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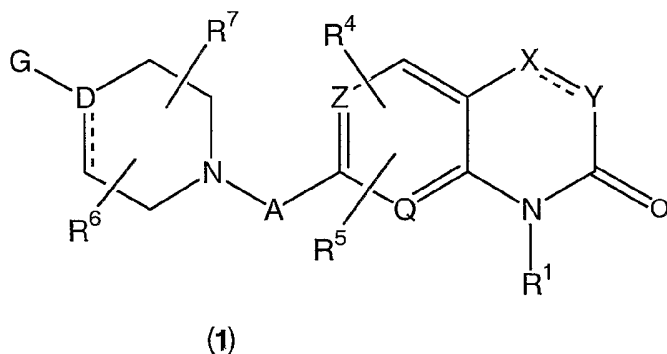
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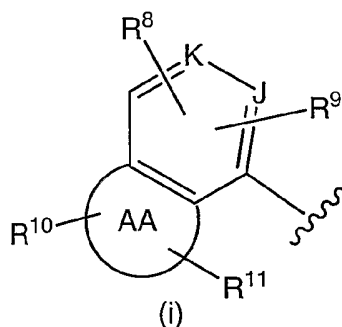
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(54) Title: ISOQUINOLINE [1,8]NAPHTHYRIDIN-2-ONES AND RELATED COMPOUNDS FOR TREATMENT OF SCHIZOPHRENIA



(57) Abstract: Compounds of formula 1 (1) are disclosed, wherein G is as shown in formula (i): (i). A of formula 1 is $-(CH_2)_nCO-$, wherein n is 4 or 5, and one or two of the carbon atoms of A can be substituted as described in the specification. D, Z, Q, X, Y, K, J, R¹, R⁴ through R⁷, and R⁹ through R¹¹ of formulae 1 and (i) are defined in the specification. Also provided are descriptions of processes for preparing compounds of formula 1, intermediates used in making the same, and pharmaceutical compositions containing such compounds and their use in the treatment of central nervous system disorders and other disorders.





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ISOQUINOLINE [1,8]NAPHTHYRIDIN-2-ONES AND RELATED COMPOUNDS
FOR THE TREATMENT OF SCHIZOPHRENIA

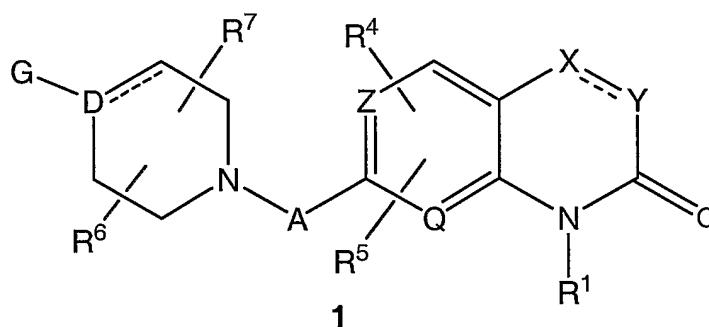
BACKGROUND OF THE INVENTION

5 This invention relates to [1,8]naphthyridin-2-ones and related compounds, methods of making such compounds, pharmaceutical compositions containing them, and their use for the treatment of schizophrenia and other central nervous system (CNS) disorders.

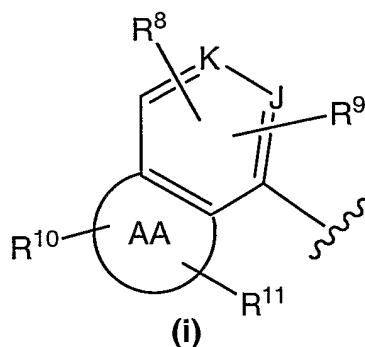
 The [1,8]naphthyridin-2-ones and related compounds of this invention bind to
10 dopamine D₂ receptors. Some exhibit activity as partial agonists of D₂ receptors, while others exhibit activity as antagonists of such receptors. Other heterocyclic derivatives that are useful for the treatment of schizophrenia are referred to in United States patent 5,350,747, which issued on September 27, 1994; in United States patent 6,127,357, which issued on October 3, 2000; in WO 93/04684, which published on March 18,
15 1993; and European patent application EP 402644A, which was published on December 19, 1990. The foregoing patents and patent applications are incorporated herein by reference in their entireties.

