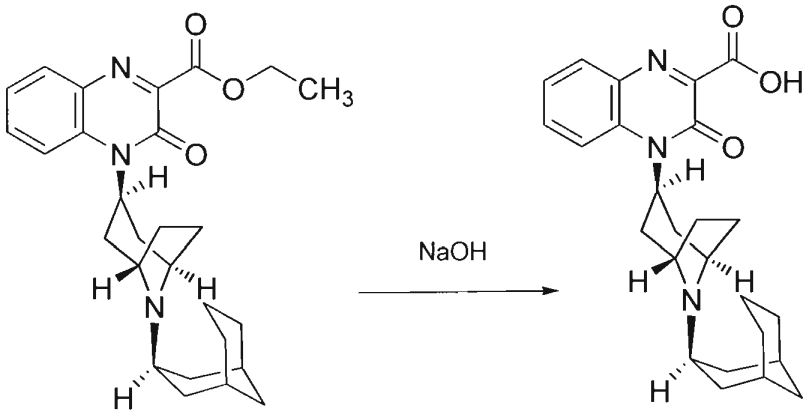
Substituted-Quinoxaline-Type Piperidine Compound **397**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 0.83-0.88 (m, 1H), 1.26 (dd, J=33.09, 17.94Hz, 3H), 1.51 (m, 11H), 1.91 (m, 8H), 2.20 (s, 3H), 2.79 (dt, J=11.62, 3.66Hz, 1H), 3.70 (s, 2H), 4.50 (q, J=7.07Hz, 2H), 5.20 (br, 1H), 7.34 (t, J=7.07Hz, 1H), 7.61 (q, J=7.92Hz, 2H), 7.91 (d, J=7.58Hz, 1H); LC/MS: *m/z*=450.1 $[M+H]^+$ (Calc: 449).

To a solution of Substituted-Quinoxaline-Type Piperidine Compound **397** (343mg, 0.763mmol) in ethanol (10mL) at a temperature of about 25°C was added 2N aqueous NaOH (1.144mL, 2.289mmol). The resulting reaction mixture was stirred at a temperature of about 25°C for 1h. Thereafter, the reaction mixture was concentrated under reduced pressure to provide a residue. The residue was diluted with water (2mL) to form a pale yellow solution,

neutralized with 2N aqueous HCl (1.144mL), and sonicated to provide a white precipitate. The precipitate was collected by filtration, washed with water, and dried for 8h under reduced pressure at 75°C to provide 312mg of Substituted-Quinoxaline-Type Piperidine Compound **361** as a colorless solid (yield 97%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **361**, 4-((*endo*)-8-((*exo*)-bicyclo[3.3.1]nonan-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **361**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 0.86 (m, 2H), 1.64 (m, 6H), 1.89 (m, 1H), 2.03 (dq, J=9.09, 2.44Hz, 2H), 2.42 (m, 9H), 3.01 (m, 2H), 3.49 (s, 1H), 4.26 (d, J=1.01Hz, 2H), 6.55 (s, 1H), 7.55 (t, J=7.33Hz, 1H), 7.92 (dd, J=9.85, 5.81Hz, 1H), 8.18 (d, J=7.58Hz, 1H), 8.40 (d, J=8.59Hz, 1H), 11.41 (s, 1H); LC/MS (100%, t_r=1.38min): *m/z*=422.5 $[M+H]^+$ (Calc: 421.5).



398 **360**

In a manner similar to that described above, Substituted-Quinoxaline-Type Piperidine Compounds **398** (yield 4% for three steps) and **360** (yield 87%) were prepared from the compound of formula **EC** by using the compound of formula **QI** in place of the compound of formula **QA**.

The identity of Substituted-Quinoxaline-Type Piperidine Compound **398**, ethyl 4-((*endo*)-8-((*endo*)-bicyclo[3.3.1]nonan-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

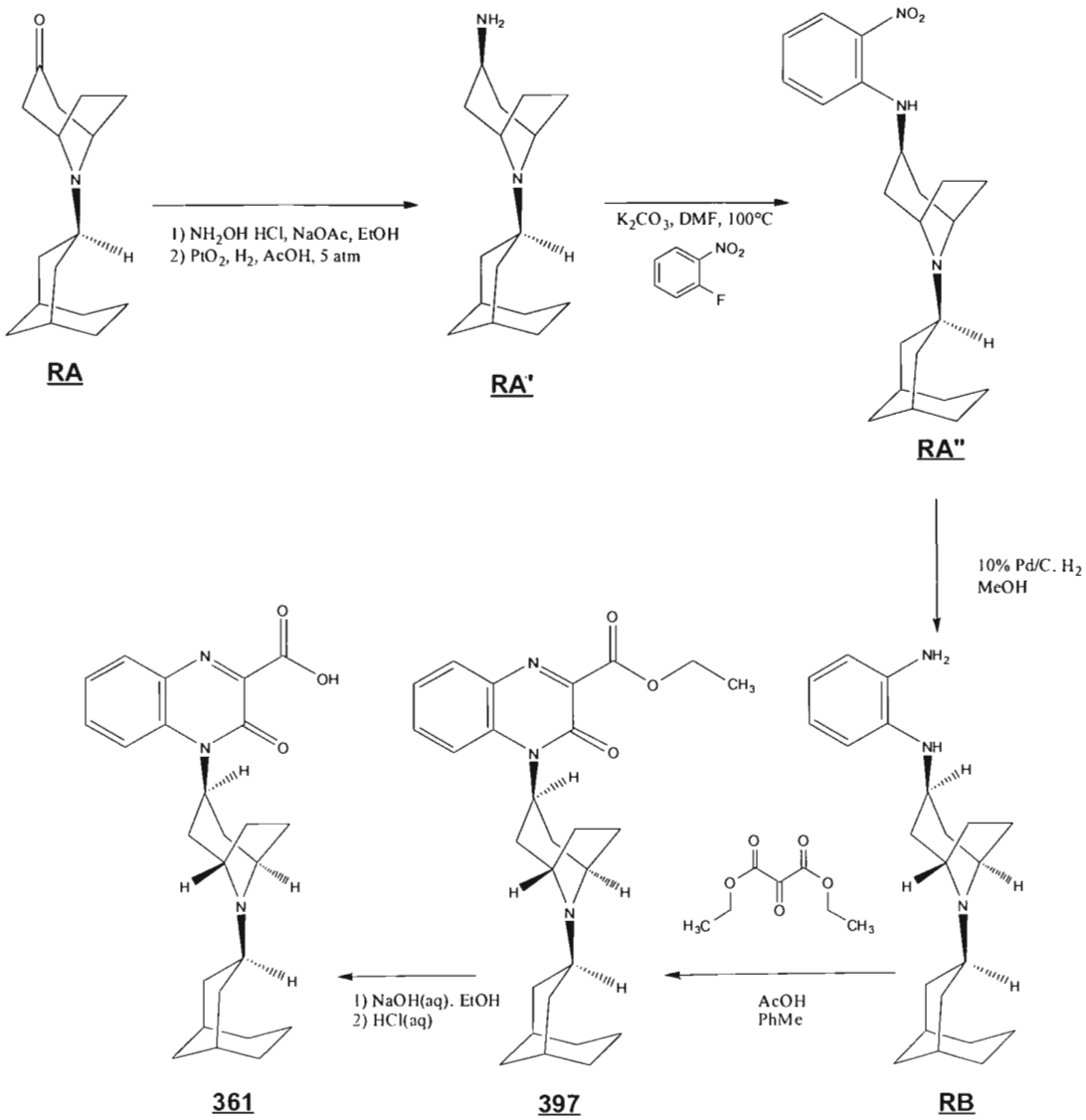
Substituted-Quinoxaline-Type Piperidine Compound **398**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 0.86 (dq, J=10.11, 2.69Hz, 1H), 1.07 (m, 3H), 1.21-1.45 (m, 10H), 1.65-2.37 (m,

15H), 3.67 (t, J=2.53Hz, 2H), 4.50 (q, J=7.07Hz, 2H), 5.18 (br, 1H), 7.35 (t, J=7.33Hz, 1H), 7.60 (t, J=9.60Hz, 2H), 7.91 (d, J=8.08Hz, 1H); LC/MS: *m/z*=450.2 $[M+H]^+$ (Calc: 449).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **360**, 4-((*endo*)-8-((*endo*)-bicyclo[3.3.1]nonan-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

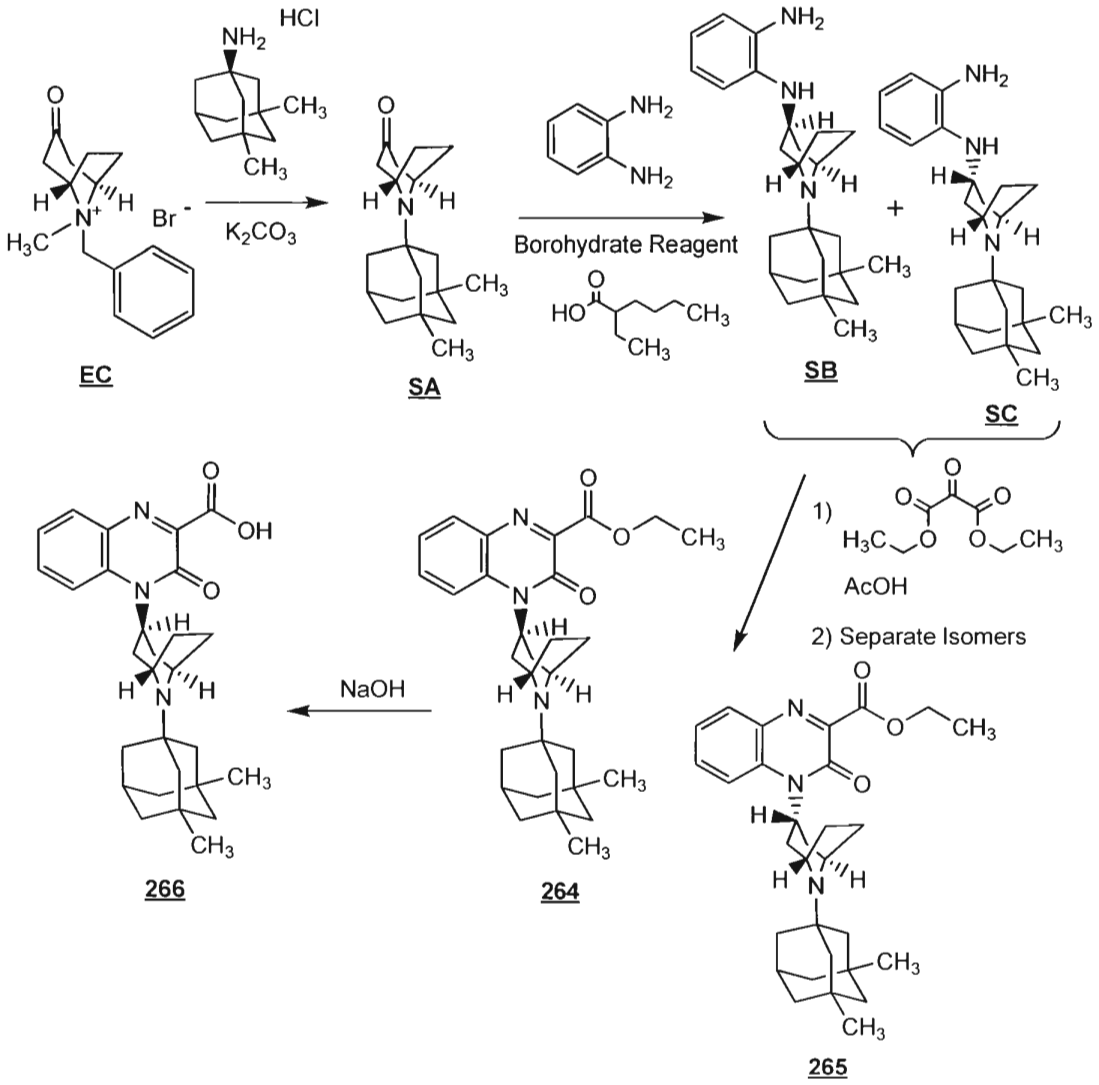
Substituted-Quinoxaline-Type Piperidine Compound **360**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 0.84-0.88 (m, 4H), 1.38-1.46 (m, 1H), 1.54-1.65 (m, 3H), 2.27 (m, 6H), 2.46 (dt, J=12.80, 4.93Hz, 3H), 2.95 (br, 3H), 4.25 (s, 2H), 6.61 (s, 1H), 7.51 (d, J=8.08Hz, 1H), 7.88 (dd, J=9.60, 5.05Hz, 1H), 8.14 (d, J=8.59Hz, 1H), 8.44 (d, J=4.04Hz, 1H), 11.55 (s, 1H); LC/MS (100%, t_r=1.48min): *m/z*=422.2 $[M+H]^+$ (Calc: 421.5).

Alternatively the compound **RB** and compound **361** can be synthesized via an alternative route, which is shown below:



In an alternative procedure, the intermediate (**RA**) can be converted to the oxime using hydroxylamine hydrochloride and sodium acetate in ethanol, and the oxime reduced to 8-exo bicyclo[3.3.1]non-3-yl-8-endo-aza-bicyclo[3.2.1]oct-3-ylamine (**RA'**) by hydrogenation using platinum oxide in acetic acid under 5 atmospheres of hydrogen. Intermediate (**RA'**) can be reacted with 2-fluoro nitrobenzene and potassium carbonate in DMF to give 8-exo-bicyclo[3.3.1]non-3-yl-8-endo-aza-bicyclo[3.2.1]oct-3-yl)-(2-nitro-phenyl)-amine (**RA''**). Finally reduction of the nitro group using 10% palladium on charcoal can give N-(exo-8-bicyclo[3.3.1]non-3-yl-8-endo-aza-bicyclo[3.2.1]oct-3-yl)benzene-1,2-diamine (**RB**).

5.44 Example 44



In a manner similar to the preparation of the compound of formula **DC** in Example 13, the compound of formula **SA** was prepared except that the compound of formula **EC** was used in place of the compound of formula **DB** and memantine hydrochloride (*i.e.*, the hydrochloride of 1-amine-3,5-dimethyl-adamantane, Sigma-Aldrich) was used in place of 1-adamantylamine (yield 5%).

The identity of the compound of formula **SA**, 8-(3,5-dimethyl-adamantan-1-yl)-8-aza-bicyclo[3.2.1]octan-3-one, was confirmed using ^{1}H NMR.

Compound **SA**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 3.95 (2H, m), 2.52 (2H, dd, J=16.7, 6.7Hz), 2.28 (2H, dd, J=16.7, 3.3Hz), 2.12 (1H, m), 1.80 (2H, m), 1.67-1.51 (9H, m), 1.37-1.23 (8H, m), 1.10 (2H, m), 0.86 (6H, s).

In a manner similar to the preparation of the compounds of formula **DD** and **DE** in Example 13, the compounds of formula **SB** and **SC** were prepared except that the compound of formula **SA** was used in place of the compound of formula **DC** (yield 85% of 1:1 **SB**:**SC**).

The identity of the compound of formula **SB**:**SC** *endo:exo* isomeric mixture, *N*-[8-3,5-dimethyl-adamantan-1-yl)-8-aza-bicyclo[3.2.1]oct-3-yl]-benzene-1,2-diamine, was confirmed using ^{1}H NMR.

Compounds **SB**:**SC**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 6.84-6.55 (4H, m), 3.90 (1H, m, isomer 1 (**SB**)), 3.80 (1H, m, isomer 2 (**SC**)), 3.69 (1H, m), 3.0 (3H, bs), 2.41 (1H, m), 2.20-2.04 (3H, m), 1.95-1.76 (5H, m), 1.62 (2H, m), 1.50-1.05 (12H, m), 1.36 (3H, s, isomer 1 (**SB**)), 1.33 (3H, s, isomer 2 (**SC**)).

To the above **SB**:**SC** mixture (1.18g, 3.1mmol) and toluene (20mL) was added acetic acid (0.2mL, 3.41mmol) followed by diethyl 2-oxomalonate (0.72mL, 4.66mmol). The reaction mixture was refluxed for 4h, cooled, diluted with EtOAc (100mL), washed with 1M aqueous K_2CO_3 solution (100mL), dried ($MgSO_4$), and evaporated to dryness under reduced pressure to provide a yellow gum. Flash chromatography of the gum with a silica gel column eluting with 400:100:10:1 hexanes:EtOAc:MeOH:ammonia provided 420mg of Substituted-Quinoxaline-Type Piperidine Compound **264** (yield 28%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **264**, *endo-N*-[8-(3,5-dimethyl-adamantan-1-yl)-8-aza-bicyclo[3.2.1]oct-3-yl]-benzene-1,2-diamine, was confirmed by ^{1}H NMR and TLC.

Substituted-Quinoxaline-Type Piperidine Compound **264**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.92 (1H, dd, J=8, 1Hz), 7.62 (1H, t, J=8Hz), 7.53 (1H, J=8Hz), 7.34 (1H, dt, J=8, 1Hz), 4.50 (2H, q, J=8.9Hz), 3.86 (1H, m), 2.23 (4H, m), 2.12 (1H, m), 1.83 (4H, m), 1.46 (2H, m), 1.43 (3H, t, J=8.9Hz), 1.26 (9H, m), 1.10 (2H, m), 0.86 (6H, s); TLC (SiO_2) 400:100:10:1 hexanes:EtOAc:MeOH:ammonia: Rf=0.26 with UV detection, Dragendorff's reagent.

Further elution with 300:100:10:1 hexanes:EtOAc:MeOH:ammonia provided 300mg of Substituted-Quinoxaline-Type Piperidine Compound **265** (yield 20%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **265**, *exo-N*-[8-(3,5-dimethyl-adamantan-1-yl)-8-aza-bicyclo[3.2.1]oct-3-yl]-benzene-1,2-diamine, was confirmed by ^{1}H NMR and TLC.

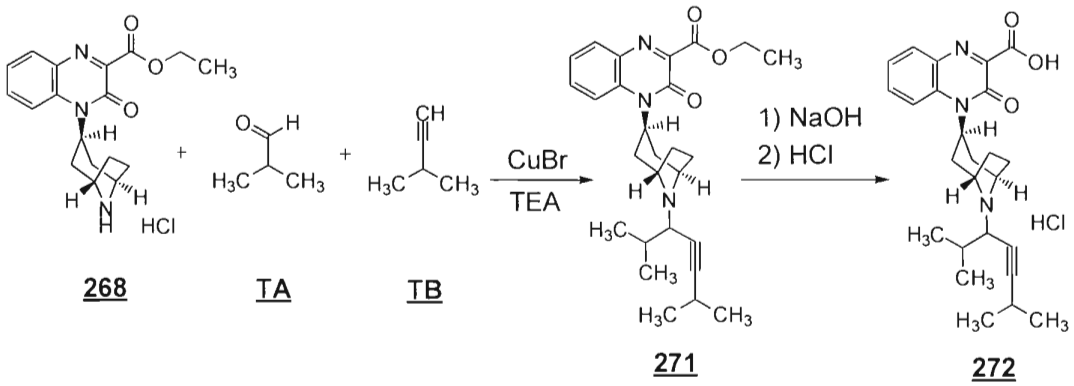
Substituted-Quinoxaline-Type Piperidine Compound **265**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 8.34 (1H, bs), 7.91 (1H, dd, J=9.2, 1.2Hz), 7.60 (1H, dt, J=9.2, 1.2Hz), 7.33 (1H, dt, J=9.2, 1.2Hz), 4.50 (2H, q, J=8Hz), 3.91 (2H, m), 2.63 (2H, t, J=16Hz), 2.15 (1H, m), 1.88-1.72 96H, m), 1.56 (4H, m), 1.52 (2H, m), 1.43 (3H, t, J=8Hz), 1.37-1.24 (8H, m), 1.13 (2H, m); TLC (SiO_2) 300:100:10:1 hexanes:EtOAc:MeOH:ammonia: Rf=0.19 with UV detection, Dragendorff's reagent.

Substituted-Quinoxaline-Type Piperidine Compound **266** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **264** in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **111** in Example 5 (yield 83%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **266**, *endo*-8-aza-bicyclo[3.2.1]oct-3-yl]-3-oxo-3,4-dihydro-quinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR.

Substituted-Quinoxaline-Type Piperidine Compound **266**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 7.92 (1H, m), 7.80 (1H, m), 7.68 (1H, bs), 7.47 (1H, m), 4.85 (1H, bs), 3.56 (2H, m), 2.49-2.12 (6H, m), 2.12-1.52 (15H, m), 1.35 (2H, m).

5.45 Example 45



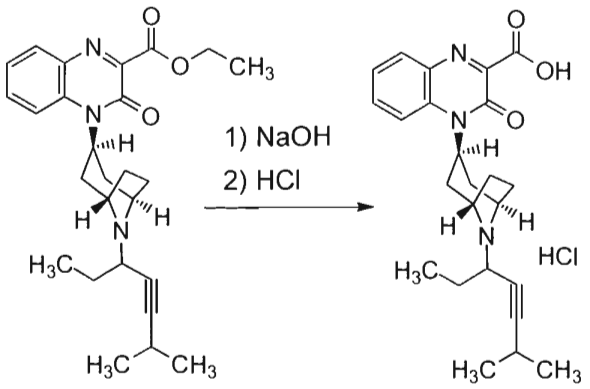
268 **TA** **TB** **271** **272**

In a dry and argon-flushed 10mL vial, CuBr (0.05eq, Sigma-Aldrich) was suspended in dry toluene (2.5mL) and stirred at a temperature of about 25°C for 30min. Thereafter, MS 4Å molecular sieves (200mg) were added, followed by 3-methylbut-1-yne (**TB**, 2.0eq, Sigma-Aldrich), isobutyraldehyde (**TA**, 1.5eq, Sigma-Aldrich), the hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **268** (200mg, 1.0eq), and TEA (1.2eq). The resulting reaction mixture was warmed to 60°C and shaken for 2h. After the molecular sieves were filtered off, the mixture was washed with diethyl ether and the filtrate was concentrated under reduced pressure to provide a residue. The residue was chromatographed with a silica gel column eluted with 2:1 Et_2O:hexanes to provide Substituted-Quinoxaline-Type Piperidine Compound **271**, ethyl 4-((*endo*)-8-(2,6-dimethylhept-4-yn-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate.

To a mixture of Substituted-Quinoxaline-Type Piperidine Compound **271** and EtOH (2mL) at 0°C was added 2N aqueous NaOH (0.3mL). The resulting reaction mixture was stirred for 1h as its temperature warmed from 0°C to about 25°C. Thereafter, the reaction mixture was diluted with $CHCl_3$ (20mL) and neutralized with 1N aqueous HCl. The organic portion was separated, concentrated under reduced pressure, and dried to provide 50mg of the hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **272** as a white solid (yield 20% for two steps).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **272**, 4-((*endo*)-8-(2,6-dimethylhept-4-yn-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid, was confirmed using ^1H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **272**: ^1H NMR: δ_H (400MHz, $CDCl_3$): 11.4 (br, 1H, HCl), 8.38 (d, 1H, J=8.9Hz), 8.14 (d, 1H, J=8.2Hz), 7.83 (dd, 1H, J=7.2Hz, 8.8Hz), 7.48 (dd, 1H, J=8.1Hz, 8.3Hz), 6.72-6.78 (m, 1H), 4.35-4.38 (m, 1H), 3.95-3.98 (m, 1H), 3.52-3.53 (m, 1H), 3.0-3.08 (m, 2H), 2.18-2.6 (m, 8H), 1.25 (d, 3H, J=6.8Hz), 1.13-1.16 (m, 6H), 1.06 (d, 3H, J=6.6Hz); LC/MS (100%, t_r=5.897): *m/z*=423.6 $[M+H]^+$.



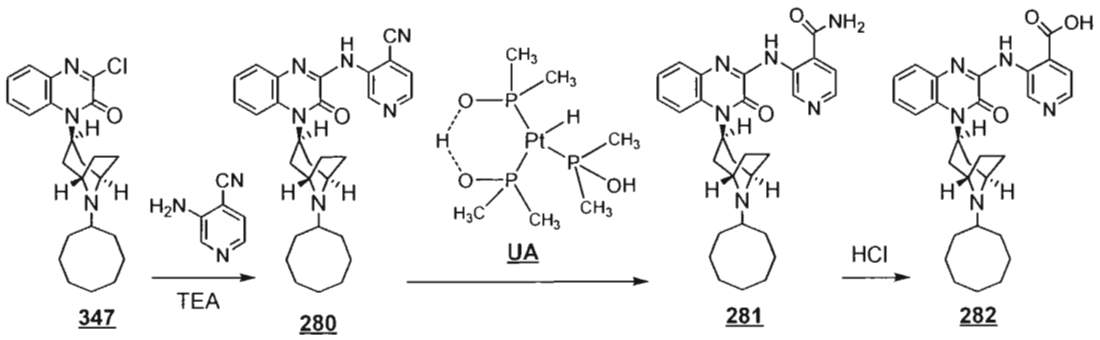
273 **274**

Substituted-Quinoxaline-Type Piperidine Compound **273**, ethyl 4-((*endo*)-8-(6-methylhept-4-yn-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was prepared from Substituted-Quinoxaline-Type Piperidine Compound **268** by using propionaldehyde (Sigma-Aldrich) in place of isobutyraldehyde. Thereafter, in a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **272**, the hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **274** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **273** (yield 30% for two steps).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **274**, 4-((*endo*)-8-(6-methylhept-4-yn-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **274**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 12.02 (br, 1H, HCl), 8.44 (d, 1H, J=8.3Hz), 8.24 (dd, 1H, J=1.5Hz, 8.2Hz), 7.93-7.97 (m, 1H), 7.57-7.61 (m, 1H), 6.66-6.71 (m, 1H), 4.55-4.58 (m, 1H), 4.09-4.13 (m, 1H), 3.54-3.59 (m, 1H), 3.02-3.14 (m, 2H), 2.36-2.72 (m, 8H), 1.21-1.26 (m, 6H), 1.16 (t, 3H, J=7.5Hz); LC/MS (100%, t_r=5.506): *m/z*=408.6 $[M+H]^+$.

5.46 Example 46



In a manner similar to Example 15, Substituted-Quinoxaline-Type Piperidine Compound **280** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **347** by using 3-aminoisonicotinonitrile (Sigma-Aldrich) in place of serine amide hydrochloride (yield 94%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **280**, 3-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)isonicotinonitrile, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **280**: ^{1}H NMR: δ_H ($CDCl_3$): 10.38 (1H, s), 9.00 (1H, s), 8.44 (1H, t, J=2.50Hz), 7.72 (1H, d, J=8.00Hz), 7.53 (1H, d, J=8.60Hz), 7.48 (1H, d, J=5.00Hz), 7.40 (1H, t, J=8.00Hz), 7.32 (1H, t, J=8.00Hz), 5.20 (1H, m), 3.69 (2H, s), 2.31 (5H, m), 2.05 (2H, m), 1.85-1.50 (16H, m); LC/MS: *m/z*=483 $[M+H]^+$ (Calc: 482.6).

To a mixture of Substituted-Quinoxaline-Type Piperidine Compound **280** (327mg, 0.678mmol), EtOH (4mL), and water (2.0mL) at a temperature of about 25°C was added the platinum catalyst complex **UA** (14.5mg, 0.034mmol), prepared according to T. Ghaffar and A.W. Parkins, *Tetrahedron Let.*, 36(47):8657-8660 (1995). The resulting reaction mixture was warmed to 80°C and stirred for 8h then concentrated under reduced pressure to provide a residue. The residue was chromatographed with a silica gel column eluted with a gradient of from 97%:3% $CHCl_3$:MeOH to 90%:10% $CHCl_3$:MeOH to provide 298mg of Substituted-Quinoxaline-Type Piperidine Compound **281** as a white solid (yield 88%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **281**, 3-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)isonicotinamide, was confirmed using ^{1}H NMR and LC/MS.

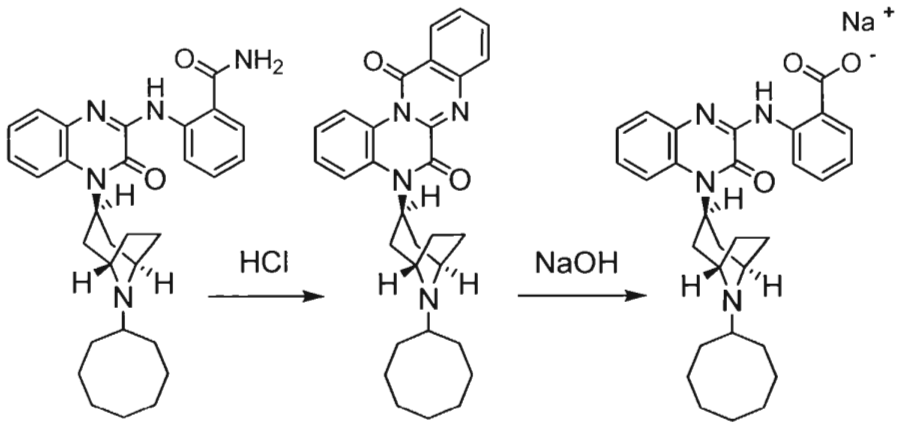
Substituted-Quinoxaline-Type Piperidine Compound **281**: ^{1}H NMR: δ_H (DMSO-d_6): 11.76 (1H, s), 10.36 (1H, s), 8.49 (1H, s), 8.38 (1H, t, J=2.40Hz), 7.97 (1H, s), 7.68 (2H, m), 7.44 (2H, m), 7.31 (1H, t, J=7.20Hz), 5.20 (1H, br), 3.65 (2H, s), 2.50-1.90 (7H, m), 1.90-1.30 (16H, m); LC/MS: *m/z*=501 $[M+H]^+$ (Calc: 500.6).

To a mixture of Substituted-Quinoxaline-Type Piperidine Compound **281** (150mg, 0.300mmol) and water (1.0mL) at 0°C was added concentrated aqueous HCl (2mL, 65.8mmol). The resulting reaction mixture was warmed to 80°C and stirred for 3h. Thereafter, upon neutralizing the reaction mixture with cold (0°C) 2N aqueous NaOH a white precipitate formed. The precipitate was filtered, washed with water, washed with MeOH, and dried under reduced pressure to provide 80mg of Substituted-Quinoxaline-Type Piperidine Compound **282** as a white solid (yield 53%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **282**, 3-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)isonicotinic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **282**: ^{1}H NMR: δ_H (DMSO-d_6): 11.66 (1H, s), 10.54 (1H, s), 10.45 (0.9H, s) 9.60 (0.1H, m), 8.44 (1H, d, J=5.00Hz), 7.97 (2H, m), 7.70 (1H, d, J=8.00Hz), 7.44 (1H, t, J=8.00Hz), 7.36 (1H, t, J=8.00Hz), 5.96 (1H, m), 4.22 (2H, m), 2.95 (1H, m), 2.70 (2H, m), 2.50-1.40 (20H, m); LC/MS (97%, t_r=1.35min): *m/z*=502 $[M+H]^+$ (Calc: 501.6).

5.47 Example 47



275 **276** **277**

In a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **281** in Example 46, Substituted-Quinoxaline-Type Piperidine Compound **275**, 2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)benzamide, was prepared except that 2-aminobenzonitrile was used in place of 3-aminoisonicotinonitrile.

To a mixture of Substituted-Quinoxaline-Type Piperidine Compound **275** (165mg, 0.330mmol) and water (4mL) at 0°C was added concentrated aqueous HCl (4mL, 47.4mmol). The resulting reaction mixture was warmed to a temperature of about 25°C and stirred for 1h. Thereafter, upon neutralizing the reaction mixture with cold (0°C) 2N aqueous NaOH a white precipitate formed. The precipitate was filtered, washed with water, and dried under reduced pressure to provide 138mg of the compound of formula **276** as a white solid (yield 81%).

The identity of the compound of formula **276**, 5-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-5*H*-quinoxalino[2,1-*b*]quinazoline-6,12-dione, was confirmed using ^{1}H NMR and LC/MS.

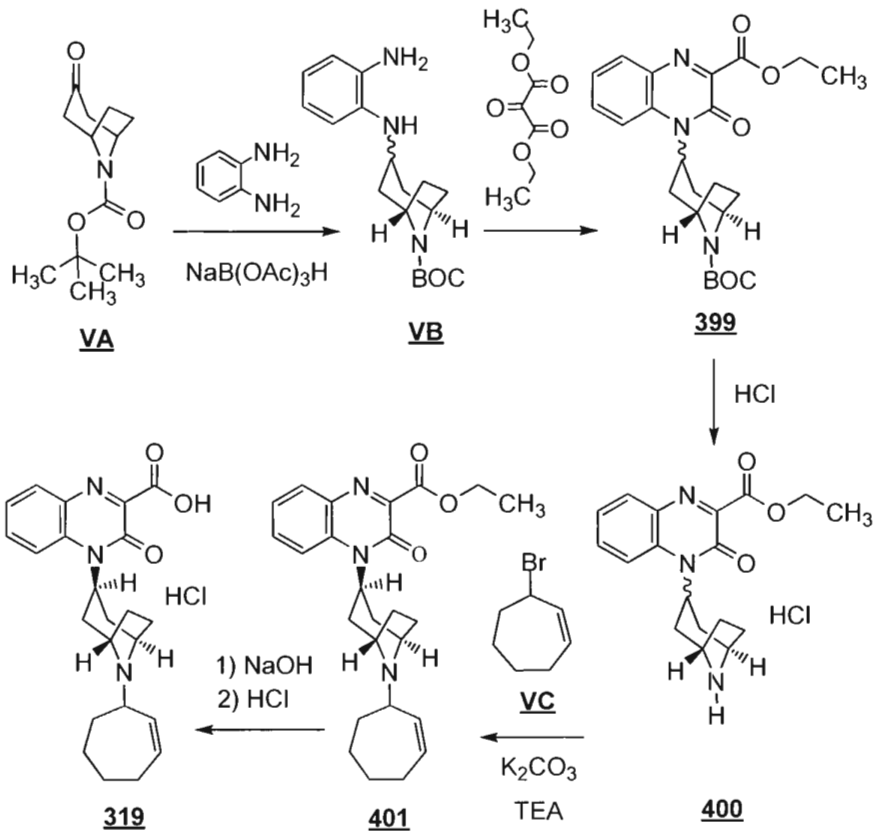
Compound **276**: ^{1}H NMR: δ_H (400MHz, DMSO): 10.05 (0.8H, s), 9.34 (0.2H, s), 8.77 (1H, d, J=8.0Hz), 8.32 (1H, d, J=8.0Hz), 7.98 (1H, t, J=8.0Hz), 7.88 (1H, d, J=8.0Hz), 7.71 (1H, t, J=8.0Hz), 7.66 (1H, d, J=8.0Hz), 7.50 (1H, t, J=8.0Hz), 7.30 (1H, t, J=8.0Hz), 5.48 (0.8H, m), 4,93 (0.2H, m), 4.26 (2H, m), 2.96 (1H, m), 2.76 (2H, m), 2.50-1.40 (20H, m); LC/MS (97%, t_r=1.73min): *m/z*=483 $[M+H]^+$ (Calc: 482.3).

To a mixture of the compound of formula **276** (90mg, 0.186mmol) and MeOH (4mL) at a temperature of about 25°C was added 2N aqueous NaOH (1.86mL, 3.73mmol). The resulting reaction mixture was warmed to a temperature of 80°C, stirred for 66h, concentrated under reduced pressure, and diluted with water (5mL) to precipitate a white solid. The precipitate was filtered and rinsed with water to provide 86mg of the sodium salt of Substituted-Quinoxaline-Type Piperidine Compound **277** (yield 88%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **277**, 2-(4-((*endo*)-8-cyclooctyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxalin-2-ylamino)benzoic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **277**: ^{1}H NMR: δ_H (400 MHz, DMSO-d_6): 14.48 (1H, s), 9.15 (1H, d, J=8.0Hz), 8.02 (1H, d, J=8.0Hz), 7.55 (1H, d, J=8.0Hz), 7.40 (1H, d, J=8.0Hz), 7.30 (2H, m), 7.23 (1H, d, J=8.0Hz), 6.93 (1H, t, J=8.0Hz), 5.10 (1H, br), 3.65 (2H, m), 3.00 (1H, m), 2.50-1.40 (22H, m); LC/MS (100%, t_r=2.24min): *m/z*=501 $[M+H]^+$ (Calc: 500.3).

5.48 Example 48



Under an argon atmosphere, a mixture of *tert*-butyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (**VA**, 9g, 3B Scientific Corp., Libertyville, IL), 1,2-phenylenediamine (9g), and sodium triacetoxyborohydride (20g) was stirred at about 25°C. To this mixture, acetic acid (4mL) was added and the resulting reaction mixture was stirred at a temperature of about 25°C for 5h. The reaction mixture was quenched with water (20mL) and MeOH (1mL) to provide the compound of formula **VB**, a mixture of the *endo* and *exo* isomers, which mixture was used as follows. The organic portion was separated, concentrated under reduced pressure, and redissolved in toluene (100mL) and AcOH (6mL). To this, diethyl 2-oxomalonate (16mL) at a temperature of 0°C was added, then the reaction mixture was warmed to 100°C and stirred for 3h. After cooling to about 25°C, the mixture was filtered over sea sand, washed with diethyl ether (50mL), and concentrated under reduced pressure to provide a residue. Chromatography of the residue with a silica gel column eluting with 1:1 hexanes:Et_2O provided 13.0g of Substituted-Quinoxaline-Type Piperidine Compound **399**, a mixture of the *endo* and *exo* isomers of ethyl 4-(8-(*tert*-butoxycarbonyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, as a brown oil. The oil was dissolved in 1,4-dioxane

(150mL), treated with 4N HCl in 1,4-dioxane (15mL), and kept at 40°C for 24h. The reaction mixture was concentrated under reduced pressure and titrated with diethyl ether to provide 7.0g of the hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **400**, a mixture of the *endo* and *exo* isomers of ethyl 4-(8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, as a white solid (yield 48% for three steps).

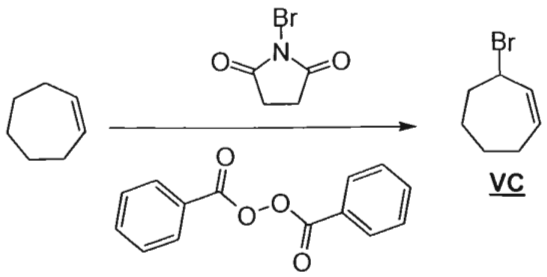
A reaction mixture of Substituted-Quinoxaline-Type Piperidine Compound **400** (200mg), 3-bromocyclohept-1-ene (**VC**, 2eq), K_2CO_3 (1.0g), TEA (1mL), and acetonitrile (4mL) was shaken at 60°C for 12h. The reaction mixture was diluted with EtOAc (10mL), filtered, and concentrated under reduced pressure to provide a residue. Chromatography of the residue with a silica gel column eluting with 1:1 hexanes:Et_2O then 1:2 hexanes:Et_2O provided 150mg of Substituted-Quinoxaline-Type Piperidine Compound **401**, ethyl 4-((*endo*)-8-(cyclohept-2-enyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, as an oil (yield 65%).

In a manner similar to the preparation of Substituted-Quinoxaline-Type Piperidine Compound **174** in Example 7, the hydrochloride of Substituted-Quinoxaline-Type Piperidine Compound **319** was prepared from Substituted-Quinoxaline-Type Piperidine Compound **401** (yield 64%).

The identity of Substituted-Quinoxaline-Type Piperidine Compound **319**, 4-((*endo*)-8-(cyclohept-2-enyl)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Piperidine Compound **319**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 13.8 (br, 1H, COOH), 12.18 (br, 1H, HCl), 8.43 (d, 1H, 8.8Hz), 8.24 (dd, 1H, 1.5Hz, 8.2Hz), 7.96 (ddd, 1H, 1.5, 7.2Hz, 8.8Hz), 7.61 (ddd, 1H, 0.8, 8.1,Hz, 8.3Hz), 6.6-6.68 (m, 1H), 6.12-6.24 (m, 2H), 4.22-4.28 (m, 2H), 3.54-3.58 (m, 1H), 3.02-3.12 (m, 2H), 2.42-2.55 (m, 4H), 2.32-2.36 (m, 2H), 2.18-2.24 (m, 2H), 2.06-2.12 (m, 2H), 1.4-1.72 (m, 4H); LC/MS (100%, t_r=4.881min): *m/z*=394.5 $[M+H]^+$.

The compound of formula **VC** was prepared as follows:



A reaction mixture of cycloheptene (12g, Sigma-Aldrich), *N*-bromosuccinimide (23g, Sigma-Aldrich), and benzoyl peroxide (0.5g, Sigma-Aldrich) in 100mL of CCl_4 was heated at 80°C for 2h. After cooling to about 25°C, the mixture was filtered, washed twice with $NaHCO_3$ (40mL for each wash), concentrated under reduced pressure, and distilled at 40°C under a pressure of 2mmHg to provide 15g of the compound of formula **VC** as colorless oil.

5.49 Example 49: *In vitro* ORL-1 Receptor Binding Assay

ORL-1 Receptor Binding Assay Procedures: Membranes from recombinant HEK-293 cells expressing the human opioid receptor-like receptor (ORL-1) (Receptor Biology) were prepared by lysing cells in ice-cold hypotonic buffer (2.5mM $MgCl_2$, 50mM HEPES, pH 7.4) (10mL/10 cm dish) followed by homogenization with a tissue grinder/Teflon pestle. Membranes were collected by centrifugation at 30,000 x g for 15min at 4°C and pellets resuspended in hypotonic buffer to a final concentration 1-3mg/mL. Protein concentrations were determined using the BioRad protein assay reagent with bovine serum albumen as a standard. Aliquots of the ORL-1 receptor membranes were stored at -80°C.

Radioligand binding assays (screening and dose-displacement) used 0.1nM [^{3}H]-nociceptin (NEN; 87.7 Ci/mmole) with 10-20µg membrane protein in a final volume of 500µL binding buffer (10mM $MgCl_2$, 1mM EDTA, 5% DMSO, 50mM HEPES, pH 7.4). Non-specific binding was determined in the presence of 10nM unlabeled nociceptin (American Peptide Company). All reactions were performed in 96-deep well polypropylene plates for 1 h at about 25°C. Binding reactions were terminated by rapid filtration onto 96-well Unifilter GF/C filter plates (Packard) presoaked in 0.5% polyethylenimine (Sigma). Harvesting was performed using a 96-well tissue harvester (Packard) followed by three filtration washes with 500µL ice-cold binding buffer. Filter plates were subsequently dried at 50°C for 2-3 hours. Fifty µL/well scintillation cocktail (BetaScint; Wallac) was added and plates were counted in a Packard Top-Count for 1 min/well. The data from screening and dose-displacement

experiments were analyzed using Microsoft Excel and the curve fitting functions in GraphPad PRISM™, v. 3.0, respectively, or an in-house function for one-site competition curve-fitting.

ORL-1 Receptor Binding Data: The Substituted-Quinoxaline-Type Piperidine Compounds will have a binding affinity (K_i) for the human ORL-1 receptor of about 1000 nM or less in one embodiment, or about 500 nM or less in another embodiment. Typically, the Substituted-Quinoxaline-Type Piperidine Compounds will have a K_i (nM) of about 300 or less for binding to ORL-1 receptors. In one embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a K_i (nM) of about 100 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a K_i (nM) of about 35 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a K_i (nM) of about 20 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a K_i (nM) of about 15 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a K_i (nM) of about 10 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a K_i (nM) of about 4 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a K_i (nM) of about 1 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a K_i (nM) of about 0.4 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a K_i (nM) of about 0.1 or less.

5.50 Example 50: *In vitro* ORL-1 Receptor Functional Assay

ORL-1 Receptor [^{35}S]GTPγS Binding Assay Procedures: Membranes from recombinant HEK-293 cells expressing the human opioid receptor-like (ORL-1) (Receptor Biology) were prepared by lysing cells in ice-cold hypotonic buffer (2.5mM $MgCl_2$, 50mM HEPES, pH 7.4) (10mL/10 cm dish) followed by homogenization with a tissue grinder/Teflon pestle. Membranes were collected by centrifugation at 30,000 x g for 15min at 4°C, and pellets resuspended in hypotonic buffer to a final concentration of 1-3mg/mL. Protein concentrations were determined using the BioRad protein assay reagent with bovine serum albumen as a standard. Aliquots of the ORL-1 receptor membranes were stored at -80°C.

Functional binding assays were conducted as follows. ORL-1 membrane solution was prepared by sequentially adding final concentrations of 0.066μg/μL ORL-1 membrane protein,

10μg/mL saponin, 3μM GDP and 0.20nM [35S]GTPγS to binding buffer (100mM NaCl, 10mM $MgCl_2$, 20mM HEPES, pH 7.4) on ice. The prepared membrane solution (190μL/well) was transferred to 96-shallow well polypropylene plates containing 10μL of 20x concentrated stock solutions of agonist/nociceptin prepared in DMSO. Plates were incubated for 30min at about 25°C with shaking. Reactions were terminated by rapid filtration onto 96-well Unifilter GF/B filter plates (Packard) using a 96-well tissue harvester (Packard) and followed by three filtration washes with 200μL ice-cold binding buffer (10mM NaH_2PO_4, 10mM Na_2HPO_4, pH 7.4). Filter plates were subsequently dried at 50°C for 2-3 hours. Fifty μL/well scintillation cocktail (BetaScint;Wallac) was added and plates were counted in Packard Top-Count for 1 min/well. Data are analyzed using the sigmoidal dose-response curve fitting functions in GraphPad PRISM v. 3.0, or an in-house function for non-linear, sigmoidal dose-response curve-fitting.

ORL-1 Receptor Functional Data: ORL-1 GTP EC_{50} is the concentration of a compound providing 50% of the maximal response for the compound at an ORL-1 receptor. Substituted-Quinoxaline-Type Piperidine Compounds typically will have an ORL-1 GTP EC_{50} (nM) of about 5000 or less to stimulate ORL-1 receptor function. In one embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have an ORL-1 GTP EC_{50} (nM) of about 1000 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have an ORL-1 GTP EC_{50} (nM) of about 100 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have an ORL-1 GTP EC_{50} (nM) of about 80 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have an ORL-1 GTP EC_{50} (nM) of about 50 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have an ORL-1 GTP EC_{50} (nM) of about 35 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have an ORL-1 GTP EC_{50} (nM) of about 15 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have an ORL-1 GTP EC_{50} (nM) of about 10 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have an ORL-1 GTP EC_{50} (nM) of about 4 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have an ORL-1 GTP EC_{50} (nM) of about 1 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have an ORL-1 GTP EC_{50} (nM) of about 0.4 or less. In another

embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have an ORL-1 GTP EC_{50} (nM) of about 0.1 or less.

ORL-1 GTP Emax (%) is the maximal effect elicited by a compound relative to the effect elicited by nociceptin, a standard ORL-1 agonist. Typically, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have an ORL-1 GTP Emax (%) of greater than about 50%. In one embodiment, the Substituted-Quinoxaline-Type Piperidine Compound Substituted-Quinoxaline-Type Piperidine Compounds will have an ORL-1 GTP Emax (%) of greater than about 75%. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have an ORL-1 GTP Emax (%) of greater than about 85%. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have an ORL-1 GTP Emax (%) of greater than about 95%. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have an ORL-1 GTP Emax (%) of about 100% or greater. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have an ORL-1 GTP Emax (%) of about 110% or greater. Typically, a Substituted-Quinoxaline-Type Piperidine Compound of the invention acting as a partial agonist will have an ORL-1 GTP Emax (%) of less than about 10%. In one embodiment, partial agonist Substituted-Quinoxaline-Type Piperidine Compounds will have an ORL-1 GTP Emax (%) of less than about 20%. In another embodiment, partial agonist Substituted-Quinoxaline-Type Piperidine Compounds will have an ORL-1 GTP Emax (%) of less than about 30%. In another embodiment, partial agonist Substituted-Quinoxaline-Type Piperidine Compounds will have an ORL-1 GTP Emax (%) of less than about 40%. In another embodiment, partial agonist Substituted-Quinoxaline-Type Piperidine Compounds will have an ORL-1 GTP Emax (%) of less than about 50%.

5.51 Example 51: *In vitro* Mu-opioid Receptor Binding Assays

<u>μ-Opioid Receptor Binding Assay Procedures</u>: Radioligand dose-displacement binding assays for μ-opioid receptors used 0.2nM[^{3}H]-diprenorphine (NEN, Boston, Mass.), with 5-20mg membrane protein/well in a final volume of 500μL binding buffer (10mM $MgCl_2$, 1mM EDTA, 5% DMSO, 50mM HEPES, pH 7.4). Reactions were carried out in the absence or presence of increasing concentrations of unlabeled naloxone. All reactions were conducted in 96-deep well polypropylene plates for 1-2 hr at about 25°C. Binding reactions were terminated by rapid filtration onto 96-well Unifilter GF/C filter plates (Packard, Meriden,

Conn.) presoaked in 0.5% polyethylemimine using a 96-well tissue harvester (Brandel, Gaithersburg, Md.) followed by performing three filtration washes with 500μL of ice-cold binding buffer. Filter plates were subsequently dried at 50°C for 2-3 hours. BetaScint scintillation cocktail (Wallac, Turku, Finland) was added (50μL/well), and plates were counted using a Packard Top-Count for 1 min/well. The data were analyzed using the one-site competition curve fitting functions in GraphPad PRISM v. 3.0 (San Diego, Calif.), or an in-house function for one-site competition curve-fitting.

μ-Opioid Receptor Binding Data: Typically, the Substituted-Quinoxaline-Type Piperidine Compounds will have a K_i (nM) of about 3000 or less for binding to μ-opioid receptors. In one embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a K_i (nM) of about 1000 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a K_i (nM) of about 650 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a K_i (nM) of about 525 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a K_i (nM) of about 250 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a K_i (nM) of about 100 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a K_i (nM) of about 10 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a K_i (nM) of about 1 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a K_i (nM) of about 0.1 or less.

5.52 Example 52: *In vitro* Mu-Opioid Receptor Functional Assays

μ-Opioid Receptor Functional Assay Procedures: [^{35}S]GTPγS functional assays were conducted using freshly thawed μ-receptor membranes. Assay reactions were prepared by sequentially adding the following reagents to binding buffer (100mM NaCl, 10mM $MgCl_2$, 20mM HEPES, pH 7.4) on ice (final condentrations indicated): membrane protein (0.026mg/mL), saponin (10mg/mL), GDP (3mM) and [^{35}S]GTPγS (0.20nM; NEN). The prepared membrane solution (190μL/well) was transferred to 96-shallow well polypropylene plates containing 10μL of 20x concentrated stock solutions of the agonist DAMGO ([D-Ala2, N-methyl-Phe4 Gly-ol5]-enkephalin) prepared in dimethyl sulfoxide (DMSO). Plates were

incubated for 30min at about 25°C with shaking. Reactions were terminated by rapid filtration onto 96-well Unifilter GF/B filter plates (Packard, Meriden, Conn.) using a 96-well tissue harvester (Brandel, Gaithersburg, Md.) followed by three filtration washes with 200μL of ice-cold wash buffer (10mM NaH_2PO_4, 10mM Na_2HPO_4, pH 7.4). Filter plates were subsequently dried at 50°C for 2-3 hr. BetaScint scintillation cocktail (Wallac, Turku, Finland) was added (50μL/well) and plates were counted using a Packard Top-Count for 1 min/well. Data were analyzed using the sigmoidal dose-response curve fitting functions in GraphPad PRISM v. 3.0, or an in-house function for non-linear, sigmoidal dose-response curve-fitting.

μ-Opioid Receptor Functional Data: μ GTP EC_{50} is the concentration of a compound providing 50% of the maximal response for the compound at a μ-opioid receptor. Substituted-Quinoxaline-Type Piperidine Compounds typically will have a μ GTP EC_{50} (nM) of about 5000 or less to stimulate μ-opioid receptor function. In one embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a μ GTP EC_{50} (nM) of about 4100 or less. In one embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a μ GTP EC_{50} (nM) of about 3100 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a μ GTP EC_{50} (nM) of about 2000 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a μ GTP EC_{50} (nM) of about 1000 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a μ GTP EC_{50} (nM) of about 100 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a μ GTP EC_{50} (nM) of about 10 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a μ GTP EC_{50} (nM) of about 1 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a μ GTP EC_{50} (nM) of about 0.4 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a μ GTP EC_{50} (nM) of about 0.1 or less.

μ GTP Emax (%) is the maximal effect elicited by a compound relative to the effect elicited by DAMGO, a standard μ agonist. Typically, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a μ GTP Emax (%) of greater than about 10%. In one embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a μ GTP Emax (%) of greater than about 20%. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a μ GTP Emax (%) of greater than about

50%. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a μ GTP Emax (%) of greater than about 65%. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a μ GTP Emax (%) of greater than about 75%. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a μ GTP Emax (%) of greater than about 88%. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a μ GTP Emax (%) of about 100% or greater.