SUMMARY OF THE INVENTION

20 The present invention relates to compounds of formula 1, below:



 wherein G is as shown in formula (i), below:



A is $-(CH_2)_nO-$ wherein n is 4 or 5, and one or two of the carbon atoms of $-(CH_2)_nO-$ can be substituted, optionally and independently, with one or two substituents that are selected, independently, from fluoro and methyl, or with two substituents attached to the same carbon atom that form, together with the carbon to which they are attached, a spirocyclopropyl or spirocyclobutyl ring;

D is N, C, or CH, provided that when D is N, each carbon atom attached to D is attached through a single bond;

J and K are independently selected from N, CH, and C, provided that at least one of J and K is N;

Z and Q are independently selected from N and CH, provided that at least one of Z and Q is N;

R^1 is hydrogen, $-C(=O)CH_3$, or (C_1-C_3) alkyl;

$-X \equiv Y-$ is $-CH_2-CH_2-$, $-CH=CH-$, $-CH_2-NH-$, $-NH-CH_2-$, $-N=CH-$, $-CH=N-$, $-O-CH_2-$, or $-CH_2-O-$, wherein $-X \equiv Y-$ can optionally be substituted, at any available bonding site, by one to four substituents R^2 , $R^{2'}$, R^3 and $R^{3'}$;

R^2 , $R^{2'}$, R^3 and $R^{3'}$ are independently selected from hydrogen, halo, cyano, oxo, hydroxy, $-C(=O)CH_3$, (C_1-C_4) alkyl, and (C_1-C_4) alkoxy, wherein the alkyl moieties of the (C_1-C_4) alkyl, (C_1-C_4) alkoxy, and $-C(=O)CH_3$ groups can be optionally substituted with from one to three fluoro atoms and can also be optionally substituted with an amino or hydroxy substituent;

R^4 and R^5 are independently selected from hydrogen, halo, cyano, hydroxy, $-C(=O)CH_3$, (C_1-C_4) alkyl, and (C_1-C_4) alkoxy, wherein the alkyl moieties of the (C_1-C_4) alkyl, (C_1-C_4) alkoxy, and $-C(=O)CH_3$ groups can be optionally substituted with from one to three fluoro atoms and can also be optionally substituted with an amino or hydroxy substituent;

R^6 and R^7 are selected, independently, from hydrogen and methyl;

R^8 , R^9 , R^{10} and R^{11} are independently selected from hydrogen, halo, $-C(=O)CH_3$, (C₁-C₄) alkyl, and (C₁-C₄) alkoxy, wherein the alkyl moieties of the (C₁-C₄) alkyl, (C₁-C₄) alkoxy, and $-C(=O)CH_3$ groups can be optionally substituted with from one to three fluoro atoms and can also be optionally substituted with an amino or hydroxy substituent;

ring AA is a saturated or unsaturated 5-, 6-, or 7-membered carbocyclic ring wherein one, two or three of the carbon atoms of ring AA that are not shared with the other fused ring of formula (i) can be replaced, optionally and independently, by a nitrogen, oxygen or sulfur atom;

and the pharmaceutically acceptable salts of such compounds.

This invention also relates to a pharmaceutical composition comprising a therapeutically effective amount of a compound of the formula **1**, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The compounds of formula **1** have useful pharmaceutical and medicinal properties.