5.53 Example 53: *In vitro* Kappa-opioid Receptor Binding Assays

κ-Opioid Receptor Binding Assay Procedures: Membranes from recombinant HEK-293 cells expressing the human kappa opioid receptor (kappa) (cloned in house) were prepared by lysing cells in ice cold hypotonic buffer (2.5mM $MgCl_2$, 50mM HEPES, pH 7.4) (10mL/10 cm dish) followed by homogenization with a tissue grinder/Teflon pestle. Membranes were collected by centrifugation at 30,000 x g for 15min at 4°C and pellets resuspended in hypotonic buffer to a final concentration of 1-3mg/mL. Protein concentrations were determined using the BioRad protein assay reagent with bovine serum albumen as a standard. Aliquots of kappa receptor membranes were stored at -80 °C.

Radioligand dose displacement assays used 0.4-0.8nM [^{3}H]-U69,593 (NEN; 40 Ci/mmole) with 10-20μg membrane protein (recombinant kappa opioid receptor expressed in HEK 293 cells; in-house prep) in a final volume of 200μL binding buffer (5% DMSO, 50mM Trizma base, pH 7.4). Non-specific binding was determined in the presence of 10μM unlabeled naloxone or U69,593. All reactions were performed in 96-well polypropylene plates for 1 h at a temperature of about 25°C. Binding reactions were determined by rapid filtration onto 96-well Unifilter GF/C filter plates (Packard) presoaked in 0.5% polyethylenimine (Sigma). Harvesting was performed using a 96-well tissue harvester (Packard) followed by five filtration washes with 200μL ice-cold binding buffer. Filter plates were subsequently dried at 50°C for 1-2 hours. Fifty μL/well scintillation cocktail (MicroScint20, Packard) was added and plates were counted in a Packard Top-Count for 1 min/well.

κ-Opioid Receptor Binding Data: In one embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have substantially activity at κ receptors. Typically, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 20,000 or less for κ receptors. In one embodiment, the Substituted-Quinoxaline-Type Piperidine

Compounds will have a Ki (nM) of about 10,000 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 5000 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 1000 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 500 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 300 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 100 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 50 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 20 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 15 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 10 or less.

5.54 Example 54: *In vitro* Kappa-Opioid Receptor Functional Assays

κ-Opioid Receptor Functional Assay Procedures: Functional [^{35}S]GTPγS binding assays were conducted as follows. Kappa opioid receptor membrane solution was prepared by sequentially adding final concentrations of 0.026μg/μL kappa membrane protein (in-house), 10μg/mL saponin, 3μM GDP and 0.20nM [^{35}S]GTPγS to binding buffer (100mM NaCl, 10mM $MgCl_2$, 20mM HEPES, pH 7.4) on ice. The prepared membrane solution (190μL/well) was transferred to 96-shallow well polypropylene plates containing 10μL of 20x concentrated stock solutions of agonist prepared in DMSO. Plates were incubated for 30min at a temperature of about 25°C with shaking. Reactions were terminated by rapid filtration onto 96-well Unifilter GF/B filter plates (Packard) using a 96-well tissue harvester (Packard) and followed by three filtration washes with 200μL ice-cold binding buffer (10mM NaH_2PO_4, 10mM Na_2HPO_4, pH 7.4). Filter plates were subsequently dried at 50°C for 2-3 hours. Fifty μL/well scintillation cocktail (MicroScint20, Packard) was added and plates were counted in a Packard Top-Count for 1 min/well.

κ-Opioid Receptor Functional Data: κ GTP EC_{50} is the concentration of a compound providing 50% of the maximal response for the compound at a κ receptor. Substituted-Quinoxaline-Type Piperidine Compounds typically will have a κ GTP EC_{50} (nM) of about 20,000 or less to stimulate κ opioid receptor function. In one embodiment, the

Substituted-Quinoxaline-Type Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 10,000 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 5000 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 2000 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 1500 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 800 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 500 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 300 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 100 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 50 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 25 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 10 or less.

κ GTP Emax (%) is the maximal effect elicited by a compound relative to the effect elicited by U69,593. Typically, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a κ GTP Emax (%) of greater than about 10%. In one embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a κ GTP Emax (%) of greater than about 15%. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a κ GTP Emax (%) of greater than about 30%. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a κ GTP Emax (%) of greater than about 40%. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a κ GTP Emax (%) of greater than about 45%. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a κ GTP Emax (%) of greater than about 75%. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a κ GTP Emax (%) of greater than about 90%. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a κ GTP Emax (%) of about 100% or greater.

5.55 Example 55: *In vitro* Delta-opioid Receptor Binding Assays

δ-Opioid Receptor Binding Assay Procedures: Radioligand dose-displacement assays used 0.2nM [^{3}H]-Naltrindole (NEN; 33.0 Ci/mmole) with 10-20μg membrane protein (recombinant delta opioid receptor expressend in CHO-K1 cells; Perkin Elmer) in a final volume of 500μL binding buffer (5mM $MgCl_2$, 5% DMSO, 50mM Trizma base, pH 7.4). Non-specific binding was determined in the presence of 25μM unlabeled naloxone. All reactions were performed in 96-deep well polypropylene plates for 1 h at a temperature of about 25°C. Binding reactions were determined by rapid filtration onto 96-well Unifilter GF/C filter plates (Packard) presoaked in 0.5% polyethylenimine (Sigma). Harvesting was performed using a 96-well tissue harvester (Packard) followed by five filtration washes with 500μL ice-cold binding buffer. Filter plates were subsequently dried at 50°C for 1-2 hours. Fifty μL/well scintillation cocktail (MicroScint20, Packard) was added and plates were counted in a Packard Top-Count for 1 min/well.

δ-Opioid Receptor Binding Data: In one embodiment, the Substituted-Quinoxaline-Type Piperdine Compounds will have substantially no activity at δ receptors. Typically, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 20,000 or less for δ receptors. In one embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 10,000 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 7500 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 6500 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 5000 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 3000 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 2500 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 1000 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 500 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 350 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 250 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 100 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a Ki (nM) of about 10 or less.

5.56 Example 56: *In vitro* Delta-Opioid Receptor Functional Assays

δ-Opioid Receptor Functional Assay Procedures: Functional [^{35}S]GTPγS binding assays were conducted as follows. Delta opioid receptor membrane solution was prepared by sequentially adding final concentrations of 0.026μg/μL delta membrane protein (Perkin Elmer), 10μg/mL saponin, 3μM GDP and 0.20nM [^{35}S]GTPγS to binding buffer (100mM NaCl, 10mM $MgCl_2$, 20mM HEPES, pH 7.4) on ice. The prepared membrane solution (190μL/well) was transferred to 96-shallow well polypropylene plates containing 10μL of 20x concentrated stock solutions of agonist prepared in DMSO. Plates were incubated for 30min at a temperature of about 25°C with shaking. Reactions were terminated by rapid filtration onto 96-well Unifilter GF/B filter plates (Packard) using a 96-well tissue harvester (Packard) and followed by three filtration washes with 200μL ice-cold binding buffer (10mM NaH_2PO_4, 10mM Na_2HPO_4, pH 7.4). Filter plates were subsequently dried at 50°C for 1-2 hours. Fifty μL/well scintillation cocktail (MicroScint20, Packard) was added and plates were counted in a Packard Top-count for 1 min/well.

δ-Opioid Receptor Functional Data: δ GTP EC_{50} is the concentration of a compound providing 50% of the maximal response for the compound at a δ receptor. Substituted-Quinoxaline-Type Piperidine Compounds typically will have a δ GTP EC_{50} (nM) of about 20,000 or less to stimulate δ opioid receptor function. In one embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a δ GTP EC_{50} (nM) of about 10,000 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a δ GTP EC_{50} (nM) of about 100 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a δ GTP EC_{50} (nM) of about 1000 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a δ GTP EC_{50} (nM) of about 90 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a δ GTP EC_{50} (nM) of about 50 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a δ GTP EC_{50} (nM) of about 25 or less. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a δ GTP EC_{50} (nM) of about 10 or less.

δ GTP Emax (%) is the maximal effect elicited by a compound relative to the effect elicited by met-enkephalin. Typically, the Substituted-Quinoxaline-Type Piperidine Compounds of the invention will have a δ GTP Emax (%) of greater than about 10%. In one embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a δ GTP

Emax (%) of greater than about 30%. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a δ GTP Emax (%) of greater than about 50%. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a δ GTP Emax (%) of greater than about 75%. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a δ GTP Emax (%) of greater than about 90%. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a δ GTP Emax (%) of about 100% or greater. In another embodiment, the Substituted-Quinoxaline-Type Piperidine Compounds will have a δ GTP Emax (%) of about 110% or greater.

5.57 Example 57: Efficacy of Receptor Binding and Activity Response

The following Tables provide results on the efficacy of binding and activity response of several Substituted-Quinoxaline-Type Piperidine Compounds to the ORL-1 receptor and, for certain Substituted-Quinoxaline-Type Piperidine Compounds, the mu-opioid receptor, the kappa-opioid receptor, and/or the delta-opioid receptor.

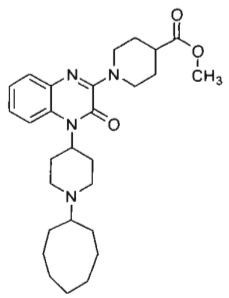
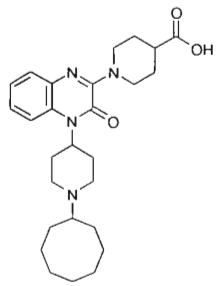
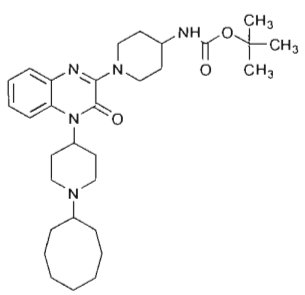
In Table 1, binding efficacy to the ORL-1 receptor was determined by the procedure in Example 49. Binding efficacy to the mu-opioid receptor was determined by the procedure in Example 51. Binding efficacy to the kappa-opioid receptor was determined by the procedure in Example 53. Binding efficacy to the delta-opioid receptor was determined by the procedure in Example 55.

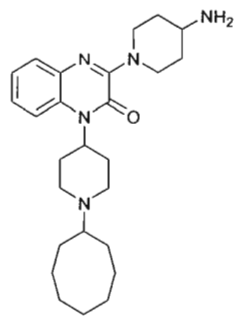
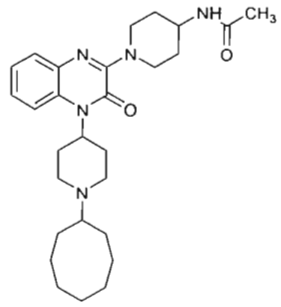
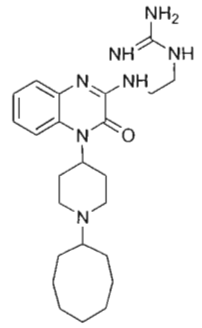
In Table 2, activity response to the ORL-1 receptor was determined by the procedure in Example 50. Activity response to the mu-opioid receptor was determined by the procedure in Example 52. Activity response to the kappa-opioid receptor was determined by the procedure in Example 54. Activity response to the delta-opioid receptor can be determined by the procedure in Example 56.

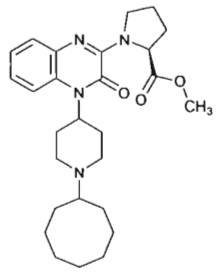
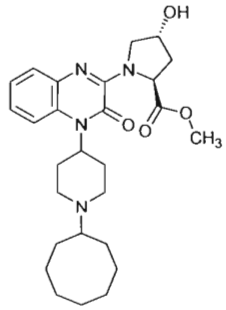
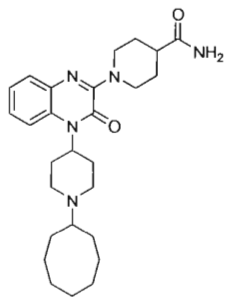
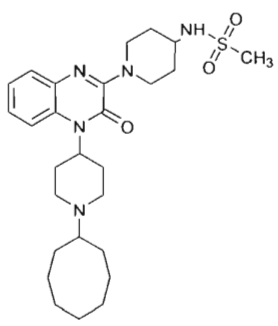
Table 1: Efficacy of Receptor Binding of Substituted-Quinoxaline-Type Piperidine Compounds

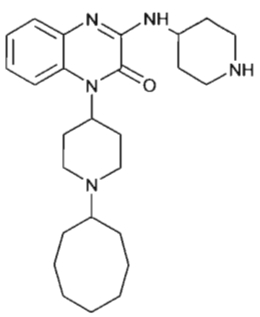
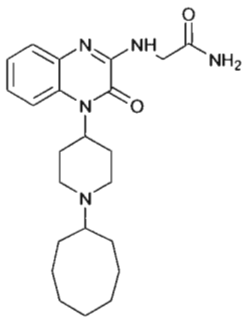
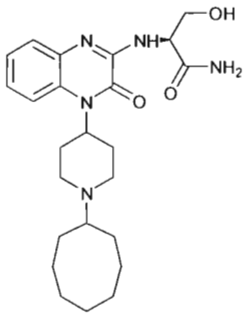
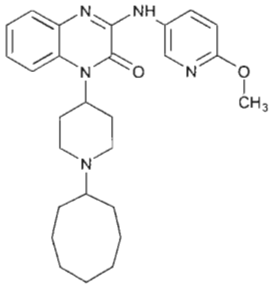
Ref No.	Compound	K_i |Average ± Std Deviation| (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta

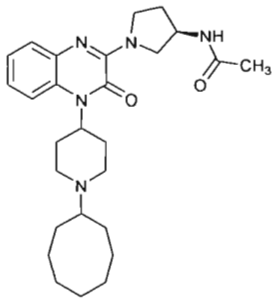
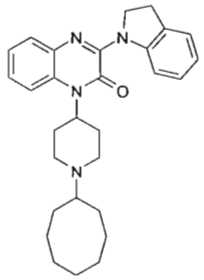
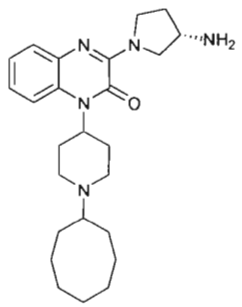
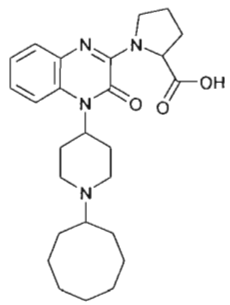
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
1		326.1 ±34.6	13470 ±1595		76337
2		67.2 ±12.0	2053 ±343	257.0 ±22.0	28064
3		153.7 ±7.0	17060 ±2280	888 ±173	$> 10^5$
4		117.5 ±12.1	3869 ±724	135.8 ±15.0	8918 ±2238
5		19.4 ±2.5	4340 ±1155	22.5 ±5.8	23220
6		152 ±25	1145 ±104	165.2 ±23.1	11122
7		156 ±24	1074 ±182	296 ±45	19610
8		322 ±79	1634 ±115		7556 ±363
9		14.2 ±3.3	1397 ±108	167.6 ±15.2	47271
10		72.1 ±9.1	1480 ±20	73.5 ±18.2	27675
11		114.9 ±24.2	1530 ±85	905 ±177	44071
12		20.9 ±3.9	2391 ±261	15.1 ±2.2	519741
13		96.5 ±18.8	3278 ±270	283 ±55	43483
14		301 ±29	3157 ±197		15188
15		15.4 ±1.8	1199 ±173	92.9 ±16.4	24560

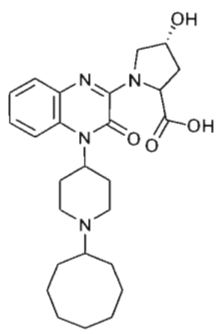
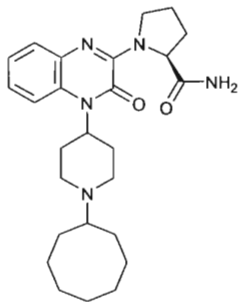
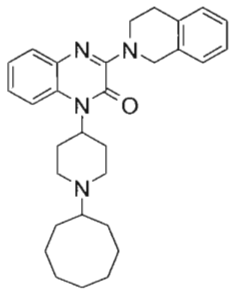
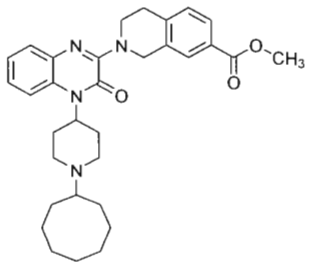
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
16		97.8 ±5.0	2313 ±247	328 ±11.3	34024
17		181.8 ±1.6	5254 ±208	622 ±102	37800
18		182 ±29	2078 ±57	303 ±9	55229
19		16.8 ±0.8	26627	11500 ±1090	545749
20		547 ±90.0			
21		74.8 ±3.5	3396 ±362	151 ±20	22592

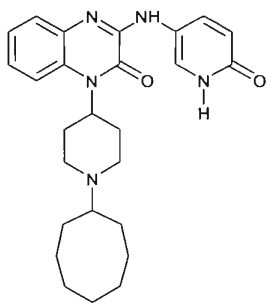
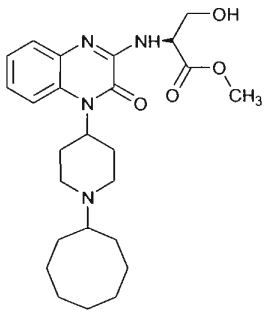
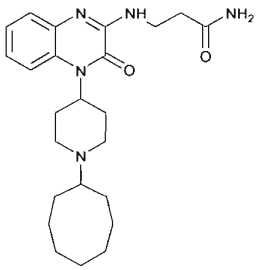
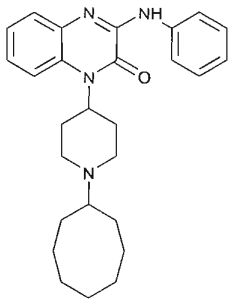
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
22		35.2 ±2.3	3037 ±579	30.4 ±2.2	19407
23		60.8 ±5.1	3942 ±1253	514 ±70	52099
24		27.0 ±5.2	5281 ±1532	852 ±61	60848
25		65.7 ±10.0	5979 ±937	1300 ±360	82251
26		7.1 ±0.3	629 ±24	191.4 ±30.4	35858

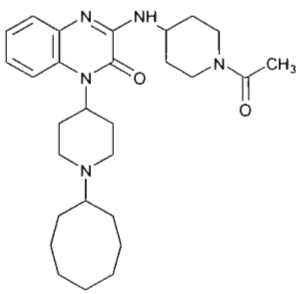
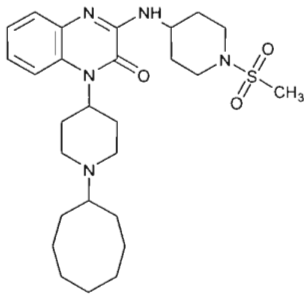
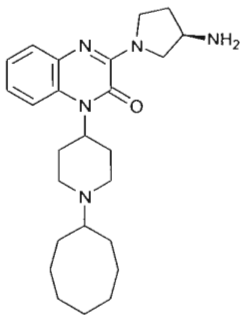
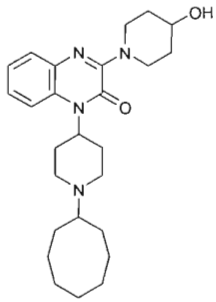
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
27		48.5 ±7.0	2438 ±493	583 ± 155.2	27790
28		156.3 ±9.4	5244 ±939	1038 ± 252	66315
29		39.8 ±2.6	3780 ±1098	481 ±87	inactive
30		57.9 ±1.3	1895 ±309	378 ± 62.4	61698

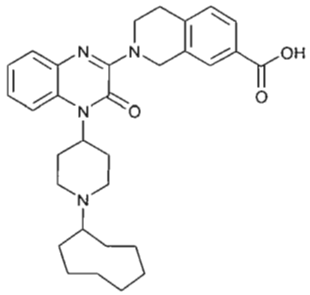
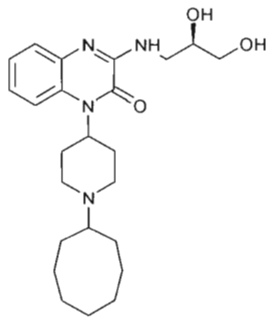
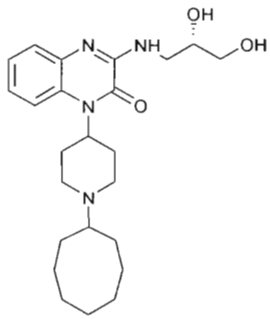
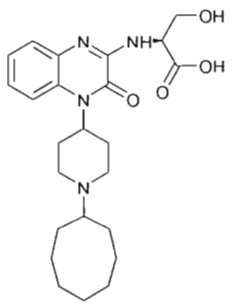
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
31		36.9 ±3.0	1488 ±321	67.5 ± 7.6	34671
32		37.4 ±7.5	6403 ±1943	354 ± 28.2	548766
33		22.9 ±4.9	3341 ±1068	1282.6 ± 212.1	96003
34		153 ±36	627 ±137	46.34 ± 5.96	26105

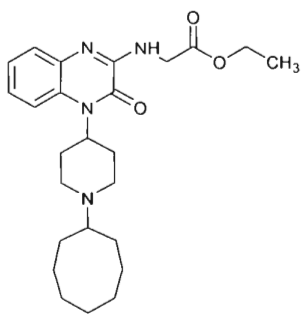
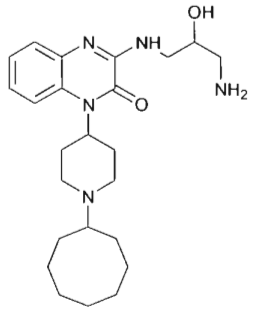
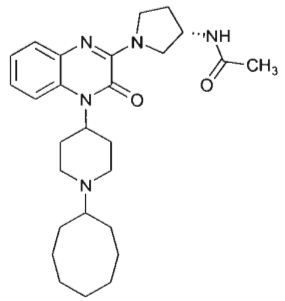
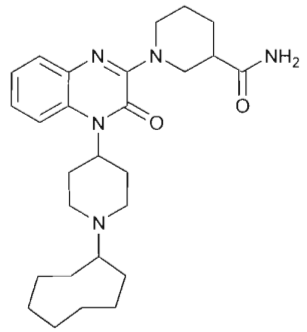
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
37		18.6 ±3.7	2064 ±346	222.01 ± 34.1	56989
38		5.7 ±1.3	1451 ±313	375 ± 79.5	6673
39		8.6 ±1.9	624 ±22	57.3 ± 7.43	52574
40		309 ±33			

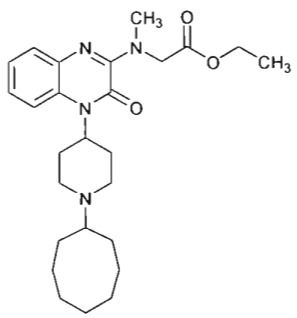
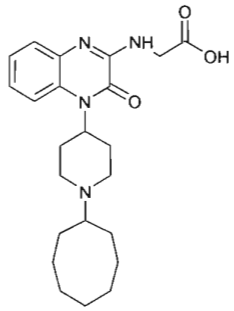
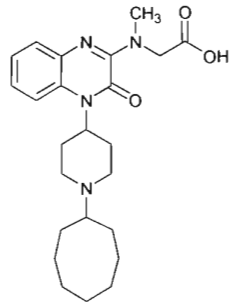
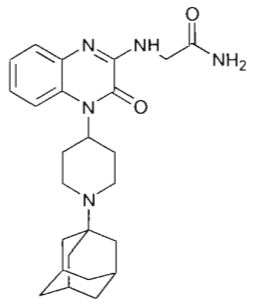
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
41		426 ±85			
42		36.9 ±4.5	1866 ±27	611.9 ± 37.1	81321
43		42.3 ±6.1	809 ±57	544.2 ± 57	38851
44		111 ±24	513 ±27	301 ± 68.4	45038

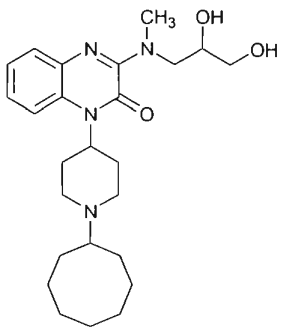
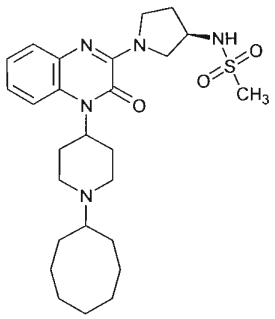
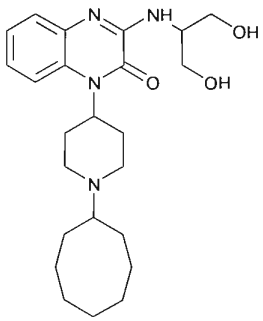
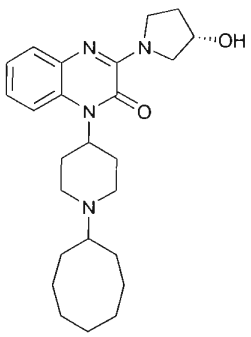
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
45		46.3 ±3.0	3986 ±1172	805 ± 97.4	46719
46		32.1 ±3.7	1414 ±337	191 ± 34.5	518930
47		42.4 ±2.7	2368 ±245	731 ± 55.1	$> 10^5$
48		355 ±31			

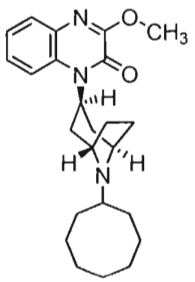
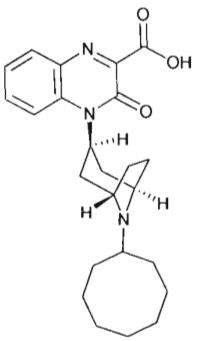
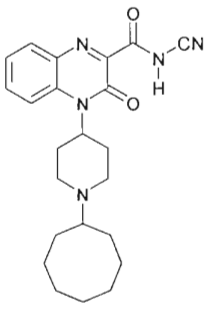
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
49		70.9 ±7.2	1345 ±153	971 ± 50.6	531427
50		35.2 ±2.1	634 ±28		59230
51		4.0 ±0.6	512 ±79	22 ± 2.1	28106
52		92 ±16	3557 ±1293	712 ± 177	43207

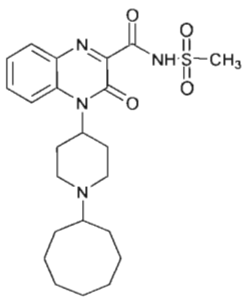
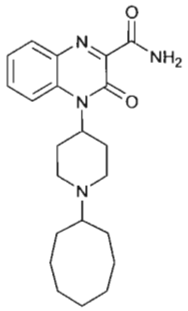
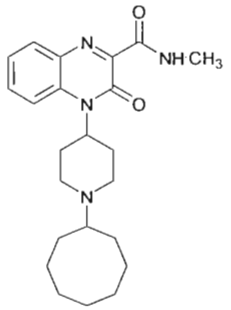
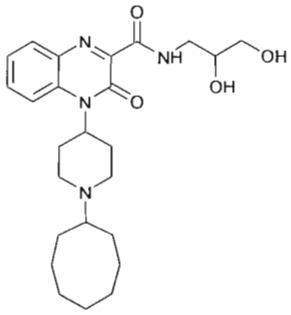
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
53		332 ±77			
54		31.9 ±4.8	5414 ±591	1195 ± 151	528011
55		24.1 ±7.0	2109 ±765	929 ± 152	530892
56		36.5 ±6.9	5056 ±1453	544 ± 30.7	19145

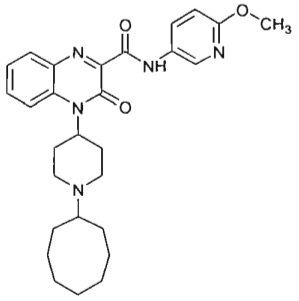
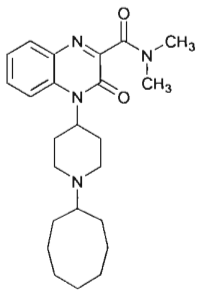
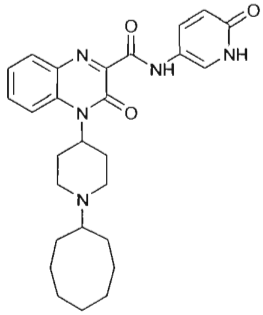
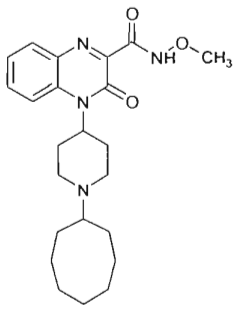
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
57		45 ±13	1360 ±468	379 ± 48.3	532394
58		14.8 ±2.0	524 ±107	175 ± 11.6	45883
59		29.9 ±1.4	3183 ±1005	457 ± 72	53164
60		130 ±29	6657 ±2010	510 ± 125	38477

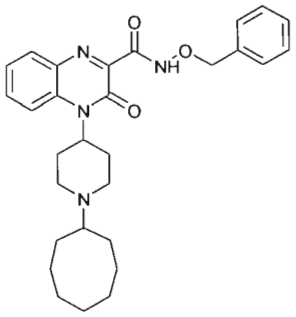
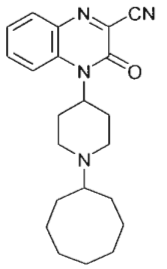
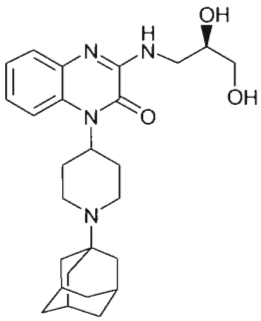
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
61		130 ±10	4412 ± 953	810 ± 170	28131
62		368 ±39			
63		438 ±36			
64		54.8 ±1.3	9284 ± 2250	4359 ± 796	inactive

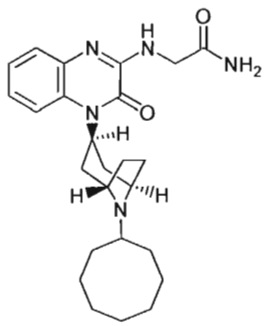
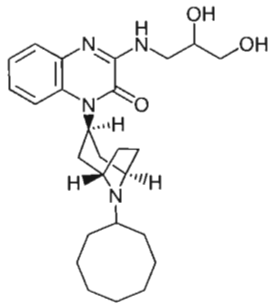
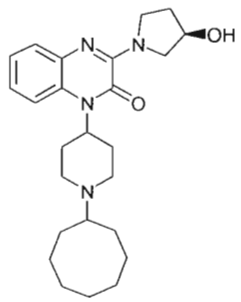
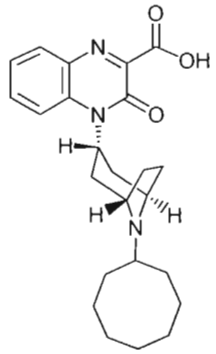
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
65		85.3 ±4.5	3642 ± 704	1149 ± 121	85587
66		15.5 ±1.3	1523 ± 106	587 ± 131	28211
67		19.1 ±0.8	3296 ± 722	666 ± 74	86219
68		49.8 ±3.7	6155 ± 354	1486 ± 180	54999

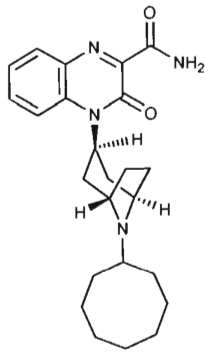
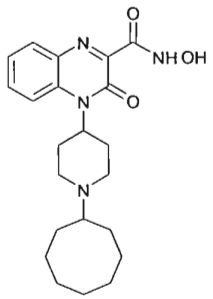
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
69		4.2 ±0.9	248 ±33	161 ± 47	13091
70		109 ±7	2511 ±193	141 ±10	13080
71		111 ±6.7	7426 ±254	1034 ±232	31727
72		220 ±17	887 ±84	23.4 ±1.1	
73		52.8 ±7.5			
74		12.6 ±0.8	678 ±9	630 ±218	47391
75		273 ±13			

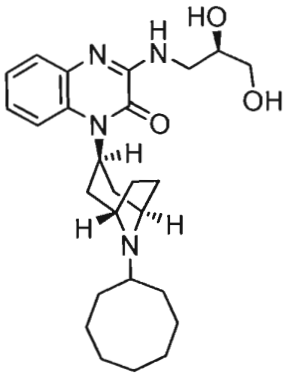
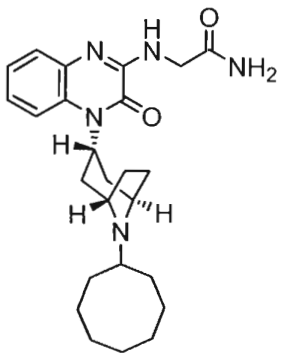
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
76		375 ±115			
77		10.9 ±1.8	1239 ±162	418 ± 42	21144
78		40.7 ±4.1	1723 ±313	618 ± 107	16831
79		51 ±12	2727 ±260	994 ± 92	20971

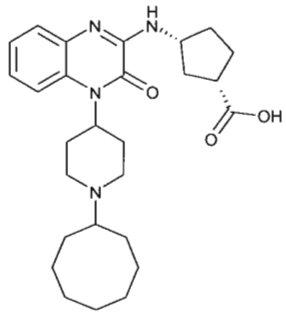
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
80		13.7 ±4.1	871 ±196	132 ± 18	23741
81		44 ±12	2787 ±843	669 ± 88	20507
82		16.2 ±4.4	2144 ±549	391 ± 71	15770
83		44 ±20	1918 ±621	586 ± 97	10177

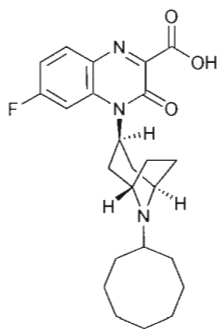
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
84		12.7 ±0.5	1914 ±277	245 ± 46	2712 ± 258
85		92.2 ±10.6	4089 ±1450	182 ±26	17850 ±3075
86		179.4 ±37.3	6758 ±810	83.5 ±12.8	9670 ±2065
87		338 ±6			
88		20.8 ±4.3	1663 ±590	536 ±56	15584
89		75.2 ±6.1	10180 ±2530	4490 ±1110	535200

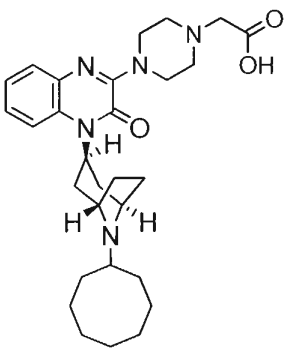
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
90		6.42 ±0.71	459.3 ±8.9	253 ±39	38310
91		5.54 ±0.23	394.3 ±4.2	224 ±14	21860
92		41.2 ±0.5	4650 ±657	688 ±189	34954
93		299 ±19			

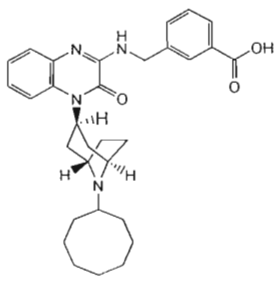
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
94		4.42 ±0.43	819 ±29	154 ±19	25250
95		10.71 ±0.64	5570 ±981	2728 ±785	53540
98		8.6 ±0.2	196 ±21	130 ±15	29200
99		109 ±10	1670 ±36	657 ±26	4470 ±170
100		8.2 ±1.2			
101		1.6 ±0.2	590 ±47	14.9 ±2.0	13970 ±180

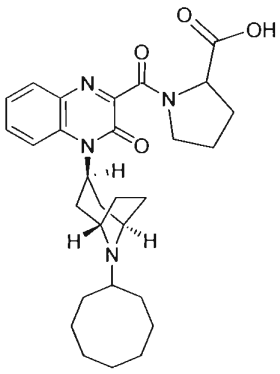
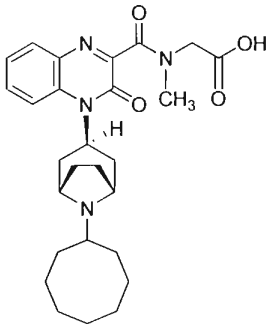
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
102		6.5 ±0.5	576 ±46	156 ±20	49120
103		233.7 ±7.8	6700 ±700	4330 ±700	26460
104		120.1 ±9.2	12100 ±1315	5350 ±1000	29775
105		288 ±39			
106		61.4 ±7.3	1172 ±35	2840 ±340	12882
107		285 ±33			

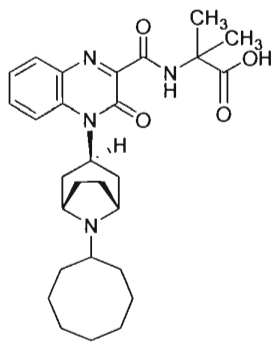
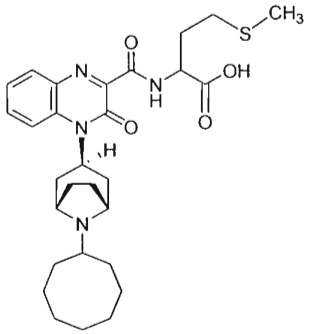
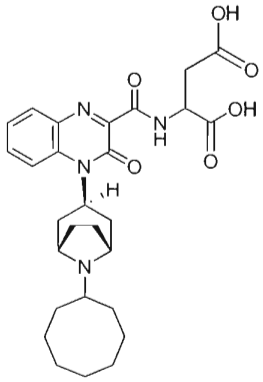
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
108		607.4 ±9.9			
109		493 ±34			
110		1716 ±177			
111		189 ±16	12825 ±600	19250	35615
112		500 ±10			
113		785 ±72			
114		52.1 ±1.0	2510 ±65	1203 ±200	24072
115		23.8 ±0.9	770 ±55	998 ±92	57741
116		836 ±34			
117		1342 ±71			
118		561 ±75			
119		73.2 ±7.1	3330 ±350	381 ±50	$> 10^5$
120		3.1 ±0.3	210 ±16	55.8 ±6.3	1710 ±340

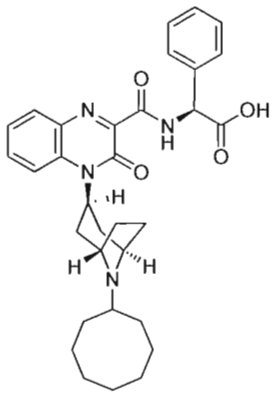
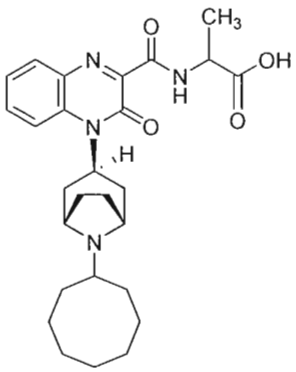
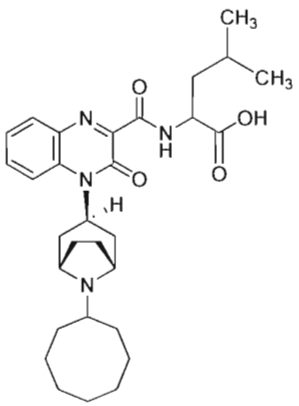
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
121		18.9 ±1.3	743 ±22	460 ±71	13563
122		7.5 ±0.4	373.7 ±1.6	161 ±29	17516
123		127.7 ±8.0	2700 ±250	743 ±148	13745
124		103 ±10	9840 ±422	2600 ±165	$> 10^5$
125		12.0 ±0.3	391.0 ±4.4	380 ±51	42000
126		43.7 ±5.2	422 ±25	422 ±21	25970
127		2.7 ±0.4	188 ±19	480 ±80	$> 10^5$
128		15.7 ±2.4	488 ±60	250 ±15	17638 ±320
129		13.5 ±1.1	462 ±30	180 ±13	26095
130		11.9 ±1.1	1320 ±270	2430 ±578	28211
131		275 ±10			
133		135.9 ±13.6	1217 ±115	501 ±80	25020
168		$> 10^5$			

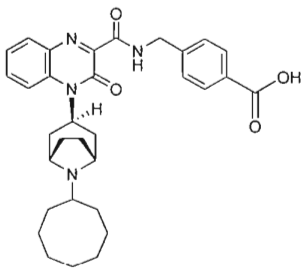
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
171		44.6 ±2.3			
226		20.4 ±4.0	3200 ±125	707 ±51	$> 10^5$
228		4.4 ±1.4	1083 ±61	3320 ±600	> 20,000
205		437 ±36			
207		39.6 ±5.7	1300 ±57	346 ±62	> 20,000
209		78.8 ±2.6	377 ±36	534 ±62	1870
188		16.3 ±2.0	723 ±126	871 ±90	16400
189		10.9 ±1.6	644.2 ±11.9	67.0 ±9.5	11430
337		26.5 ±1.6	706 ±121	220.0 ±7.7	8840
211		34.7 ±2.9	713 ±48	568 ±29	> 20,000
191		60.4 ±3.4	1990 ±289	1493 ±154	37410
193		11.1 ±0.3	6100 ±56	224 ±21	> 20,000

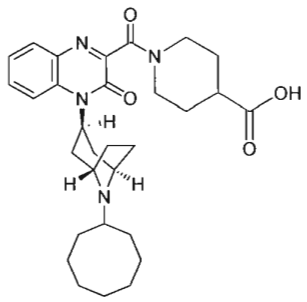
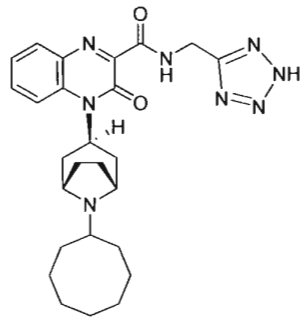
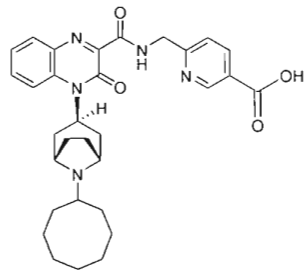
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
212		14.6 ±0.4	1140 ±60	25.9 ±1.8	> 20,000
218		10.6 ±0.5	2530 ±270	863 ±45	> 20,000
194		158.0 ±9.7	3920 ±915	256 ±38	> 20,000
196		46.1 ±1.4	5200 ±370	1650 ±203	8880 ±970
221		16.8 ±0.4	10900 ±1150	740 ±145	> 20,000
197		74.5 ±5.7	8900 ±410	890 ±230	> 20,000
199		237.3 ±8.4	> 20,000	920 ±360	> 20,000
201		44.8 ±1.8	1600 ±260	1360 ±170	2740 ±850
216		15.8 ±1.1	2250 ±530	134 ±22	> 20,000
203		140 ±20	1470 ±210	750 ±58	> 20,000
180		456 ±74			
305		149 ±23	4420 ±250	780 ±53	> 20,000
174		71.4 ±2.5	2918 ±37	488 ±21	> 20,000

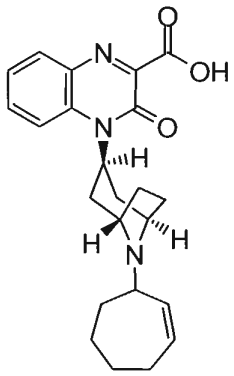
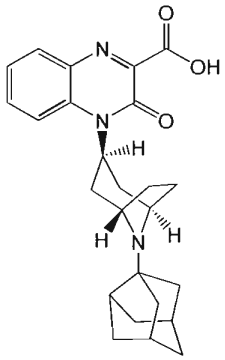
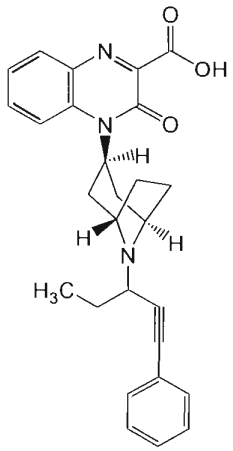
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
176		101.9 ±4.5	4700 ±238	1153 ±165	1305 ±39
178		10.60 ±0.02	2807 ±307	429 ±75	> 20,000
277		538 ±40			
231		61.7 ±0.7	11942 ± 294	2032 ± 286	547704
306		114.9 ±16.8	1458 ±173	350 ±13	22330
307		170 ±24	1375 ±182	478 ±45	23090

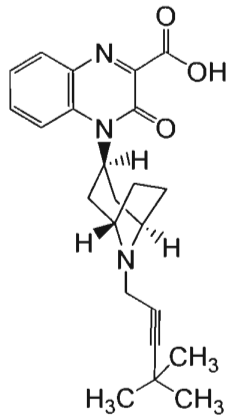
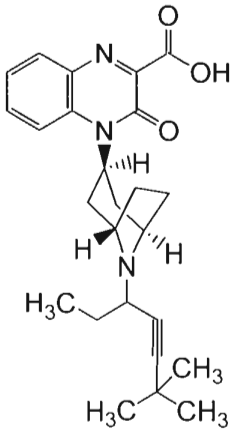
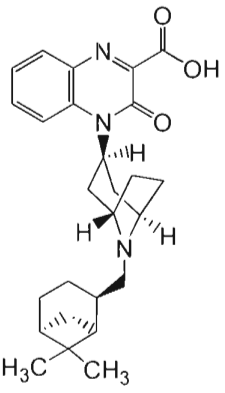
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
308		77.5 ±17.1	60.2 ±5.8	144 ±16	12160
309		62.9 ±9.8	784 ±43	210 ±11	2045
310		127.6 ±9.3	770 ±37	229 ±23	8680

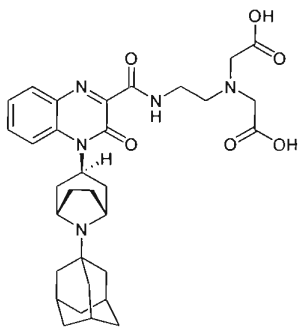
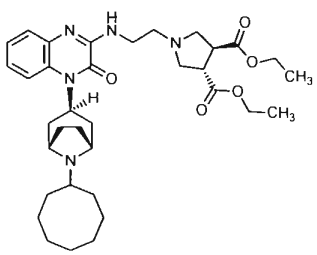
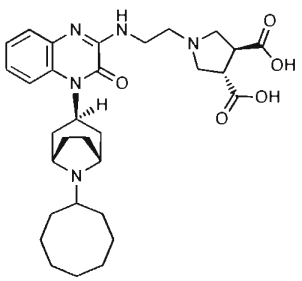
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
311		24.6 ±3.0	400 ±48	49.3 ±2.4	2570
240		40.3 ±3.3	480 ±40	46.3 ±3.8	41190
312		35.9 ±6.6	263 ±11	172 ±41	14500
313		35.8 ±9.1	452 ±49	35.3 ±1.3	2220
241		17.7 ±3.6	679 ±69	440 ±79	10900

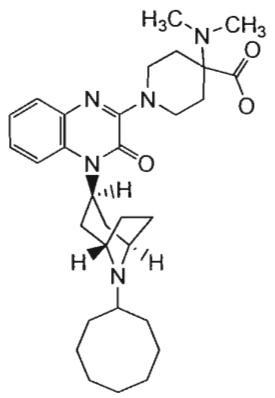
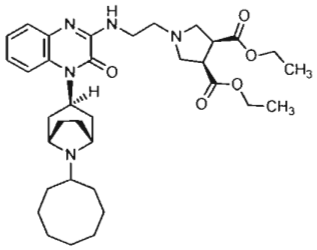
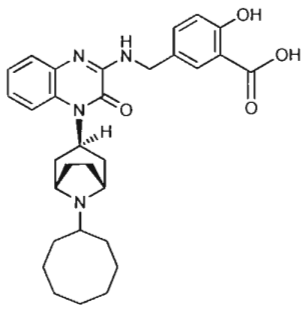
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
253		131.4 ±9.2	5300 ±900	2055 ±427	68750
257		1187 ±103			
248		911 ±139			
249		260 ±14	46010	6000 ±2040	533100
259		962 ±62			
255		400 ±22			
251		3294 ±219			
314		59.7 ±4.1	1792 ±112	909 ±49	4925
153		22.2 ±1.8	459 ±18	66.0 ±15.6	530900
261		596 ±16			
245		912 ±72			
243		1345 ±67			
247		89.9 ±8.1	10970	3500 ±623	533800

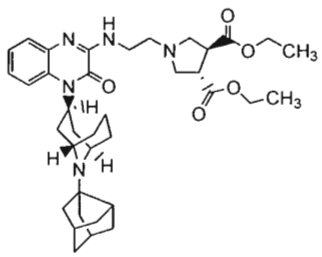
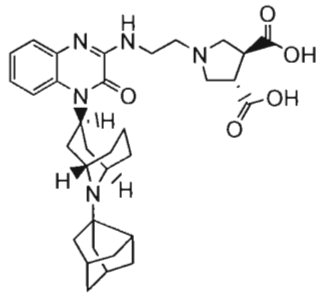
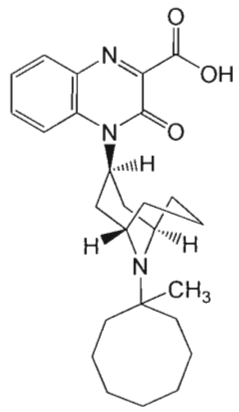
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
316		632 ±114			
317		157 ±29	1160 ±19	1720 ±210	> 20,000
272		740 ±105			
274		383 ±45			
270		52.1 ±7.4	2660 ±256	1600 ±307	> 20,000
235		18.1 ±0.8	14300 ±2650	1116 ±18	> 20,000
318		60.8 ±7.9	1930 ±335	835 ±83	7730 ±255

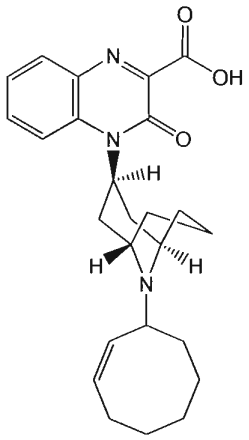
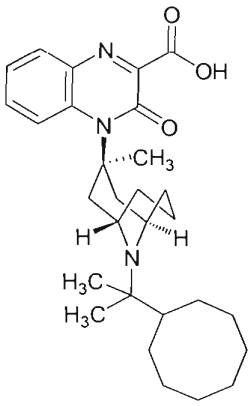
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
319		611 ±78			
320		15.4 ±4.0	1865 ±240	3090 ±1300	15010 ±380
321		> 20,000			

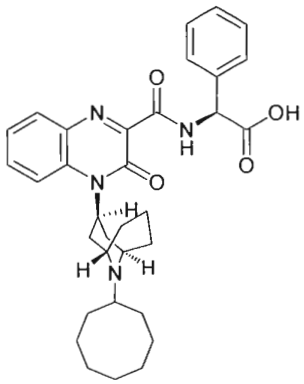
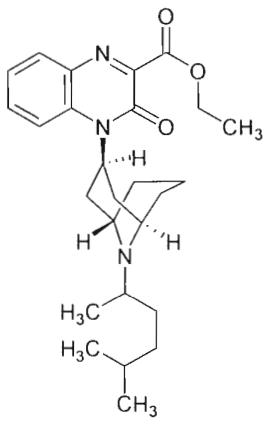
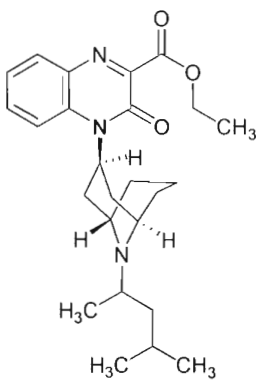
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
322		2841 ±961			
323		205 ±35	2800 ±450	> 20,000	> 20,000
324		398 ±59			
233		144 ±37			

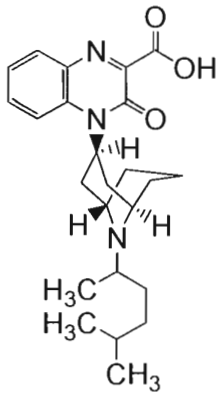
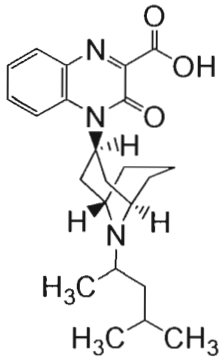
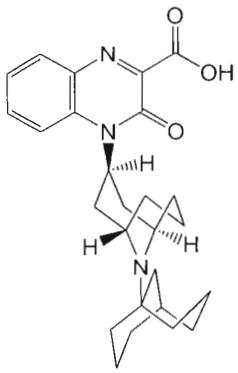
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
325		82 ±24			
266		4.1 ±0.6	679 ±54	1430 ±86	> 20,000
263		47.5 ±6.1	39554	5625 ±1424	525570
237		30.2 ±0.4	16252 ± 3179	2473 ± 85	524333
239		45.5 ±4.4	57791	3272 ± 398	537763
326		24.6 ±1.2	10098	16.2 ±2.2	> 20,000
279		29.9 ±0.7	16913	447 ±79	> 20,000
327		104.2 ±5.8	37211	672.5 ±182.5	> 20,000

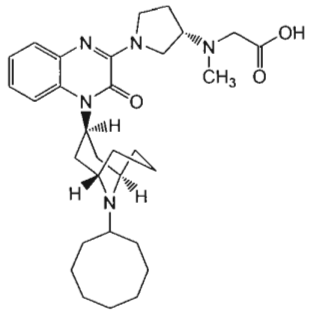
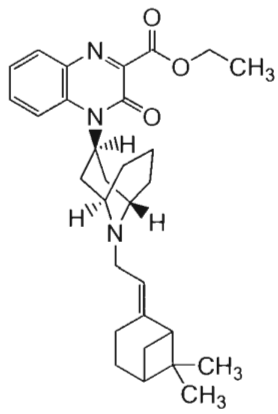
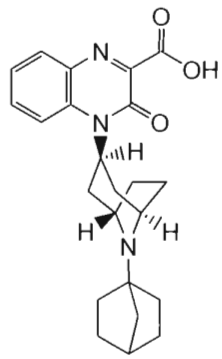
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
282		502 ±82	1445 ± 106	64.2 ± 8.5	32209
284		21.5 ±1.5	8927 ±524	223.4 ±12.1	72511
328		7.7 ±0.1	3877 ±261	102.0 ±6.9	18818 ±507
329		62.2 ±7.5	7122 ±605	31.2 ±8.4	67102
330		66.1 ±5.4			

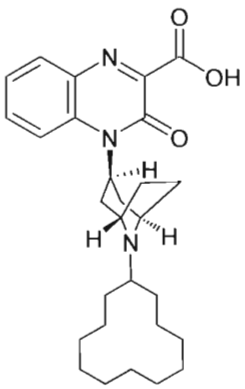
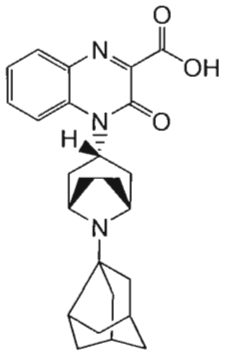
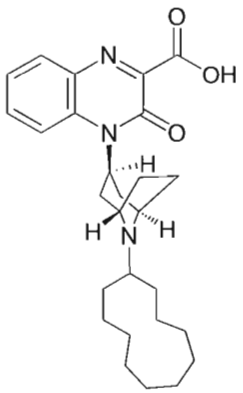
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
331		493.3 ±60.2			
332		587.2 ±38.3			
333		29.1 ±2.1	17180 ±6501	5035 ±984	39396
334		38.1 ±7.2	4750 ±262	6866 ±1903	16831 ±820
335		8.6 ±0.7	> 20,000	5154 ±809	> 20,000
286		2.8 ±0.8	> 20,000	16760 ±1446	> 20,000

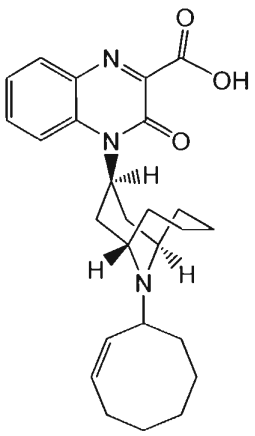
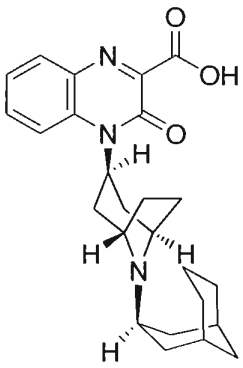
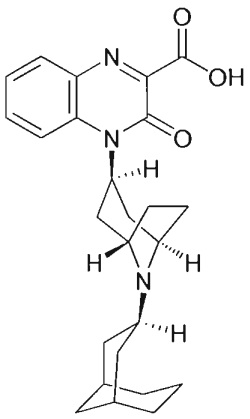
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
288		1.8 ±0.3	2060 ±199	565 ±62	> 20,000
336		3.6 ±0.6	3291 ±186	365 ±98	5437 ±796
290		1.4 ±0.1	699 ±100	375 ±157	3155 ±1282
292		8.5 ±0.9	3429 ±865	4470 ±160	2141 ±507
294		2.5 ±0.1	709 ±94	425 ±112	1606 ±155
299		289 ±15			

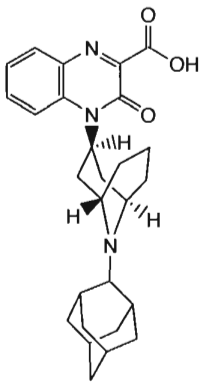
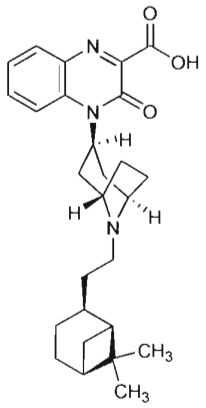
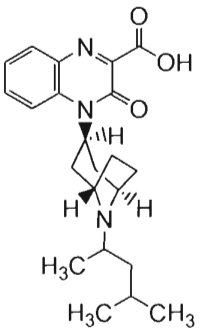
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
300		9.0 ±1.5	443	63.4 ±8.8	106 ±30
296		4.8 ±0.9	1029 ± 108	1547 ± 604	1970 ± 259
298		2.0 ±0.1	396 ± 5.5	469 ± 157	1523 ± 523
301		29.8 ±4.0	487 ± 61	162 ± 35	1396 ± 241
302		9.9 ±0.8	160 ± 18	85.4 ± 18.8	2863 ± 334

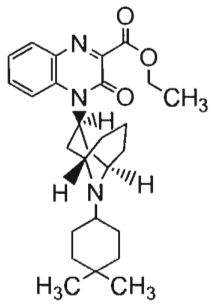
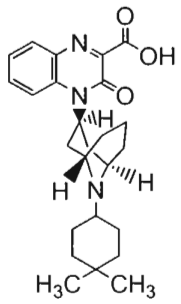
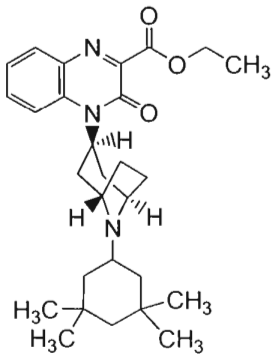
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
303		35.4 ±0.6	664 ± 79	1582 ± 393	1102 ± 456
304		13.8 ±2.1	397 ± 71	523 ± 75	667 ± 232
222		30.2 ±2.8	1862 ± 433	2889 ± 593	2027 ± 582
350		382 ±74			
351		33.5 ±3.3	368 ±97	129.5 ±14.4	11275

Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
352		11.5 ±1.3	307.1 ±4.0	49.7 ±3.8	1743 ±57
353		22.9 ±1.6	689 ±64	589 ±211	1159 ±260
354		10.5 ±2.2	292 ±81	20.6 ±1.1	386 ±73
355		128.0 ±7.9	5490 ±85	3891 ±920	> 20,000

Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
356		43.1 ±3.4	1436 ±215	76 ±21	18180
357		364 ±18			
358		9.0 ±1.1	1600 ±55	640 ±126	8900 ±2390

Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
359		11.6 ±1.5	407 ±33	1756 ±308	1011 ±239
360		202.8 ±7.1	3825 ±576	2691 ±189	> 20,000
361		5.7 ±0.4	4450 ±1224	6143 ±1617	> 20,000
362		2.4 ±0.2	1631 ±77	2280 ±213	4763 ±509

Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
363		250 ± 22	14374	10240 ± 2400	7100 ± 1560
364		1.4 ± 0.1	670 ± 220	63 ± 15	758 ± 95
365		1828 ± 123			
366		50.0 ± 4.7	1759 ± 276	480.5 ± 26.5	2856 ± 763

Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
367		374 ± 73			
368		828 ± 126			
369		178 ± 17	4032 ± 1010	5345 ± 1725	> 20,000
370		1300 ± 50			

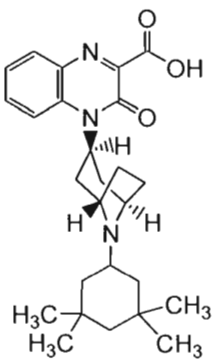
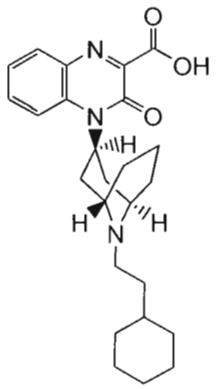
Ref No.	Compound	K_i [Average ± Std Deviation] (nM)			
		ORL-1	Opioid Receptor		
			Mu	Kappa	Delta
371		496 ± 68			
372		188 ± 17			

Table 2: Activity Response of Substituted-Quinoxaline-Type Piperidine Compounds

Ref No.	GTPγS (EC_{50}: nM, Emax: %) [mean ± SEM]					
	ORL-1		Opioid Receptor			
			Mu		Kappa	
	EC_{50}	E_{max}	EC_{50}	E_{max}	EC_{50}	E_{max}
1	1850±190	43±1.7				
2	580±92	47.3±2.0			2110 ± 424	14.7 ± 1.5
3	602±95	51.7±3.7				
4	1001±105	83±1.5			846±80	30.5±2.9
5	293±47	73±3.5			801±208	13±0.6
6	76±74	85.3±4.4			1643±150	34.7±1.7
7	979±40	67.3±1.9			9777 ± 2022	14.7 ± 1.5
8	4560±1120	55.7±4.2				
9	79.1±6.9	39±1.5			1523±153	12±0.6
10	553±59	34±1.5			2227±565	39.8±4.8
11	900±48	45.7±1.8				
12	452±66	47.7±3.5			1404±86	28±2.1
13	1690±166	68. 7±2.4				
14	4650±238	54.7±2.6				
15	179±24	93.7±5.4			794±14	28.3±3.2
16	3745±93	61±2			10810 ± 3960	16 ± 3.1
17	7871±2230	100±9			6663 ± 286	7 ± 1.2
18	1284±84	69.0±2.7			5125 ± 716	28.3 ± 3.4
19	286±30	115.3±6.7				
21	1466±50	71.7±1.2			460±130	13±1.2
22	440±39	64±3.6			690±86	31±1.2
23	950±94	73.7±2.3			1896 ± 380	6.83 ± 0.6
24	611±71	78±2.3			7122 ± 1182	15.7 ± 2.6
25	781±26	79±2.5				
26	108.6±5.9	85.3±2.7	2883 ± 1286		2076±302	17.3±0.9
27	969±89	92.3±0.9				
28	1880±285	80.3±1.2				
29	468±81	85±0.6			3812 ± 747	8.25 ± 0.48
30	699±19	92.7±3.5			3967 ± 1203	9.67 ± 1.5
31	335±32	76.3±3.9			1400±49	39.3±2.0
32	406±42	76±0.6			7031 ± 662	29 ± 3.5
33	211±21	71.3±3.7				
34	1077±140	43±2.1			187 ± 41.6	26 ± 7
37	265±31	97.7±4.8			1499 ± 281	29 ± 5.1
38	71.2±8.1	119.7±2.7			8763 ± 1214	7 ± 1.2
39	88±30	78±10			285 ± 54	12.7 ± 4.1
42	543±27	86.3±2.4			4367 ± 1002	8.67 ± 0.33
43	474±67	88.3±2.7	6439 ± 1518	1.77 ± 0.4	311.2 ± 39.6	12.67 ± 1.5
44	392.2±6.6	38±3.8	8696 ± 3404	4 ± 1	980 ± 155	20.33 ± 1.9
45	169±58	98.7±9.5			5331 ± 608	10 ± 0.6
46	399±56	112.7±2.3			4105 ± 223	30 ± 1.5
47	418.7±12.7	98.7±4.4			3515 ± 466	10.67 ± 1.2
49	808±110	76.3±5.4			5398 ± 125	9.33 ± 0.7
50	367±11	68±2.5	689761	6 ± 4		

Ref No.	GTPγS (EC_{50}: nM, Emax: %) [mean ± SEM]					
	ORL-1		Opioid Receptor			
			Mu		Kappa	
	EC_{50}	E_{max}	EC_{50}	E_{max}	EC_{50}	E_{max}
51	49.1±8.2	107±3.1	6125 ± 419	2.33 ± 0.7	276 ± 42	11 ± 2.5
52	957±35	99±4.6			2816 ± 93	9 ± 0.6
54	464±28	100.3±3.3				
55	421±50	106.7±3.7			4862 ± 1205	9.33 ± 0.9
56	113±11	48.7±1.9			2545 ± 960	14 ± 1
57	486±34	85.3±5.0			5238 ± 1981	12 ± 1
58	151.4±7.9	96±2.9	13779 ± 5344	4.67 ± 0.3	5930 ± 1751	13 ± 1.5
59	383+63	106.5±3.8			5040 ± 774	12 ± 0.6
60	2137±661	88.7±6.3			6901 ± 1020	16.67 ± 0.7
61	1234±238	73.3±2.3			7826 ± 1712	7.67 ± 1.8
64	457±90	87.7±2.3				
65	348±22	107.7±3.3				
66	107.6±15.1	109.3±5.4			3543 ± 1799	13.7 ± 1.2
67	84.9±4.3	78.3±3.8			6571 ± 1028	16.7 ± 0.3
68	478±6.4	101±5.9				
70	788±44	54.7±1.3			2103±403	12.7±0.9
71	964±116	65.3±2.6				
72	1479±116	42.0±2.9			297±195	47.0±1.2
73	377±115	15.7±1.7				
74	184±21	113.3±3.3	4066±137	10.0±0.6	1222±349	11.3±1.5
77	97.8±9.7	128±4.7				
78	363±20	102.3±5.7			3463 ± 1057	11.3 ± 1.3
79	703±39	88.3±2.4			3885 ± 1542	11.3 ± 1.2
81	469±8	79.3±3.2			1709 ± 376	4.7 ± 0.7
82	181.4±9.8	102±3.2			3019 ± 559	8
83	558±77	79±2.5			1981 ± 152	11.3 ± 1.5
84	182±22	105.3±1.7			4013 ± 406	33.3 ± 0.9
85	197±35	67.0±3.2	3118±525	22±2	1936±141	27.0±1.7
86	422±40	116.7±7.4	529310		362±54	11.8±0.6
88	201±27	110.7±2.9			2278 ± 266	16 ± 0.6
89	806±85	74.3±3.4				
90	72.7±13.7	104.7±3.8	3569 ± 1391	9.7 ± 0.3	6001 ± 444	9.3 ± 1.4
91	51.7±14.3	113.7±2.0	6198 ± 677	16.3 ± 1.2	4145±457	10.3±0.9
92	510±100	74.3±6.0			2267 ± 101	3.3 ± 0.7
94	61.3±5.6	113±8	7001 ± 3621	13 ± 2.1	1125 ± 434	17 ± 2.7
95	92±14	103.3±5.2				
98	93.1±8.3	83.3±8.0	2150±390	14	3150±860	12.7±2.7
99	1230±158	74.7±4.5			$> 10^5$	0.7±0.9
100	19.1±3.6	29±2				
101	17.0±4.2	105.7±5.0	4900±2050	9.7±0.7	32770	15.3±4.1
102	103±18	112.3±6.3	4500±1500	8.7±3.4	960±167	5.7±0.3
103	3240±400	73.7±4.4				
104	2428±219	86.3±5.2				
106	400±44	55.3±5.8				
111	3024±477	84±10				
114	924±42	73±2				
115	43.6±0.9	35.3±2.3	1061±52	93	3512±647	18±2

Ref No.	GTPγS (EC_{50}: nM, Emax: %) [mean ± SEM]					
	ORL-1		Opioid Receptor			
			Mu		Kappa	
	EC_{50}	E_{max}	EC_{50}	E_{max}	EC_{50}	E_{max}
119	3663±171	62.0±1.5			5997±517	59.3±2.3
120	41.3±4.2	94.0±3.6	79340		831±86	8.7±0.3
121	265±27	89.7±5.4	3485±445	9.7±1.2	2930±132	10.7±1.2
122	67.6±3.0	87.3±3.9	5111±1661	8.7±0.3	1365±285	8.3±0.9
123	2351±369	110.5±6.5			3779±1268	9.0±1.2
124	1358±89	115±5				
125	66.9±7.1	107.3±2.4	3600±825	10.8±2.1	2560±470	10.3±1.8
126	594±83	105.0±0.6	3580±140	10.6±1.2	4680±975	8.3±0.9
127	31.3±3.8	127.0±5.3	1365±250	12.5±1.4	2450±490	17
128	209±31	102.7±2.7	1350±125	12.0±0.8	4340±610	12.7±1.5
129	182.6±7.5	107.7±3.7	1750±40	9.7±0.6	3855±572	8.3±0.3
130	40.6±2.4	59.7±0.3	336±47	23±1		
133	473±27	81.3±3.0	1138±281	9±1	1138 ± 281	9 ± 1
226	357±84	83			4567±1257	7.7 ± 0.3
228	53.6±8.4	101.3				
207	946±85	60			1943±548	6.0 ± 1.5
209	1211±54	69	1750±76	10.5	9700±3550	3.7
188	103.7±14.3	36.5	4940±525	11.5	3340±1590	3.3
189	175±13	90	>20,000	21	>20,000	0.25
337	438±15	78	7120±380	9.1	>20,000	10.7
211	337±20	38	1080±235	4.2	2260±480	9
191	956±67	67 ± 1.5				
193	94.4±19.0	34.5 ± 1.6			4727±1215	13 ± 2.1
212	195±13	78.7 ± 3			382±97	6.7 ± 1.8
218	85±17	53.7 ± 2.3			4839±2411	9.7 ± 1.8
194	1760±119	46.7 ± 1.9			>20,000	0
196	293±23	40.3 ± 2.3				
221	277.1±5.6	80.3 ± 3.8			4458±865	9.3 ± 1.3
197	517±48	31.3 ± 1.8			5960±561	7.7 ± 1.2
199	1774±296	39 ± 1			>20,000	0
201	1299±240	84 ± 1.2				
216	397±26	81 ± 3			>20,000	0.3
203	3856±15	73.3 ± 1.7			4587±1293	6.3
305	394±53	42.3 ± 2.9			>20,000	1.0
174	1619±224	69.7 ± 5.2			>20,000	0.3
176	1519±105	50.3 ± 4.4				
178	125.0±8.4	83.3 ± 5.4			3206 ± 379	6.3 ± 0.9
306	548±57	82.3±3.7			2194±744	5.7±0.3
307	400±72	54.0±2.3			4787±336	11.3±1.2
308	379±58	97.7±2.9	63410	10.3±0.3	28900	24.7±8.7
309	659±155	92.7±2.3	7780±689	33.2±4.3	24960	32.3±9.2
310	419±62	81.3±3.2	7406±723	16.0±1.7	8526±2196	14.0±6.7
311	78.6±12.5	74.7±1.8	20640	14.0	28150	31.3±3.8
240	103±23	58.3±1.9	9871±1430	7.7±0.6	6241±2805	10.3±5.3
312	138.2±8.1	56.5±2.3	10896±666	17.7±0.7	11751±4518	20.3±2.6
313	269±53	67±53	21190	12.3±0.3	3946±2100	12.0±4.0
241	114±16	87.3±5.0	3922±139	11.0±0.6	450±180	3.7±0.3
253	3573±302	67.8±1.9				

Ref No.	GTPγS (EC_{50}: nM, Emax: %) [mean ± SEM]					
	ORL-1		Opioid Receptor			
			Mu		Kappa	
	EC_{50}	E_{max}	EC_{50}	E_{max}	EC_{50}	E_{max}
249	4252±181	95.8±3.6				
314	453±66	61.0±0.6			4425±1516	10.3±0.9
153	210±21	58.3±1.6	643±13	3.0±0.4	667025	1.0±2.0
247	271±16	33.3±2.2				
317	647±27	58.3±3.9				
270	1016±203	99.3±1.3				
235	207±10	88±5				
318	236±13	44 ± 1.7			2177±656	6.7 ± 1.9
320	103.6±7.8	80 ± 4.8				
233	503±105	29 ± 3				
325	109±14	15 ± 1.2				
266	33.8±1.0	80 ± 2.2	395.4 ± 43.3	6.6 ± 0.7		
263	298±26	69 ± 2.9				
326	214±31	68±3			429±62	11.7 ± 0.3
279	471±54	59±2			>20,000	4.3 ± 1.3
282	211.7±0.9	58±1.2			13444±962	10.0 ± 1.2
284	618±47	73.3±3.7			>20,000	8.0 ± 1
328	101.6±5.2	75.3±1.9			4397±1592	15.0 ± 2.5
329	321±28	66.3±2.4			552±77	13.0 ± 1.7
330	75.4±9.1	19±1.5				
333	1831±159	60.0±1.7				
334	293±15	68.7±3.4				
335	174±10	117±5				
286	17±2.7	105.3±5.7				
288	11.6±0.6	104±4.6			>20,000	3.3 ± 1.9
336	32.0±5.0	80.3±2.2			>20,000	6.0 ± 1.5
290	11.1±1.0	96.5 ± 1.9	3389 ± 838	17.3 ± 2.9	1770±421	12.7
292	106.0±3.8	97.5 ± 1.3				
294	28.1±2.1	106.3 ± 0.9	5705 ± 574	14.7 ± 1.5	1258±258	20.0
300	53.1±8.5	57.7 ± 2	5265 ± 1497	12 ± 1.8	208 ± 70	8.7 ± 1.3
301	208±16	82.0 ± 2	6181 ± 1252	40.7 ± 3.2	1506 ± 494	10 ± 0.6
302	85±4	98.3 ± 1.7	1365 ± 251	56 ± 6.5	1484 ± 367	7 ± 0.6
303	298±23	90.0 ± 2	5468 ± 552	45.7 ± 7.8		
304	150±6	102.7 ± 2.7	1727 ± 402	50.7 ± 2.9	3269 ± 939	6.7 ± 1.2
351	361±58	53.3±0.6	36425	20.0±0.6	46490	63±11
352	199±40	80.0±1.7	1727±321	8.9±0.5	3734±971	13.0±2.3
353	219±20	57.0	6980±1255	31.7	7660±1140	20.0
354	37.55±1.31	87.0	1409±248	21.7	>20,000	5.3
355	1855±414	74.7 ± 3.8				
356	686±41	93.3 ± 8			>20,000	3.3 ± 1.2
358	62.6±14.1	101.3 ± 5.7			1960±806	11.7 ± 2.3
359	133.7±2.7	89.7± 5.2	3615±730	28.7± 1.2		
360	1667.1±18.4	57.3± 4.1				
361	57.2±3.1	58.7 ± 2.4				
362	4.0 ± 0.9	47.8				
363	4088±1164	67.0 ± 5.8				
364	9.22±0.44	61.8	571.8	9.5	>20,000	9.8

Ref No.	GTPγS (EC_{50}: nM, Emax: %) |mean ± SEM|					
	ORL-1		Opioid Receptor			
			Mu		Kappa	
	EC_{50}	E_{max}	EC_{50}	E_{max}	EC_{50}	E_{max}
366	925±101	86.5± 2.6			1169±368	30.3
369	545±85	37.7± 0.7				
372	214±57	20.7 ± 3.8				

5.58 Example 58: *In Vivo* Assays for Prevention or Treatment of Pain

Test Animals: Each experiment uses rats weighing between 200-260g at the start of the experiment. The rats are group-housed and have free access to food and water at all times, except prior to oral administration of a Substituted-Quinoxaline-Type Piperidine Compound when food is removed for 16 hours before dosing. A control group acts as a comparison to rats treated with a Substituted-Quinoxaline-Type Piperidine Compound. The control group is administered the carrier for the Substituted-Quinoxaline-Type Piperidine Compound. The volume of carrier administered to the control group is the same as the volume of carrier and Substituted-Quinoxaline-Type Piperidine Compound administered to the test group.

Acute Pain: To assess the actions of a Substituted-Quinoxaline-Type Piperidine Compound for the treatment or prevention of acute pain, the rat tail flick test can be used. Rats are gently restrained by hand and the tail exposed to a focused beam of radiant heat at a point 5 cm from the tip using a tail flick unit (Model 7360, commercially available from Ugo Basile of Italy). Tail flick latencies are defined as the interval between the onset of the thermal stimulus and the flick of the tail. Animals not responding within 20 seconds are removed from the tail flick unit and assigned a withdrawal latency of 20 seconds. Tail flick latencies are measured immediately before (pre-treatment) and 1, 3, and 5 hours following administration of a Substituted-Quinoxaline-Type Piperidine Compound. Data are expressed as tail flick latency(s) and the percentage of the maximal possible effect (% MPE), *i.e.*, 20 seconds, is calculated as follows:

$$\%\ \text{MPE} = \frac{|\ (\text{post administration latency}) - (\text{pre-administration latency})\ |}{(\text{20 s pre-administration latency})} \times 100$$

The rat tail flick test is described in F.E. D'Amour *et al.*, "A Method for Determining Loss of Pain Sensation," *J. Pharmacol. Exp. Ther.* 72:74-79 (1941).

Inflammatory Pain: To assess the actions of a Substituted-Quinoxaline-Type Piperidine Compound for the treatment or prevention of inflammatory pain, the Freund's complete adjuvant ("FCA") model of inflammatory pain was used. FCA-induced inflammation of the rat hind paw is associated with the development of persistent inflammatory mechanical hyperalgesia and provides reliable prediction of the anti-hyperalgesic action of clinically useful analgesic drugs (L. Bartho *et al.*, "Involvement of capsaicin-sensitive neurons in hyperalgesia and enhanced opioid antinociception in inflammation," *Naunyn-Schmiedeberg's Archives of Pharmacol.* 342:666-670 (1990)). The left hind paw of each animal was administered a 50 µL intraplantar injection of 50% FCA. 24 hour post injection, the animal was assessed for response to noxious mechanical stimuli by determining the PWT, as described below. Rats were then administered a single injection of 1, 3, 10 or 30 mg/kg of either a Substituted-Quinoxaline-Type Piperidine Compound; 30 mg/kg of a control selected from Celebrex, indomethacin or naproxen; or carrier. Responses to noxious mechanical stimuli were then determined 1, 3, 5 and 24 hours post administration. Percentage reversal of hyperalgesia for each animal was defined as:

$$\% \text{ Reversal} = \frac{|\text{(post administration PWT)} - \text{(pre-administration PWT)}|}{|\text{(baseline PWT)} - \text{(pre-administration PWT)}|} \times 100$$

Assessments of the actions of the Substituted-Quinoxaline-Type Piperidine Compounds that were tested revealed these compounds were efficacious, *e.g.*, Substituted-Quinoxaline-Type Piperidine Compounds significantly reduced FCA-induced thermal hyperalgesia, with ED_{50} values of from about 0.1 mg/kg to about 20 mg/kg and maximum % reversal values of from about 20% to about 100%. For example, for Substituted-Quinoxaline-Type Piperidine Compound **241** the ED_{50} value for reversal of thermal hyperalgesia was 2.7 mg/kg at 1 hour after administration, 3.8 mg/kg at 3 hours after administration, and 2.3 mg/kg at 5 hours after administration of Substituted-Quinoxaline-Type Piperidine Compound **241**. Additionally, the maximum % reversal of thermal hyperalgesia was about 80% at 3 hours after administration of Substituted-Quinoxaline-Type Piperidine Compound **241**. And, for Substituted-Quinoxaline-Type Piperidine Compound **74** the ED_{50} value for reversal of thermal hyperalgesia was 8.5 mg/kg at 1 hour after administration, 4.0mg/kg at 3 hours after

administration, and 7.8 mg/kg at 5 hours after administration of Substituted-Quinoxaline-Type Piperidine Compound **74**. Additionally, the maximum % reversal of thermal hyperalgesia was about 80% at 3 hours after administration of Substituted-Quinoxaline-Type Piperidine Compound **74**.

Moreover, for the Substituted Quinoxaline-Type Piperidine Compound **362**, the ED_{50} value for reversal of thermal hyperalgesia was 0.8 mg/kg at 1 hour after administration, 1.5 mg/kg at 3 hours after administration, and 3.0 mg/kg at 5 hours after administration of Substituted Quinoxaline-Type Piperidine Compound **362**. Additionally, the % reversal of thermal hyperalgesia after administration of a 3 mg/kg dose was 86% at 1 hour after administration, 51% at 3 hours after administration, and 27% at 5 hours after administration of Substituted Quinoxaline-Type Piperidine Compound **362**. And, for Substituted Quinoxaline-Type Piperidine Compound **361**, upon administration of a 5 mg/kg dose, the % reversal of thermal hyperalgesia was 36% reversal at 1 hour after administration, 90% reversal at 3 hours after administration, and 70% reversal at 5 hours after administration of Substituted Quinoxaline-Type Piperidine Compound **361**. And, for Substituted Quinoxaline-Type Piperidine Compound **358**, upon administration of 5 mg/kg dose, the % reversal of thermal hyperalgesia was 34% reversal at 1 hour after administration, 46% reversal at 3 hours after administration, and 79% reversal at 5 hours after administration of Substituted Quinoxaline-Type Piperidine Compound **358**.

Substituted Quinoxaline-Type Piperidine Compounds **358**, **361**, and **362** also have surprisingly and desirably reduced abnormal behavioral side effects, such as reduced sedation, hyperactivity and/or hypoactivity. Additionally and surprisingly, Substituted Quinoxaline-Type Piperidine Compound **362** has reduced cardiovascular side effects. These side effects were determined using known methods: an *in vitro* hERG (human ether a-go-go gene) assay as disclosed in Z. Zhou et al., "Properties of HERG Channels Stably Expressed in HEK 293 Cells Studied at Physiological Temperature," *Biophysical J.* 74:230-241 (1998); and APD (action potential duration) in guinea pig purkinje fibers as disclosed in J.A. Hey, "The Guinea Pig Model for Assessing Cardiotoxic Proclivities of Second Generation Antihistamines," *Arzneimittelforschung* 46(8):834-837 (1996).

Neuropathic Pain: To assess the actions of a Substituted-Quinoxaline-Type Piperidine Compound for the treatment or prevention of neuropathic pain, either the Seltzer model or the Chung model can be used.

In the Seltzer model, the partial sciatic nerve ligation model of neuropathic pain is used to produce neuropathic hyperalgesia in rats (Z. Seltzer *et al.*, "A Novel Behavioral Model of Neuropathic Pain Disorders Produced in Rats by Partial Sciatic Nerve Injury," *Pain* 43:205-218 (1990)). Partial ligation of the left sciatic nerve is performed under isoflurane/O_2 inhalation anaesthesia. Following induction of anesthesia, the left thigh of the rat is shaved and the sciatic nerve exposed at high thigh level through a small incision and is carefully cleared of surrounding connective tissues at a site near the trocanther just distal to the point at which the posterior biceps semitendinosus nerve branches off of the common sciatic nerve. A 7-0 silk suture is inserted into the nerve with a 3/8 curved, reversed-cutting mini-needle and tightly ligated so that the dorsal 1/3 to ½ of the nerve thickness is held within the ligature. The wound is closed with a single muscle suture (4-0 nylon (Vicryl)) and vetbond tissue glue. Following surgery, the wound area is dusted with antibiotic powder. Sham-treated rats undergo an identical surgical procedure except that the sciatic nerve is not manipulated. Following surgery, animals are weighed and placed on a warm pad until they recover from anesthesia. Animals are then returned to their home cages until behavioral testing begins. The animal is assessed for response to noxious mechanical stimuli by determining PWT, as described below, prior to surgery (baseline), then immediately prior to and 1, 3, and 5 hours after drug administration for rear paw of the animal. Percentage reversal of neuropathic hyperalgesia is defined as:

$$\% \text{ Reversal} = \frac{|\text{(post administration PWT)} - \text{(pre-administration PWT)}|}{|\text{(baseline PWT)} - \text{(pre-administration PWT)}|} \times 100$$

In the Chung model, the spinal nerve ligation model of neuropathic pain is used to produce mechanical hyperalgesia, thermal hyperalgesia and tactile allodynia in rats. Surgery is performed under isoflurane/O_2 inhalation anaesthesia. Following induction of anaesthesia, a 3 cm incision is made and the left paraspinal muscles are separated from the spinous process at the L_4-S_2 levels. The L_6 transverse process is carefully removed with a pair of small rongeurs to identify visually the L_4-L_6 spinal nerves. The left L_5 (or L_5 and L_6) spinal nerve(s) is isolated and tightly ligated with silk thread. A complete hemostasis is confirmed and the wound is sutured using non-absorbable sutures, such as nylon sutures or stainless steel staples. Sham-treated rats undergo an identical surgical procedure except that the spinal nerve(s) is not manipulated. Following surgery animals are weighed, administered a subcutaneous (s.c.)

injection of saline or ringers lactate, the wound area is dusted with antibiotic powder and they are kept on a warm pad until they recover from the anesthesia. Animals are then returned to their home cages until behavioral testing begins. The animals are assessed for response to noxious mechanical stimuli by determining PWT, as described below, prior to surgery (baseline), then immediately prior to and 1, 3, and 5 hours after being administered a Substituted-Quinoxaline-Type Piperidine Compound for the left rear paw of the animal. The animal can also be assessed for response to noxious thermal stimuli or for tactile allodynia, as described below. The Chung model for neuropathic pain is described in S.H. Kim, "An Experimental Model for Peripheral Neuropathy Produced by Segmental Spinal Nerve Ligation in the Rat," *Pain* 50(3):355-363 (1992).

Response to Mechanical Stimuli as an Assessment of Mechanical Hyperalgesia: The paw pressure assay can be used to assess mechanical hyperalgesia. For this assay, hind paw withdrawal thresholds (PWT) to a noxious mechanical stimulus are determined using an analgesymeter (Model 7200, commercially available from Ugo Basile of Italy) as described in C. Stein, "Unilateral Inflammation of the Hindpaw in Rats as a Model of Prolonged Noxious Stimulation: Alterations in Behavior and Nociceptive Thresholds," *Pharmacol. Biochem. and Behavior* 31:451-455 (1988). The maximum weight that can be applied to the hind paw is set at 250 g and the end point is taken as complete withdrawal of the paw. PWT is determined once for each rat at each time point and either only the affected (ipsilateral) paw is tested, or both the ipsilateral and contralateral (non-injured) paw are tested.

Response to Thermal Stimuli as an Assessment of Thermal Hyperalgesia: The plantar test can be used to assess thermal hyperalgesia. For this test, hind paw withdrawal latencies to a noxious thermal stimulus are determined using a plantar test apparatus (commercially available from Ugo Basile of Italy) following the technique described by K. Hargreaves *et al.*, "A New and Sensitive Method for Measuring Thermal Nociception in Cutaneous Hyperalgesia," *Pain* 32(1):77-88 (1988). The maximum exposure time is set at 32 seconds to avoid tissue damage and any directed paw withdrawal from the heat source is taken as the end point. Three latencies are determined at each time point and averaged. Either only the affected (ipsilateral) paw is tested, or both the ipsilateral and contralateral (non-injured) paw are tested.

Assessment of Tactile Allodynia: To assess tactile allodynia, rats are placed in clear, plexiglass compartments with a wire mesh floor and allowed to habituate for a period of at

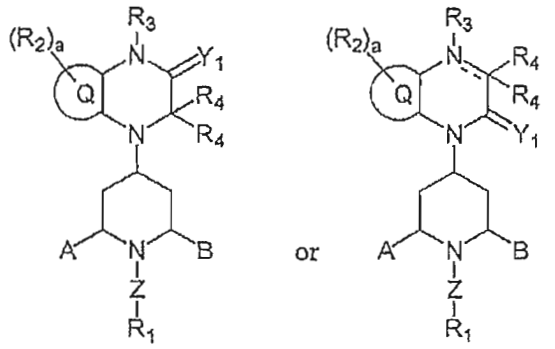
least 15minutes. After habituation, a series of von Frey monofilaments are presented to the plantar surface of the left (operated) foot of each rat. The series of von Frey monofilaments consists of six monofilaments of increasing diameter, with the smallest diameter fiber presented first. Five trials are conducted with each filament with each trial separated by approximately 2 minutes. Each presentation lasts for a period of 4-8 seconds or until a nociceptive withdrawal behavior is observed. Flinching, paw withdrawal or licking of the paw are considered nociceptive behavioral responses.

The invention is not to be limited in scope by the specific embodiments disclosed in the examples that are intended as illustrations of a few aspects of the invention and any embodiments that are functionally equivalent are within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art and are intended to fall within the scope of the appended claims.

A number of references have been cited, the entire disclosures of which are incorporated herein by reference for all purposes.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound according to Formula (I) or (II):



(I) or (II)

or a pharmaceutically acceptable derivative thereof wherein:

Y_1 is O or S;

Q is selected from fused benzo or (5- or 6-membered)heteroaryl;

each R_2 is independently selected from:

(a) -halo, -CN, -NO_2, -OT_3, -$C(=O)T_3$, -$C(=O)OT_3$, -$C(=O)N(T_1)(T_2)$, -$S(=O)_3H$, -$S(=O)T_3$, -$S(=O)_2T_3$, -$S(=O)_2N(T_1)(T_2)$, -$N(T_1)(T_2)$, -$N(T_3)C(=O)T_3$, -$N(T_3)C(=O)N(T_1)(T_2)$, -$N(T_3)S(=O)_2T_3$, or -$N(T_3)S(=O)_2N(T_1)(T_2)$; or

(b) -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_1-C_6)alkoxy, -(C_3-C_7)cycloalkyl, -(C_6-C_{14})bicycloalkyl, -(C_8-C_{20})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_7-C_{14})bicycloalkenyl, -(C_8-C_{20})tricycloalkenyl, -(5- or 6-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_8 groups; or

(c) -phenyl, -naphthalenyl, -(C_{14})aryl, or -(5- or 6-membered)heteroaryl, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_7 groups;

a is an integer selected from 0, 1 or 2;

the dashed line in the 6-membered, nitrogen-containing ring that is fused to the Q group denotes the presence or absence of a bond, and when that dashed line denotes the presence of a bond then R_3 and one R_4 are absent;

R_3 is selected from:

(a) -H; or

(b) -(C_1-C_4)alkyl which is unsubstituted or substituted with 1, 2 or 3 groups independently selected from -OH, -(C_1-C_4)alkoxy, -$N(R_6)_2$, -C(=O)OR_9, or -C(=O)$N(R_6)_2$; or

(c) -(C_3-C_7)cycloalkyl which is unsubstituted or substituted with 1, 2 or 3 groups independently selected from -OH, -(C_1-C_4)alkyl, -(C_1-C_4)alkoxy, -$N(R_6)_2$, -C(=O)OR_9, or -C(=O)$N(R_6)_2$;

each R_4 is independently selected from:

(a) -H; or

(b) -halo, -CN, or -NO_2; or

(c) -X, -(C_1-C_6)alkyl-X, -(5- or 6-membered)heterocycle-X, or -(5- or 6-membered)heterocycle-(C_1-C_6)alkyl-X; or

(d) -C(=Y)CN, -C(=Y)X, -C(=Y)T_3, -C(=Y)YX, -C(=Y)YT_3, -C(=Y)$N(T_1)(T_2)$, -C(=Y)$N(R_9)$CN, -C(=Y)$N(R_9)$X, -C(=Y)$N(R_9)$YH, -C(=Y)$N(R_9)$YX, -C(=Y)$N(R_9)YCH_2$X, -C(=Y)$N(R_9)YCH_2CH_2$X, or -C(=Y)$N(R_9)S(=O)_2T_3$; or

(e) -$N(R_9)$X, -$N(R_9)$-CH_2X, -$N(R_9)$-CH_2CH_2X, -$N(R_9)CH_2N(R_9)C(=N(R_{12}))N(R_{12})_2$, -$N(R_9)$-$CH_2CH_2N(R_9)C(=N(R_{12}))N(R_{12})_2$, -$N(T_1)(T_2)$, -$N(T_3)C(=Y)T_3$, -$N(T_3)C(=Y)YT_3$, -$N(T_3)C(=Y)N(T_1)(T_2)$, -$N(T_3)S(=O)_2T_3$, or -$N(T_3)S(=O)_2N(T_1)(T_2)$; or

(f) -YH, -CH_2YH, -CH_2CH_2YH, -YX_2 or -YT_3; or

(g) -S(=O)T_3, -$S(=O)_2T_3$, -S(=O)$N(T_1)(T_2)$, -$S(=O)_2N(T_1)(T_2)$, -S(=O)X, or -$S(=O)_2$X;

X is:

(a) -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_1-C_6)alkoxy, -(C_3-C_7)cycloalkyl, -(C_6-C_{14})bicycloalkyl, -(C_8-C_{20})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_7-C_{14})bicycloalkenyl, -(C_8-C_{20})tricycloalkenyl, -(5- or 6-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_8 groups; or

(b) -phenyl, -naphthalenyl, -(C_{14})aryl, or -(5- or 6-membered)heteroaryl, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_7 groups;

each Y is independently selected from O or S;

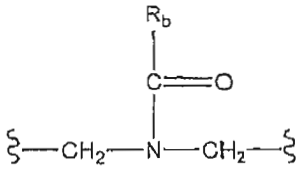
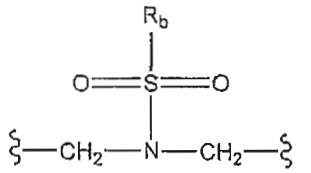
A and B are independently selected from:

(a) -H, -CN, -C(=O)OT_3, or -C(=O)$N(T)_1(T_2)$; or

(b) -(C_3-C_{12})cycloalkyl, -(C_3-C_{12})cycloalkoxy, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, or -(C_1-C_6)alkoxy, each of which is unsubstituted or substituted with 1 or 2 substituents independently selected from -OH, -$S(=O)_2NH_2$, -$N(R_6)_2$, =NR_6, -$C(=O)OT_3$, -$CON(R_6)_2$, -$N(R_6)C(=O)R_9$, and -(5- or 6-membered)heterocycle, or 1, 2 or 3 independently selected -halo; or

(c) A-B can together form a (C_2-C_6)bridge, which is unsubstituted or substituted with 1, 2, 3, 4, 5, 6, 7 or 8 substituents independently selected from -OH, -(C_1-C_4)alkyl, -halo, and -$C(halo)_3$, and which bridge optionally contains -HC=CH- or -O- within the (C_2-C_6)bridge; wherein the 6-membered, nitrogen-containing ring that is fused to the Q group can be in the *endo*- or *exo*- configuration with respect to the A-B bridge; or

(d) A-B can together form a -CH_2-$N(R_a)$-CH_2- bridge, a


bridge, or a

bridge;

wherein the 6-membered, nitrogen-containing ring that is fused to the Q group can be in the *endo*- or *exo*- configuration with respect to the A-B bridge;

R_a is selected from -H, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -CH_2-C(=O)-R_c, -(CH_2)-C(=O)-OR_c, -(CH_2)-C(=O)-$N(R_c)_2$, -(CH_2)$_2$-O-R_c, -(CH_2)$_2$-$S(=O)_2$-$N(R_c)_2$, R_c, or -(CH_2)$_2$-$N(R_c)S(=O)_2$-R_c;

R_b is selected from:

(a) -H, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(3- to 7-membered)heterocycle, -$N(R_c)_2$, -$N(R_c)$-(C_3-C_7)cycloalkyl, or -$N(R_c)$-(3- to 7-membered)heterocycle; or

(b) -phenyl, -naphthalenyl, or-(5- or 6-membered)heteroaryl, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_7 groups; or

(c) -$N(R_c)$-phenyl, -$N(R_c)$-naphthalenyl, -$N(R_c)$-(C_{14})aryl, or -$N(R_c)$-(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_7 groups;

each R_c is independently selected from -H or -(C_1-C_4)alkyl;

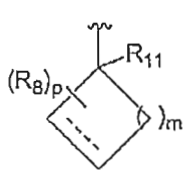
Z is -[(C_1-C_{10})alkyl optionally substituted by R_1]$_h$-, wherein h is 0 or 1; or -(C_1-C_{10})alkyl-$NR_6C(=Y)$-;

each R_1 is independently selected from:

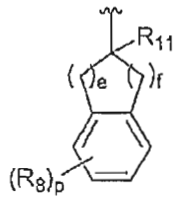
(a) -halo, -CN, -OH, $-CH_2OH$, $-CH_2CH_2OH$, $-NO_2$, $-N(R_6)_2$, $-S(=O)NH_2$, $-S(=O)_2NH_2$, $-C(=O)OV_1$, or $-C(=O)CN$; or

(b) $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-O(C_1-C_6)$alkyl, $-(C_3-C_7)$cycloalkoxy, $-(C_6-C_{14})$bicycloalkyl, $-(C_8-C_{20})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_7-C_{14})$bicycloalkenyl, $-(C_8-C_{20})$tricycloalkenyl, -(3- to 7-membered)heterocycle, -(7- to 10-membered)bicycloheterocycle wherein the -(7-to 10-membered)bicycloheterocycle is selected from -quinolinyl, -isoquinolinyl, -chromonyl, -coumarinyl, -indolyl, -indolizinyl, -benzo[b]furanyl, - benzo[b]thiophenyl, -indazolyl, -purinyl, -4H-quinolizinyl, -isoquinolyl, -quinolyl, -phthalazinyl, -napthyridinyl, -carbazolyl, -β-carbolinyl, -indolinyl, -isoindolinyl, -1, 2, 3, 4-tetrahyroquinolinyl, -1, 2, 3, 4-tetrahydroisoquinolinyl, and pyrrolopyrrolyl, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_8 groups; or

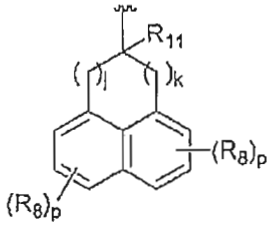
(c)



(i)



(ii)



(iii)

; or

(d) -phenyl, -naphthalenyl, $-(C_{14})$aryl, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with an R_7 group; or

$-Z-R_1$ is 3,3-diphenylpropyl- optionally substituted at the 3 carbon of the propyl with -CN, $-C(=O)N(R_6)_2$, $-C(=O)OV_1$, or -tetrazolyl; or

$-Z-R_1$ is $-(C_1-C_4)$alkyl substituted with tetrazolyl;

each R_6 is independently selected from -H, $-(C_1-C_6)$alkyl, or $-(C_3-C_7)$cycloalkyl, or two R_6 groups attached to the same nitrogen atom can together form a 5- to 8-membered ring, wherein the number of atoms in the ring includes the nitrogen atom, and in which one of the 5- to 8-membered ring carbon atoms is optionally replaced by O, S, or $N(T_3)$;

each R_7 is independently selected from $-(C_1-C_4)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-OR_9$, $-SR_9$, $-C(halo)_3$, $-CH(halo)_2$, $-CH_2(halo)$, -CN, -halo, $-N_3$, $-NO_2$, $-CH=N(R_9)$, $-N(R_9)_2$, $-N(R_9)OH$, $-N(R_9)S(=O)R_{12}$, $-N(R_9)S(=O)_2R_{12}$, $-N(R_9)C(=O)R_{12}$, $-N(R_9)C(=O)N(T_1)(T_2)$, $-N(R_9)C(=O)OR_{12}$, $-C(=O)R_9$, $-C(=O)N(T_1)(T_2)$, $-C(=O)OR_9$, $-OC(=O)R_9$, $-OC(=O)N(T_1)(T_2)$, $-OC(=O)OR_9$, $-S(=O)R_9$, or $-S(=O)_2R_9$;

each R_8 is independently selected from -(C_1-C_4)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(5- or 6-membered)heteroaryl, -(C_1-C_6)alkylCOOR$_9$, -OR$_9$, -SR$_9$, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -CN, =O, =S, -halo, -N_3, -NO_2, -CH=N(R$_9$), -N(R$_9$)(C_1-C_6)alkylCOOR$_9$, -N(R$_9$)$_2$, -N(R$_9$)OH, -N(R$_9$)S(=O)R$_{12}$, -N(R$_9$)S(=O)$_2$R$_{12}$, -N(R$_9$)C(=O)R$_{12}$, -N(R$_9$)C(=O)N(T_1)(T_2), -N(R$_9$)C(=O)OR$_{12}$, -C(=O)R$_9$, -C(=O)N(T_1)(T_2), -C(=O)OR$_9$, -OC(=O)R$_9$, -OC(=O)N(T_1)(T_2), -OC(=O)OR$_9$, -S(=O)R$_9$, or -S(=O)$_2$R$_9$;

each R$_9$ is independently selected from -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -benzyl, -(3- to 6-membered)heterocycle, -C(halo)$_3$, -CH(halo)$_2$, or -CH_2(halo);

if h is 0, then R_{11} can be selected from -H, -CN, -C(=O)OR$_9$, or -C(=O)N(R$_6$)$_2$ or R_{11} can be -(C_1-C_4)alkyl which is unsubstituted or substituted with -OH, -(C_1-C_4)alkoxy, -N(R$_6$)$_2$, -C(=O)OR$_9$, or -C(=O)N(R$_6$)$_2$;

if h is 1, then R_{11} can be selected from -H, -CN, -OH, -halo, -C(=O)OR$_9$, or -C(=O)N(R$_6$)$_2$ or R_{11} can be -(C_1-C_4)alkyl which is unsubstituted or substituted with -OH, -(C_1-C_4)alkoxy, -N(R$_6$)$_2$, -C(=O)OR$_9$, or -C(=O)N(R$_6$)$_2$;

otherwise, where Z is -(C_1-C_{10})alkyl-NR$_6$C(=Y)-, then R_{11} can be selected from -H, -CN, -C(=O)OR$_9$, or -C(=O)N(R$_6$)$_2$ or R_{11} can be -(C_1-C_4)alkyl which is unsubstituted or substituted with -OH, -(C_1-C_4)alkoxy, -N(R$_6$)$_2$, -C(=O)OR$_9$, or -C(=O)N(R$_6$)$_2$;

each R_{12} is independently selected from -H or -(C_1-C_4)alkyl;

m is an integer selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 11;

e and f are each an integer independently selected from 0, 1, 2, 3, 4, or 5 provided that $2 \leq (e + f) \leq 5$;

j and k are each an integer independently selected from 0, 1, 2, 3, or 4 provided that $1 \leq (j + k) \leq 4$;

each p is an integer independently selected from 0 or 1;

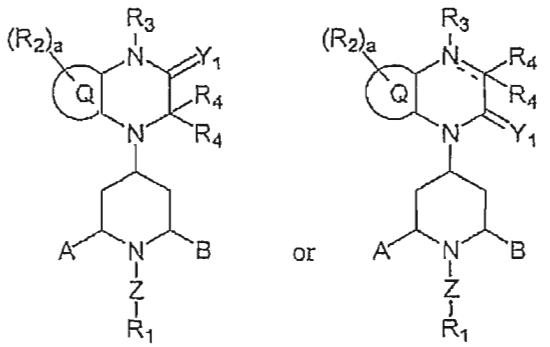
each T_1, T_2, and T_3 is independently -H or -(C_1-C_{10})alkyl which is unsubstituted or substituted with 1, 2 or 3 independently selected R$_8$ groups and, optionally, in which any -(C_1-C_{10})alkyl carbon atom except the carbon atom bonded directly to the atom to which T_1, T_2, or T_3 is attached is independently replaced by O, S, or N(R$_6$), or T_1 and T_2 can together form a 5- to 8-membered ring where the number of atoms in the ring includes the nitrogen atom to which T_1 and T_2 are bonded, said 5- to 8-membered ring is unsubstituted or substituted with 1, 2 or 3 independently selected R$_8$ groups and, optionally, any carbon atom in said 5- to 8-membered ring is independently replaced by O, S, or N(R$_6$);

each V_1 is independently selected from -H, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -phenyl, or -benzyl; and

each halo is independently selected from -F, -Cl, -Br, or -I,

wherein the pharmaceutically acceptable derivative is selected from the group consisting of pharmaceutically acceptable salt, solvate, radiolabeled, stereoisomer, enantiomer, diastereomer, other stereoisomeric form, racemic mixture, geometric isomer, and/or tautomer.

2. A compound according to Formula (I) or (II):



(I) (II)

or a pharmaceutically acceptable derivative thereof wherein:

Y_1 is O or S;

Q is selected from fused benzo or (5- or 6-membered)heteroaryl;

each R_2 is independently selected from:

(a) -halo, -CN, -NO_2, -OT_3, -C(=O)T_3, -C(=O)OT_3, -C(=O)N(T_1)(T_2), -S(=O)$_3$H, -S(=O)T_3, -S(=O)$_2T_3$, -S(=O)$_2$N(T_1)(T_2), -N(T_1)(T_2), -N(T_3)C(=O)T_3, -N(T_3)C(=O)N(T_1)(T_2), -N(T_3)S(=O)$_2T_3$, or -N(T_3)S(=O)$_2$N(T_1)(T_2); or

(b) -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_1-C_6)alkoxy, -(C_3-C_7)cycloalkyl, -(C_6-C_{14})bicycloalkyl, -(C_8-C_{20})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_7-C_{14})bicycloalkenyl, -(C_8-C_{20})tricycloalkenyl, -(5- or 6-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_8 groups; or

(c) -phenyl, -naphthalenyl, -(C_{14})aryl, or -(5- or 6-membered)heteroaryl, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_7 groups;

a is an integer selected from 0, 1 or 2;

the dashed line in the 6-membered, nitrogen-containing ring that is fused to the Q group denotes the presence or absence of a bond, and when that dashed line denotes the presence of a bond then R_3 and one R_4 are absent;

R_3 is selected from:

(a) -H; or

(b) -(C_1-C_4)alkyl which is unsubstituted or substituted with 1, 2 or 3 groups independently selected from -OH, -(C_1-C_4)alkoxy, -$N(R_6)_2$, -C(=O)OR_9, or -C(=O)$N(R_6)_2$; or

(c) -(C_3-C_7)cycloalkyl which is unsubstituted or substituted with 1, 2 or 3 groups independently selected from -OH, -(C_1-C_4)alkyl, -(C_1-C_4)alkoxy, -$N(R_6)_2$, -C(=O)OR_9, or -C(=O)$N(R_6)_2$;

each R_4 is independently selected from:

(a) -H; or

(b) -halo, -CN, or -NO_2; or

(c) -X, -(C_1-C_6)alkyl-X, -(5- or 6-membered)heterocycle-X, or -(5- or 6-membered)heterocycle-(C_1-C_6)alkyl-X; or

(d) -C(=Y)CN, -C(=Y)X, -C(=Y)T_3, -C(=Y)YX, -C(=Y)YT_3, -C(=Y)$N(T_1)(T_2)$, -C(=Y)$N(R_9)$CN, -C(=Y)$N(R_9)$X, -C(=Y)$N(R_9)CH_2CH_2N(T_1)(T_2)$, -C(=Y)$N(R_9)$YH, -C(=Y)$N(R_9)$YX, -C(=Y)$N(R_9)YCH_2$X, -C(=Y)$N(R_9)YCH_2CH_2$X, or -C(=Y)$N(R_9)S(=O)_2T_3$; or

(e) -$N(R_9)$X, -$N(R_9)$-CH_2X, -$N(R_9)$-CH_2CH_2X, -$N(R_9)$-$CH_2CH_2N(R_9)$X, -$N(R_9)CH_2CH_2N(T_1)(T_2)$, -$N(R_9)CH_2$C(=Y)X, -$N((C_1$-$C_6)$alkyl-C(=O)$OR_9)_2$, -$N(R_9)CH_2N(R_9)C(=N(R_{12}))N(R_{12})_2$, -$N(R_9)$-$CH_2CH_2N(R_9)C(=N(R_{12}))N(R_{12})_2$, -$N(T_1)(T_2)$, -$N(T_3)$C(=Y)$T_3$, -$N(T_3)$C(=Y)$YT_3$, -$N(T_3)$C(=Y)$N(T_1)(T_2)$, -$N(T_3)S(=O)_2T_3$, or -$N(T_3)S(=O)_2N(T_1)(T_2)$; or

(f) -YH, -CH_2YH, -CH_2CH_2YH, -YX, or -YT_3; or

(g) -S(=O)T_3, -$S(=O)_2T_3$, -S(=O)$N(T_1)(T_2)$, -$S(=O)_2N(T_1)(T_2)$, -S(=O)X, or -$S(=O)_2$X;

X is:

(a) -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_1-C_6)alkoxy, -(C_3-C_7)cycloalkyl, -(C_6-C_{14})bicycloalkyl, -(C_8-C_{20})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_7-C_{14})bicycloalkenyl, -(C_8-C_{20})tricycloalkenyl, -(5- or 6-membered)heterocycle, or -(7- to 10-

membered)bicycloheterocycle, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_8 groups; or

(b) -phenyl, -benzyl, -naphthalenyl, -(C_{14})aryl, -(C_1-C_6)alkyl-(5- or 6-membered)heteroaryl or -(5- or 6-membered)heteroaryl, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_7 groups;

each Y is independently selected from O or S;

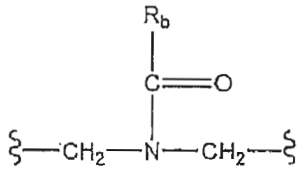
A and B are independently selected from:

(a) -H, -CN, -C(=O)OT_3, or -C(=O)N$(T)_1(T_2)$; or

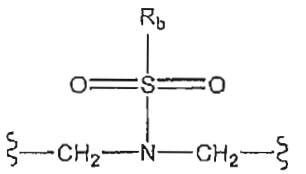
(b) -(C_3-C_{12})cycloalkyl, -(C_3-C_{12})cycloalkoxy, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, or -(C_1-C_6)alkoxy, each of which is unsubstituted or substituted with 1 or 2 substituents independently selected from -OH, -S(=O)$_2NH_2$, -N$(R_6)_2$, =NR_6, -C(=O)OT_3, -CON$(R_6)_2$, -N(R_6)C(=O)R_9, and -(5- or 6-membered)heterocycle, or 1, 2 or 3 independently selected -halo; or

(c) A-B can together form a (C_2-C_6)bridge, which is unsubstituted or substituted with 1, 2, 3, 4, 5, 6, 7 or 8 substituents independently selected from -OH, -(C_1-C_4)alkyl, -halo, and -C(halo)$_3$, and which bridge optionally contains -HC=CH- or -O- within the (C_2-C_6)bridge; wherein the 6-membered, nitrogen-containing ring that is fused to the Q group can be in the *endo*- or *exo*- configuration with respect to the A-B bridge; or

(d) A-B can together form a -CH_2-N(R_a)-CH_2- bridge, a



bridge, or a



bridge;

wherein the 6-membered, nitrogen-containing ring that is fused to the Q group can be in the *endo*- or *exo*- configuration with respect to the A-B bridge;

R_a is selected from -H, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -CH_2-C(=O)-R_c, -(CH_2)-C(=O)-OR_c, -(CH_2)-C(=O)-N$(R_c)_2$, -$(CH_2)_2$-O-R_c, -$(CH_2)_2$-S(=O)$_2$-N$(R_c)_2$, R_c, or -$(CH_2)_2$-N(R_c)S(=O)$_2$-R_c;

R_b is selected from:

(a) -H, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(3- to 7-membered)heterocycle, -N$(R_c)_2$, -N(R_c)-(C_3-C_7)cycloalkyl, or -N(R_c)-(3- to 7-membered)heterocycle; or

(b) -phenyl, -naphthalenyl, or-(5- or 6-membered)heteroaryl, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_7 groups; or

(c) $-N(R_c)$-phenyl, $-N(R_c)$-naphthalenyl, $-N(R_c)$-(C_{14})aryl, or $-N(R_c)$-(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_7 groups;

each R_c is independently selected from -H or $-(C_1-C_4)$alkyl;

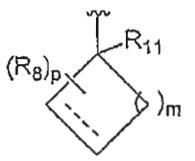
Z is $-[(C_1-C_{10})$alkyl optionally substituted by $R_1]_h-$, wherein h is 0 or 1; $-[(C_2-C_{10})$alkenyl optionally substituted by $R_1]$; or $-(C_1-C_{10})$alkyl-$NR_6C(=Y)-$;

each R_1 is independently selected from:

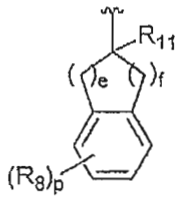
(a) -halo, -CN, -OH, $-CH_2OH$, $-CH_2CH_2OH$, $-NO_2$, $-N(R_6)_2$, $-S(=O)NH_2$, $-S(=O)_2NH_2$, $-C(=O)OV_1$, or $-C(=O)CN$; or

(b) $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-O(C_1-C_6)$alkyl, $-(C_3-C_7)$cycloalkoxy, $-(C_6-C_{14})$bicycloalkyl, $-(C_8-C_{20})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_7-C_{14})$bicycloalkenyl, $-(C_8-C_{20})$tricycloalkenyl, -(3- to 7-membered)heterocycle, -(7- to 10-membered)bicycloheterocycle wherein the –(7-to 10-membered)bicycloheterocycle is selected from –quinolinyl, -isoquinolinyl, -chromonyl, -coumarinyl, -indolyl, -indolizinyl, -benzo[b]furanyl, - benzo[b]thiophenyl, -indazolyl, -purinyl, -4H-quinolizinyl, -isoquinolyl, -quinolyl, -phthalazinyl, -napthyridinyl, -carbazolyl, -β-carbolinyl, -indolinyl, -isoindolinyl, -1, 2, 3, 4-tetrahyroquinolinyl, -1, 2, 3, 4-tetrahydroisoquinolinyl, and pyrrolopyrrolyl, each of which is unsubstituted or substituted with 1, 2, or 3 independently selected R_8 groups; or

(c)

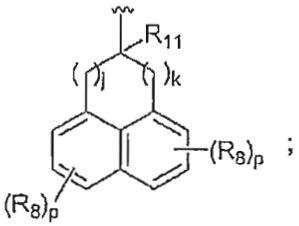


(i)



(ii)

, or



(iii)

; or

(d) -phenyl, -naphthalenyl, $-(C_{14})$aryl, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with an R_7 group; or

-Z-R_1 is 3,3-diphenylpropyl- optionally substituted at the 3 carbon of the propyl with -CN, $-C(=O)N(R_6)_2$, $-C(=O)OV_1$, or -tetrazolyl; or

-Z-R_1 is $-(C_1-C_4)$alkyl substituted with tetrazolyl;

each R_6 is independently selected from -H, -(C_1-C_6)alkyl, or -(C_3-C_7)cycloalkyl, or two R_6 groups attached to the same nitrogen atom can together form a 5- to 8-membered ring, wherein the number of atoms in the ring includes the nitrogen atom, and in which one of the 5- to 8-membered ring carbon atoms is optionally replaced by O, S, or N(T_3);

each R_7 is independently selected from -(C_1-C_4)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -OR_9, -SR_9, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -CN, -halo, -N_3, -NO_2, -CH=N(R_9), -N(R_9)$_2$, -N(R_9)OH, -N(R_9)S(=O)R_{12}, -N(R_9)S(=O)$_2R_{12}$, -N(R_9)C(=O)R_{12}, -N(R_9)C(=O)N(T_1)(T_2), -N(R_9)C(=O)OR_{12}, -C(=O)R_9, -C(=O)N(T_1)(T_2), -C(=O)OR_9, -OC(=O)R_9, -OC(=O)N(T_1)(T_2), -OC(=O)OR_9, -S(=O)R_9, or -S(=O)$_2R_9$;

each R_8 is independently selected from -(C_1-C_4)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(5- or 6-membered)heteroaryl, -phenyl, -(C_1-C_6)alkylCOOR_9, -OR_9, -SR_9, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -CN, =O, =S, -halo, -N_3, -NO_2, -CH=N(R_9), -N(R_9)(C_1-C_6)alkylCOOR_9, -N(R_9)$_2$, -N(R_9)OH, -N(R_9)S(=O)R_{12}, -N(R_9)S(=O)$_2R_{12}$, -N(R_9)C(=O)R_{12}, -N(R_9)C(=O)N(T_1)(T_2), -N(R_9)C(=O)OR_{12}, -C(=O)R_9, -C(=O)-C(=O)OR_9, -C(=O)N(T_1)(T_2), -C(=O)OR_9, -OC(=O)R_9, -OC(=O)N(T_1)(T_2), -OC(=O)OR_9, -S(=O)R_9, or -S(=O)$_2R_9$;

each R_9 is independently selected from -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -benzyl, -(3- to 6-membered)heterocycle, -C(halo)$_3$, -CH(halo)$_2$, or -CH_2(halo);

if h is 0, then R_{11} can be selected from -H, -CN, -C(=O)OR_9, or -C(=O)N(R_6)$_2$ or R_{11} can be -(C_1-C_4)alkyl which is unsubstituted or substituted with -OH, -(C_1-C_4)alkoxy, -N(R_6)$_2$, -C(=O)OR_9, or -C(=O)N(R_6)$_2$;

if h is 1, then R_{11} can be selected from -H, -CN, -OH, -halo, -C(=O)OR_9, or -C(=O)N(R_6)$_2$ or R_{11} can be -(C_1-C_4)alkyl which is unsubstituted or substituted with -OH, -(C_1-C_4)alkoxy, -N(R_6)$_2$, -C(=O)OR_9, or -C(=O)N(R_6)$_2$;

otherwise, where Z is -(C_1-C_{10})alkyl-NR_6C(=Y)-, then R_{11} can be selected from -H, -CN, -C(=O)OR_9, or -C(=O)N(R_6)$_2$ or R_{11} can be -(C_1-C_4)alkyl which is unsubstituted or substituted with -OH, -(C_1-C_4)alkoxy, -N(R_6)$_2$, -C(=O)OR_9, or -C(=O)N(R_6)$_2$;

each R_{12} is independently selected from -H or -(C_1-C_4)alkyl;

m is an integer selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 11;

e and f are each an integer independently selected from 0, 1, 2, 3, 4, or 5 provided that $2 \leq (e + f) \leq 5$;

j and k are each an integer independently selected from 0, 1, 2, 3, or 4 provided that $1 \leq (j + k) \leq 4$;

each p is an integer independently selected from 0, 1, 2, 3 or 4;

each T_1, T_2, and T_3 is independently -H or -(C_1-C_{10})alkyl which is unsubstituted or substituted with 1, 2 or 3 independently selected R_8 groups and, optionally, in which any -(C_1-C_{10})alkyl carbon atom except the carbon atom bonded directly to the atom to which T_1, T_2, or T_3 is attached is independently replaced by O, S, or N(R_6), or T_1 and T_2 can together form a 5- to 8-membered ring where the number of atoms in the ring includes the nitrogen atom to which T_1 and T_2 are bonded, said 5- to 8-membered ring is unsubstituted or substituted with 1, 2 or 3 independently selected R_8 groups and, optionally, any carbon atom in said 5- to 8-membered ring is independently replaced by O, S, or N(R_6);

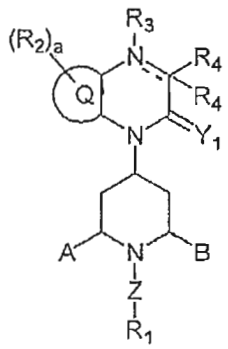
each V_1 is independently selected from -H, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -phenyl, or -benzyl; and

each halo is independently selected from -F, -Cl, -Br, or -I;

with the proviso that if Z is -[(C_1-C_{10})alkyl optionally substituted by R_1]$_h$ and h=0 then R_4 is not COOH,

wherein the pharmaceutically acceptable derivative is selected from the group consisting of pharmaceutically acceptable salt, solvate, radiolabeled, stereoisomer, enantiomer, diastereomer, other stereoisomeric form, racemic mixture, geometric isomer, and/or tautomer.

3. The compound according to any one of claims 1 or 2, wherein the compound is a compound of formula (II):



(II)

or a pharmaceutically acceptable derivative thereof.

4. The compound according to any one of claims 1 to 3, wherein Y_1 is O.

5. The compound according to any one of claims 1 to 4, wherein the dashed line is present, one R_4 is present, and preferably R_3 is absent.

6. The compound according to any one of claims 1 to 5, wherein Q is selected from benzo, pyridino, pyrimidino, pyrazino, and pyridazino, and preferably Q is selected from benzo and pyridino, wherein preferably the 2- and 3-positions of the pyridino are fused to the 6-membered, nitrogen-containing ring and more preferably Q is benzo.

7. The compound according to any one of claims 1 to 6, wherein a is 0.

8. The compound according to any one of claims 1 to 7, wherein each R_4 is independently selected from:

(a) -C(=Y)YX, wherein preferably each Y is O and preferably X is -H or -(C_1-C_6)alkyl; or

(b) -N(R_9)X, wherein preferably X is -(C_1-C_6)alkyl substituted with one R_8 group, -(5- or 6-membered)heterocycle substituted with one R_8 group, -phenyl substituted with one R_7 group, or -(5- or 6-membered)heteroaryl substituted with one R_7 group.

9. The compound according to claim 8, wherein each R_7 or R_8 is -C(=O)OR_9, wherein preferably each R_9 is -H.

10. The compound according to claim 8, wherein R_4 is -C(=O)OX and preferably R_4 is -C(=O)OH.

11. The compound according to claim 8, wherein R_4 is -N(H)X, wherein X is a -(5- or 6-membered)heterocycle substituted with one R_8 group, wherein R_8 is -C(=O)OR_9 and preferably R_8 is -C(=O)OH and preferably R_8 is attached to X at a ring position either ortho to or meta to the point of attachment of X to the N of -N(H)X.

12. The compound according to claim 8, wherein R_4 is -N(H)X, wherein X is -(C_1-C_6)alkyl substituted with one R_8 group, wherein R_8 is -C(=O)OR_9 and preferably R_8 is -C(=O)OH.

13. The compound according to any one of claims 1 to 7, wherein at least one R_4 is -(5- or 6-membered)heterocycle-X, wherein X is phenyl or -(5- or 6-membered)heteroaryl each of which is substituted with one R_7 group, wherein preferably R_7 is -C(=O)OR_9, wherein preferably R_9 is –H and more preferably R_7 is -C(=O)OR_9 and even more preferably R_7 is attached to X at a ring position either ortho to or meta to the point of attachment of X to the -(5- or 6-membered)heterocycle of -(5- or 6-membered)heterocycle-X.

14. The compound according to any one of claims 1 to 7, wherein at least one R_4 is -(5- or 6-membered)heterocycle-(C_1-C_6)alkyl-X, wherein X is phenyl or -(5- or 6-membered)heteroaryl each of which is substituted with one R_7 group, wherein preferably R_7 is -C(=O)OR_9, wherein preferably R_9 is –H and more preferably the -C(=O)OR_9 group is

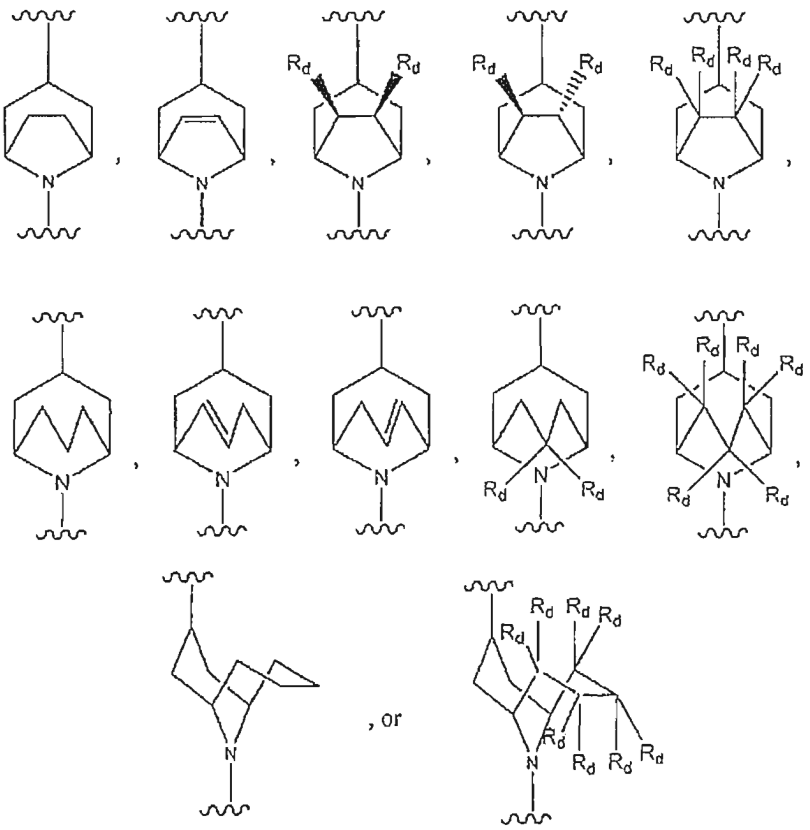
attached to the phenyl or -(5- or 6-membered)heteroaryl at a ring position either ortho to or meta to the point of attachment of the phenyl or -(5- or 6-membered)heteroaryl to the (C_1-C_6)alkyl of the -(5- or 6-membered)heterocycle-(C_1-C_6)alkyl-X.

15. The compound according to any one of claims 1 to 7, wherein each R_4 is independently selected from X, wherein at least one X is -(5- or 6-membered)heterocycle or -(5- or 6-membered)heteroaryl, each of which is optionally substituted with -C(=O)OR_9 wherein preferably R_9 is –H, and more preferably the -C(=O)OR_9 group is attached to the -(5- or 6-membered)heterocycle or -(5- or 6-membered)heteroaryl at a ring position either ortho to or meta to the point of attachment of the -(5- or 6-membered)heterocycle or -(5- or 6-membered)heteroaryl to the 6-membered, nitrogen-containing ring that is fused to the Q group.

16. The compound according to claim 15, wherein at least one X is -tetrazolyl.

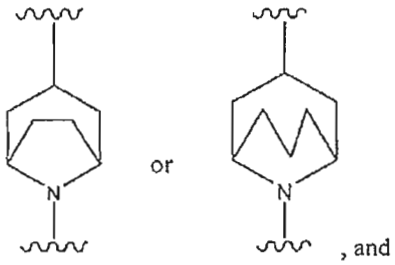
17. The compound according to any one of claims 1 to 16, wherein A and B are independently selected from -H or -(C_1-C_6)alkyl and preferably A and B are each -H.

18. The compound according to any one of claims 1 to 16, wherein A and B together form a bridge such that the bridged-piperidine is selected from the group consisting of:



wherein each R_d is independently selected from -H, -(C_1-C_4)alkyl, -halo, or -C(halo)$_3$.

19. The compound according to any one of claims 1-16 and 18, wherein A and B together form a bridge such that the bridged-piperidine is selected from the group consisting of:

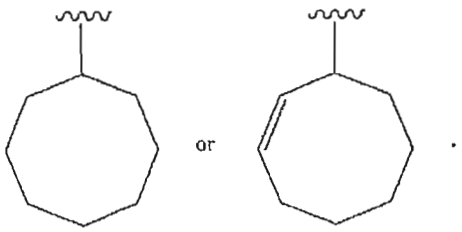


, and

wherein preferably the 6-membered, nitrogen-containing ring that is fused to the Q group is in the *endo* configuration with respect to the A-B bridge of the bridged-piperidine.

20. The compound according to any one of claims 1 to 19, wherein h is 0 and R_1 is -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{14})cycloalkyl, -(C_3-C_{14})cycloalkenyl, -(C_6-C_{14})bicycloalkyl, -(C_7-C_{14})bicycloalkenyl, or -(C_8-C_{20})tricycloalkyl, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_8 groups and preferably R_1 is -(C_3-C_{14})cycloalkyl, -(C_3-C_{14})cycloalkenyl, -(C_6-C_{14})bicycloalkyl, -(C_7-C_{14})bicycloalkenyl, or -(C_8-C_{20})tricycloalkyl, each of which is unsubstituted or substituted with 1, 2, or 3 independently selected R_8 groups.

21. The compound according to any one of claims 1 to 20, wherein h is 0 and R_1 is selected from the group consisting of:



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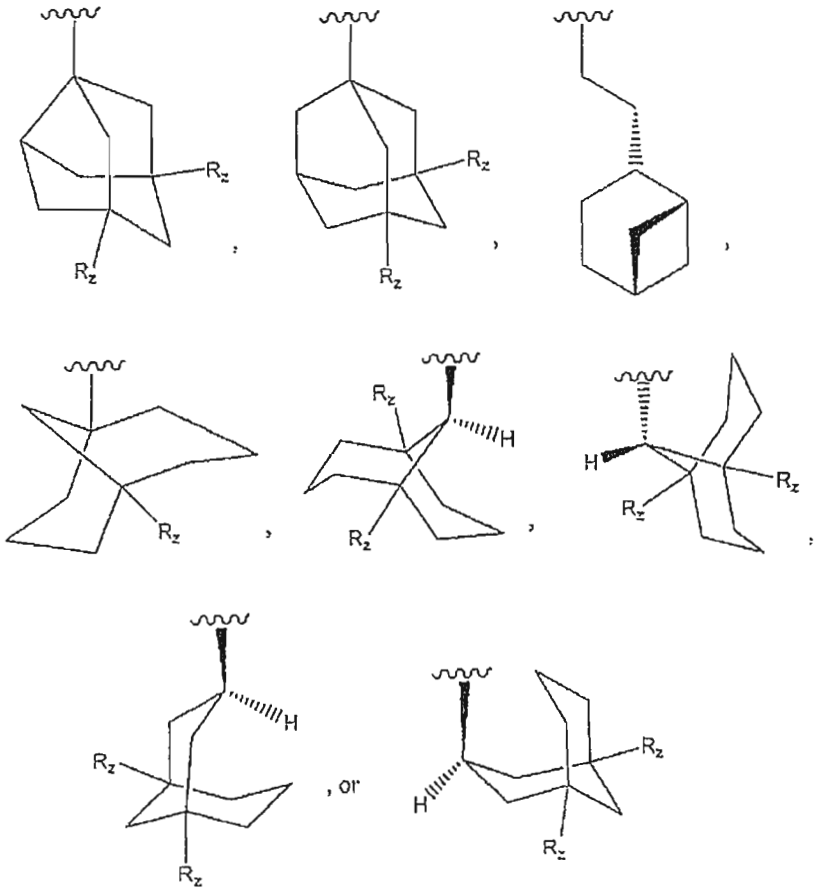
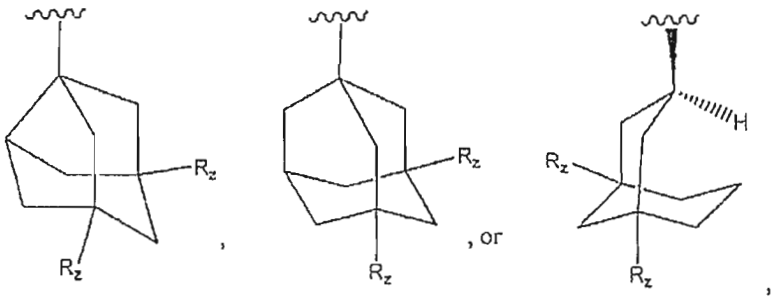
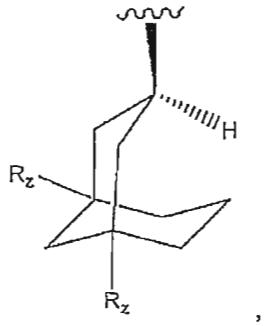
22. The compound according to any one of claims 1 to 20, wherein h is 0 and R_1 is selected from the group consisting of:



wherein each R_z is independently selected from -H, -(C_1-C_4)alkyl, -OH, and -CN and preferably each R_7 is independently selected from –H and –CH_3 and wherein more preferably h is 0 and R_1 is selected from the group consisting of:



wherein each R_z is independently selected from -H, -(C_1-C_4)alkyl, -OH, and -CN and preferably each R_z is independently selected from -H and -CH_3, and even more preferably h is 0 and R_1 is:



,

wherein each R_z is -H.

23. The compound according to any one of claims 1 to 6, wherein a is 1 and R_2 is -halo, preferably R_2 is -F.

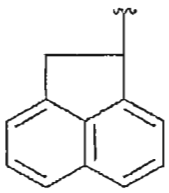
24. The compound according to any one of claims 1 to 20, 22 and 23, wherein the R_1-group is in the *exo*-configuration with respect to the A-B bridge of the bridged piperidine.

25. The compound as in any one of claims 1 to 19, wherein -Z-R_1 is selected from:

(a) (C_6-C_{12})cycloalkyl, wherein preferably -Z-R_1 is cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, or cyclododecyl; or

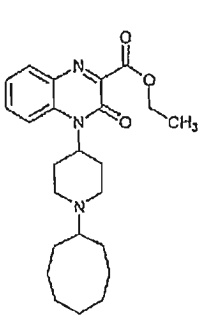
(b) (C_5-C_{12})cycloalkenyl, wherein preferably -Z-R_1 is cyclohexenyl, cycloheptenyl, or cyclooctenyl; or

(c)


; or

(d) (C_6-C_{12})cycloalkyl optionally substituted by one -(C_1-C_4)alkyl.

26. The compound as in any one of claims 1 or 2, wherein the compound is selected from the group consisting of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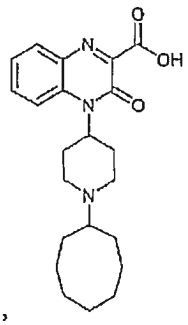
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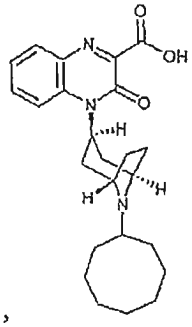
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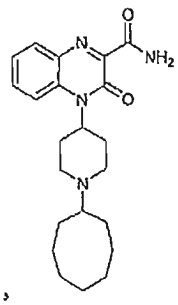
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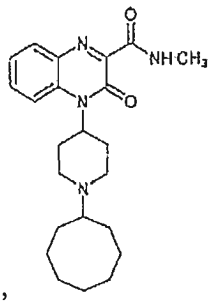
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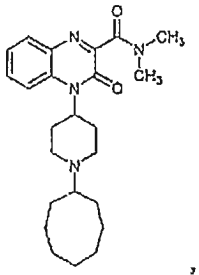
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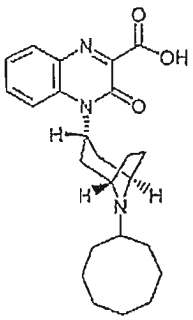
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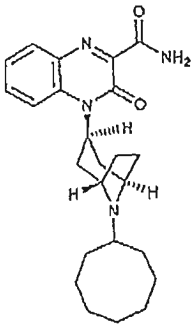
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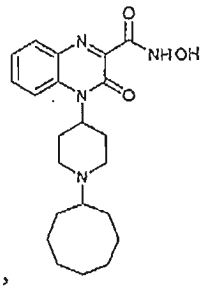
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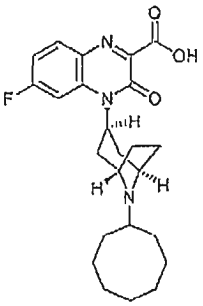
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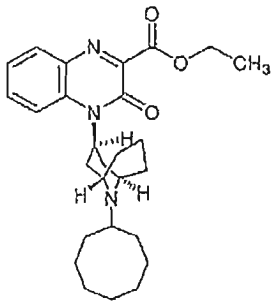
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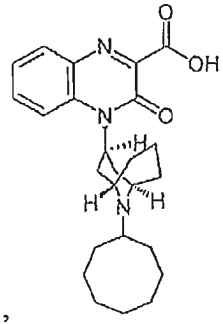
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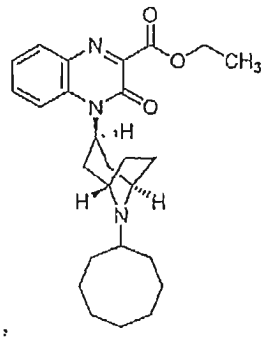
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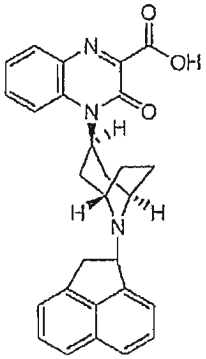
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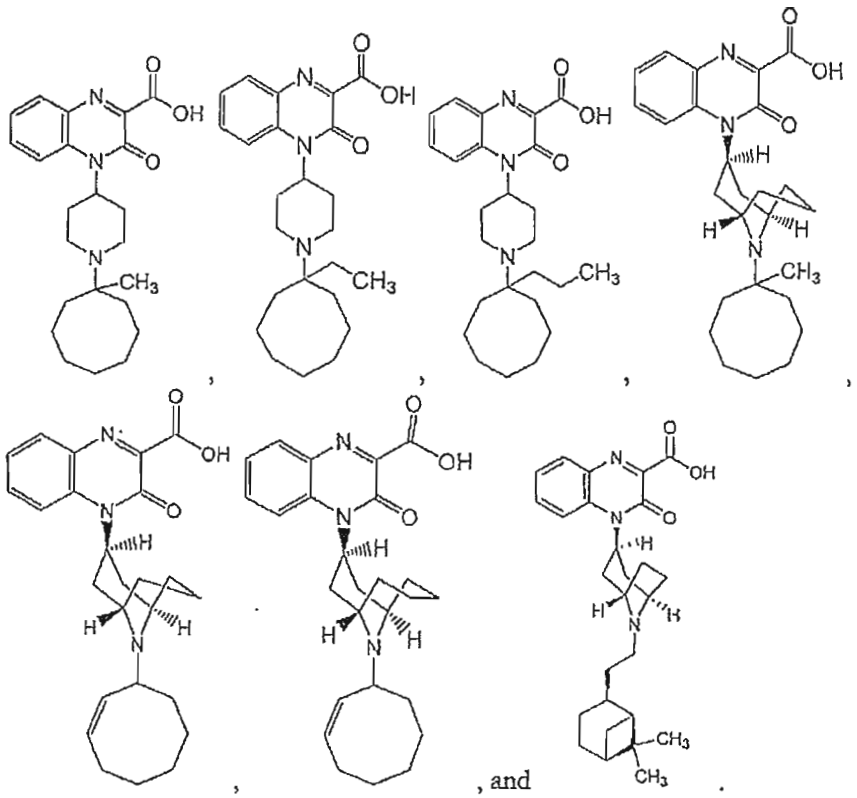


, and .

27. The compound as in any one of claims 1 to 26, wherein the pharmaceutically acceptable derivative is a pharmaceutically acceptable salt.

28. The compound as in any one of the claims 1 to 27 wherein the pharmaceutically acceptable derivative is a HCl-salt, a sodium salt or a potassium salt.

29. A composition comprising an effective amount of the compound or a pharmaceutically acceptable derivative of the compound as in any one of claims 1 to 28 and a pharmaceutically acceptable carrier or excipient.

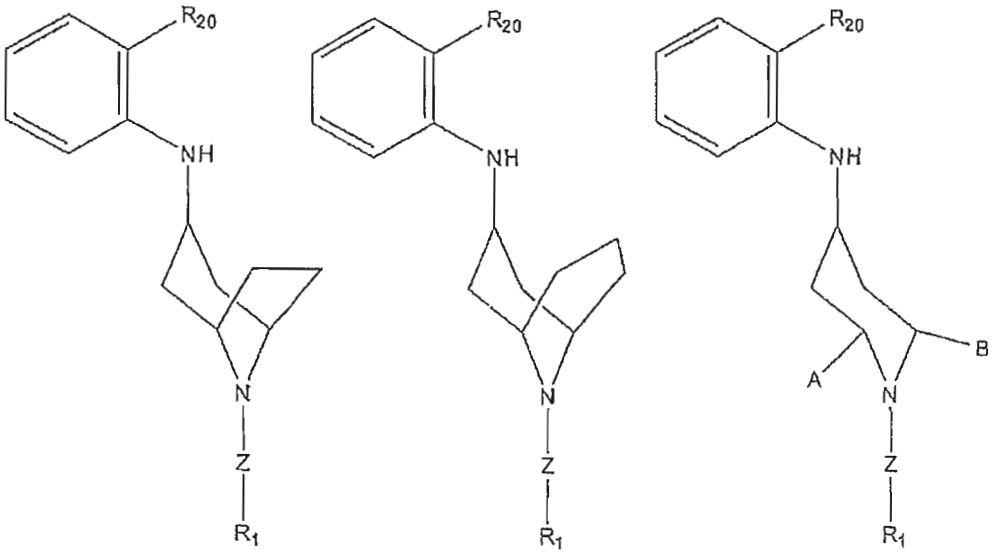
30. A method for modulating ORL-1 receptor function in a cell, comprising contacting a cell capable of expressing the ORL-1 receptor with an effective amount of the compound or a pharmaceutically acceptable derivative of the compound as in any one of claims 1 to 28.

31. The method of claim 30, wherein the compound or the pharmaceutically acceptable derivative of the compound acts as an agonist at the ORL-1 receptor, a partial agonist at the ORL-1 receptor or as an antagonist at the ORL-1 receptor.

32. A kit comprising a container containing an effective amount of the compound or a pharmaceutically acceptable derivative of the compound as in any one of claims 1 to 28.

33. A method for preparing a composition, comprising the step of admixing a compound or a pharmaceutically acceptable derivative of the compound as in any one of claims 1 to 28 and a pharmaceutically acceptable carrier or excipient.

34. A compound according to Formula (III), (IV), or (V):



(III) (IV) (V)

or a pharmaceutically acceptable derivative thereof wherein:

the C_2 or C_3-bridge of the bridged piperidine ring of compounds of Formula (III) and (IV) may be unsubstituted or substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from -OH, -(C_1-C_4)alkyl, -halo, and -C(halo)$_3$,

A and B of Formula (V) are independently selected from:

(a) -H, -CN, -C(=O)OT_3, or -C(=O)N(T_1)(T_2); or

(b) -(C_3-C_{12})cycloalkyl, -(C_3-C_{12})cycloalkoxy, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, or -(C_1-C_6)alkoxy, each of which is unsubstituted or substituted with 1 or 2 substituents independently selected from -OH, -S(=O)$_2$NH_2, -N(R_6)$_2$, =NR_6, -C(=O)OT_3, -CON(R_6)$_2$, -N(R_6)C(=O)R_9, and -(5- or 6-membered)heterocycle, or 1, 2 or 3 independently selected -halo;

each Y is independently selected from O or S,

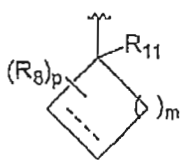
Z is -[(C_1-C_{10})alkyl optionally substituted by R_1]$_n$-, and wherein the (C_1-C_{10})alkyl is selected from the group consisting of -ethyl, -n-propyl, -n-butyl, -n-pentyl, -n-hexyl, -n-heptyl, -n-octyl, -n-nonyl, and -n-decyl, -*iso*-propyl, -*sec*-butyl, -*iso*-butyl, -*tert*-butyl, -*iso*-pentyl, -

neopentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-ethylbutyl, 2-ethylbutyl, 3-ethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,2-dimethylhexyl, 1,3-dimethylhexyl, 3,3-dimethylhexyl, 1,2-dimethylheptyl, 1,3-dimethylheptyl, and 3,3-dimethylheptyl wherein h is 0 or 1; or-[(C_1-C_{10})alkenyl optionally substituted by R_1] or -(C_1-C_{10})alkyl-$NR_6C(=Y)$-;

R_1 is selected from

(a) -(C_1-C_{10})alkyl, wherein the (C_1-C_{10})alkyl is selected from the group consisting of -ethyl, -n-propyl, -n-butyl, -n-pentyl, -n-hexyl, -n-heptyl, -n-octyl, -n-nonyl, and -n-decyl, -*iso*-propyl, -*sec*-butyl, -*iso*-butyl, -*tert*-butyl, -*iso*-pentyl, -neopentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-ethylbutyl, 2-ethylbutyl, 3-ethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,2-dimethylhexyl, 1,3-dimethylhexyl, 3,3-dimethylhexyl, 1,2-dimethylheptyl, 1,3-dimethylheptyl, and 3,3-dimethylheptyl -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -O(C_1-C_6)alkyl, -(C_3-C_7)cycloalkoxy, -(C_6-C_{14})bicycloalkyl, -(C_8-C_{20})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_7-C_{14})bicycloalkenyl, -(C_8-C_{20})tricycloalkenyl, -(3- to 7-membered)heterocycle, -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_8 groups; or

(b)



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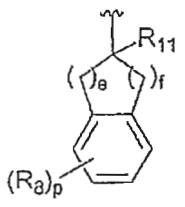
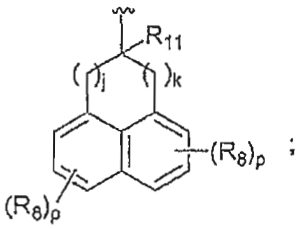


, or


;

(i) (ii) (iii) ; or

-Z-R_1 is 3,3-diphenylpropyl- optionally substituted at the 3 carbon of the propyl with -CN, -C(=O)$N(R_6)_2$, -C(=O)OV_1, or -tetrazolyl; or

-Z-R_1 is -(C_1-C_4)alkyl substituted with tetrazolyl;

each R_6 is independently selected from -H, -(C_1-C_6)alkyl, or -(C_3-C_7)cycloalkyl, or two R_6 groups attached to the same nitrogen atom can together form a 5- to 8-membered ring, wherein the number of atoms in the ring includes the nitrogen atom, and in which one of the 5- to 8-membered ring carbon atoms is optionally replaced by O, S, or N(T_3);

each R_8 is independently selected from -(C_1-C_4)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(5- or 6-membered)heteroaryl, -phenyl, -(C_1-C_6)alkylCOOR$_9$, -OR$_9$, -SR$_9$, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -CN, =O, =S, -halo, -N_3, -NO_2, -CH=N(R$_9$), -N(R$_9$)(C_1-C_6)alkylCOOR$_9$, -C(=O)-C(=O)OR$_9$, -N(R$_9$)$_2$, -N(R$_9$)OH, -N(R$_9$)S(=O)R$_{12}$, -N(R$_9$)S(=O)$_2$R$_{12}$, -N(R$_9$)C(=O)R$_{12}$, -N(R$_9$)C(=O)N(T_1)(T_2), -N(R$_9$)C(=O)OR$_{12}$, -N((C_1-C_6)alkyl-C(=O)OR$_9$)$_2$, -C(=O)R$_9$, -C(=O)-C(=O)OR$_9$, -C(=O)N(T_1)(T_2), -C(=O)OR$_9$, -OC(=O)R$_9$, -OC(=O)N(T_1)(T_2), -OC(=O)OR$_9$, -S(=O)R$_9$, or -S(=O)$_2$R$_9$;

each R_9 is independently selected from -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -benzyl, -(3- to 6-membered)heterocycle, -C(halo)$_3$, -CH(halo)$_2$, or -CH_2(halo);

if h is 0, then R_{11} can be selected from -H, -CN, -C(=O)OR$_9$, or -C(=O)N(R$_6$)$_2$ or R_{11} can be -(C_1-C_4)alkyl wherein the (C_1-C_4)alkyl is selected from the group consisting of -ethyl, -n-propyl, and -n-butyl, -*iso*-propyl, -*sec*-butyl, -*iso*-butyl, and -*tert*-butyl which is unsubstituted or substituted with -OH, -(C_1-C_4)alkoxy, -N(R$_6$)$_2$, -C(=O)OR$_9$, or -C(=O)N(R$_6$)$_2$;

if h is 1, then R_{11} can be selected from -H, -CN, -OH, -halo, -C(=O)OR$_9$, or -C(=O)N(R$_6$)$_2$ or R_{11} can be -(C_1-C_4)alkyl which is unsubstituted or substituted with -OH, -(C_1-C_4)alkoxy, -N(R$_6$)$_2$, -C(=O)OR$_9$, or -C(=O)N(R$_6$)$_2$;

otherwise, where Z is -(C_1-C_{10})alkyl-NR$_6$C(=Y)-, then R_{11} can be selected from -H, -CN, -C(=O)OR$_9$, or -C(=O)N(R$_6$)$_2$ or R_{11} can be -(C_1-C_4)alkyl which is unsubstituted or substituted with -OH, -(C_1-C_4)alkoxy, -N(R$_6$)$_2$, -C(=O)OR$_9$, or -C(=O)N(R$_6$)$_2$;

each R_{12} is independently selected from -H or -(C_1-C_4)alkyl;

R_{20} is selected from NO_2 or NH_2,

m is an integer selected from 0, 1, 2, 3, 4, 6, 7, 8, 9, 10, or 11;

e and f are each an integer independently selected from 0, 1, 2, 3, 4, or 5 provided that $2 \leq (e + f) \leq 5$;

j and k are each an integer independently selected from 0, 1, 2, 3, or 4 provided that $1 \leq (j + k) \leq 4$;

each p is an integer independently selected from 0, 1, 2, 3 or 4;

each T_1, T_2, and T_3 is independently -H or -(C_1-C_{10})alkyl which is unsubstituted or substituted with 1, 2 or 3 independently selected R_8 groups and, optionally, in which any -(C_1-C_{10})alkyl carbon atom except the carbon atom bonded directly to the atom to which T_1, T_2, or T_3 is attached is independently replaced by O, S, or N(R_6), or T_1 and T_2 can together form a 5- to 8-membered ring where the number of atoms in the ring includes the nitrogen atom to which T_1 and T_2 are bonded, said 5- to 8-membered ring is unsubstituted or substituted with 1, 2 or 3 independently selected R_8 groups and, optionally, any carbon atom in said 5- to 8-membered ring is independently replaced by O, S, or N(R_6);

each V_1 is independently selected from -H, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -phenyl, or -benzyl; and

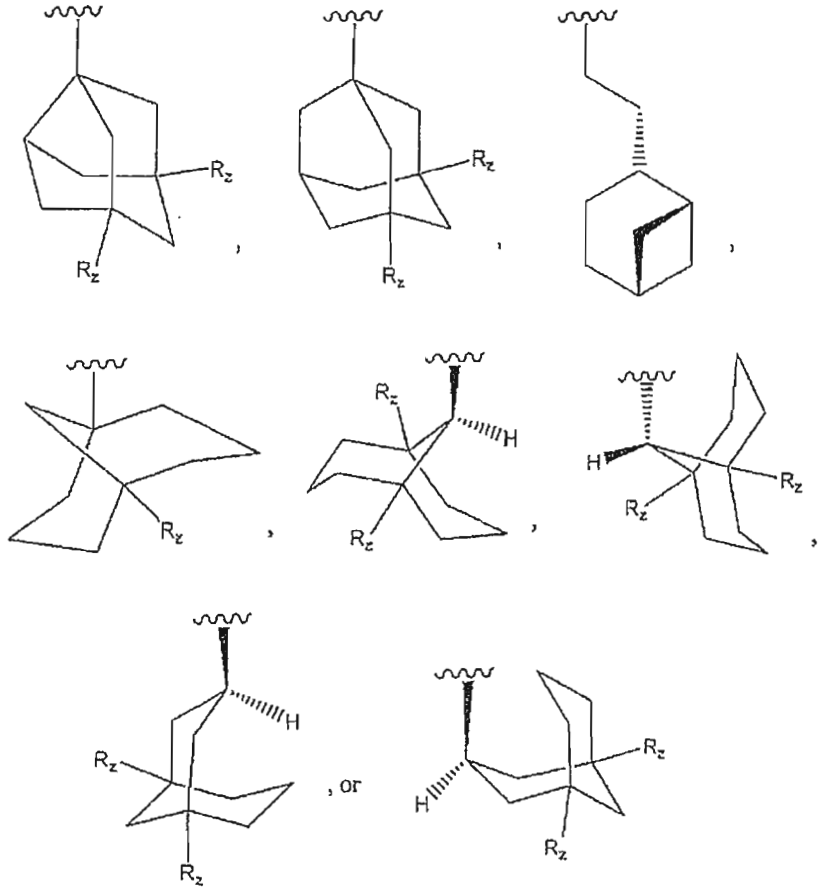
each halo is independently selected from -F, -Cl, -Br, or I, and

wherein the pharmaceutically acceptable derivative is selected from the group consisting of pharmaceutically acceptable salt, solvate, radiolabeled, stereoisomer, enantiomer, diastereomer, other stereoisomeric form, racemic mixture, geometric isomer, and/or tautomer, and

wherein the compound is not (R)-N-[1-(5-fluoro-acenapthen-1-yl)-piperidin-4-yl]-benzene-1,2-diamine.

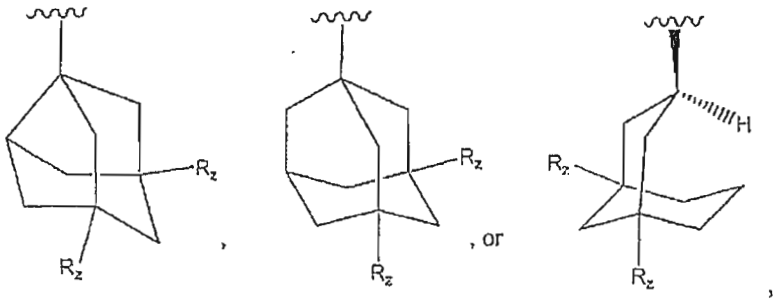
35. The compound according to claim 34, wherein h is 0 and R_1 is -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{14})cycloalkyl, -(C_3-C_{14})cycloalkenyl, -(C_6-C_{14})bicycloalkyl, -(C_7-C_{14})bicycloalkenyl, or -(C_8-C_{20})tricycloalkyl, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_8 groups and preferably R_1 is -(C_3-C_{14})cycloalkyl, -(C_3-C_{14})cycloalkenyl, -(C_6-C_{14})bicycloalkyl, -(C_7-C_{14})bicycloalkenyl, or -(C_8-C_{20})tricycloalkyl, each of which is unsubstituted or substituted with 1, 2 or 3 independently selected R_8 groups.

36. The compound according to any one of claims 34 and 35, wherein h is 0 and R_1 is selected from the group consisting of:

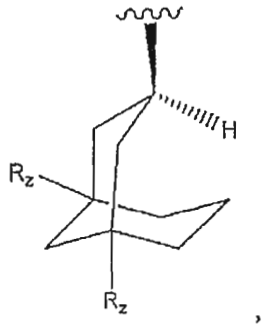


wherein each R_z is independently selected from -H, -(C_1-C_4)alkyl, -OH, and -CN and preferably each R_z is independently selected from -H and -CH_3 and preferably

h is 0 and R_1 is selected from the group consisting of:



wherein each R_z is independently selected from -H, -(C_1-C_4)alkyl, -OH, and -CN and preferably each R_z is independently selected from -H and -CH_3 and more preferably h is 0 and R_1 is:



wherein each R_z is -H.

37. The compound as in any one of claims 34 or 35, wherein -Z-R_1 is selected from:

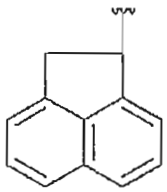
(a) cyclononyl, cyclodecyl, cycloundecyl, or cyclododecyl;

or

(b) cyclohexenyl or cycloheptenyl

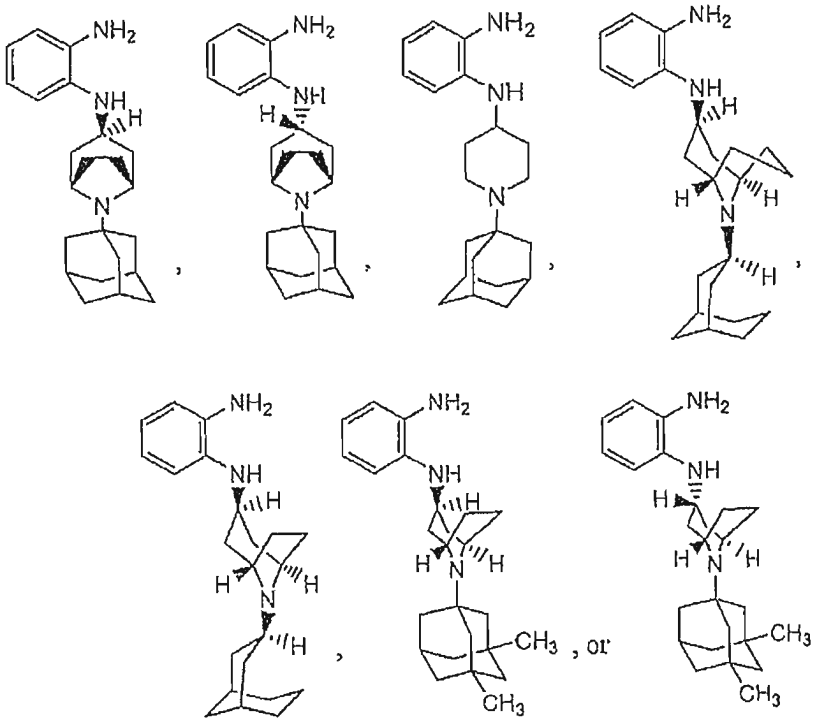
or

(c)


; or

(d) cycloundecyl.

38. The compound according to claim 36, wherein the compound is selected from



, or

39. Use of a compound or a pharmaceutically acceptable derivative thereof of any one of claims 1 to 28 in the production of a medicament for modulating ORL-1 receptor function in a cell, comprising contacting a cell capable for expressing ORL-1 receptor with an effective amount of the compound or a pharmaceutically acceptable derivative of the compound as in any one of claims 1 to 28.

40. The use of claim 39, wherein the compound or the pharmaceutically acceptable derivative of the compound acts as an agonist at the ORL-1 receptor, a partial agonist at the ORL-1 receptor or as an antagonist at the ORL-1 receptor.

41. Use of a compound or a pharmaceutically acceptable derivative thereof of any one of claims 1 to 28 in the production of a medicament for treating pain, a memory disorder, obesity, constipation, depression, dementia, Parkinsonism, anxiety, cough, diarrhea, high blood pressure, epilepsy, anorexia/cachexia, urinary incontinence, or drug abuse in an animal, comprising administering to an animal in need thereof an effective amount of the compound or a pharmaceutically acceptable derivative of the compound as in any one of claims 1 to 28.