The invention also relates to a pharmaceutical composition for treating a disorder or condition selected from single episodic or recurrent major depressive disorders, dysthymic disorders, depressive neurosis and neurotic depression, melancholic depression; atypical depression; bipolar disorder; cyclothymic disorder; conduct disorder; disruptive behavior disorder; attention deficit hyperactivity disorder; behavioral disturbances associated with mental retardation, autistic disorder, and conduct disorder; anxiety disorders; borderline personality disorder; schizophrenia and other psychotic disorders; delirium, dementia, and amnestic and other cognitive or neurodegenerative disorders; movement disorders, dyskinesias; extra-pyramidal movement disorders; chemical dependencies and additions; behavioral addictions; and ocular disorders, comprising: an amount of a compound of formula **1**, or a pharmaceutically acceptable salt thereof that is effective in treating the disorder or condition, and a pharmaceutically acceptable carrier.

The invention further relates to a pharmaceutical composition for treating a disorder or condition selected from those listed above, comprising: (a) a compound of formula **1**, or a pharmaceutically acceptable salt thereof; and (b) an antidepressant or an anti-anxiety agent; and (c) a pharmaceutically acceptable carrier; wherein active agents

(a) and (b) are not the same and are present in amounts that render the combination of them effective in treating said disorder or condition.

This invention also relates to a method of treating a disorder or condition selected from those listed above, comprising administering to a mammal in need of
5 such treatment an amount of a compound according to formula 1, or a pharmaceutically acceptable salt thereof, that is effective in treating the disorder or condition.

The invention also relates to a method of treating a disorder or condition selected from those listed above, comprising administering to a mammal in need of such treatment (a) a compound of formula 1, or a pharmaceutically acceptable salt
10 thereof; and (b) an antidepressant or an anti-anxiety agent; wherein the active agents (a) and (b) are not the same and are present in amounts that render the combination of them effective in treating the disorder or condition.

The term “alkyl”, as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties or
15 combinations thereof. Examples of “alkyl” groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, iso- sec- and tert-butyl, pentyl, hexyl, heptyl, 3-ethylbutyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, and the like.

The term “alkoxy”, as used herein, unless otherwise indicated, means “alkyl-O-
20 ”, wherein “alkyl” is as defined above. Examples of “alkoxy” groups include, but are not limited to, methoxy, ethoxy, propoxy, butoxy and pentoxy.

The term “aryl”, as used herein, unless otherwise indicated, includes an aromatic ring system with no heteroatoms as ring members, which can be either unsubstituted or substituted with one, two or three substituents selected from the group
25 consisting of halo, (C₁-C₄)alkyl optionally substituted with from one to three fluorine atoms and (C₁-C₄)alkoxy optionally substituted with from one to three fluorine atoms.

The term “aryloxy”, as used herein, unless otherwise indicated, means “aryl-O-”, wherein “aryl” is as defined above.

The term “one or more substituents”, as used herein, refers to a number of
30 substituents that equals from one to the maximum number of substituents possible based on the number of available bonding sites.

The terms “halo” and “halogen”, as used herein, unless otherwise indicated, include, fluoro, chloro, bromo and iodo.

The term "therapeutically effective amount," as used herein, refers to a quantity of active agent sufficient to treat one or more of the disorders or conditions referred to above, when one or more doses of a pharmaceutical composition of the invention are administered to a subject with one or more of the disorders or conditions. In
5 determining what constitutes a therapeutically effective amount of an active agent in a composition or delivered in a method of the present invention, a number of factors will generally be considered, including the experience of the medical practitioner or veterinarian administering the composition, published clinical studies, the subject's age, sex, weight and general condition, as well as the type and extent of the disorder or
10 condition being treated, and the use of other medications, if any, by the subject. Determination of a proper dose for a particular situation, and preparation of a pharmaceutical composition containing a suitable dose of active agent for that situation, is within the skill of the medical or veterinary arts.

The term "treating", as used herein, refers to reversing, alleviating, inhibiting
15 the progress of, or preventing the disorder or condition to which such term applies, or preventing one or more symptoms of such condition or disorder.

The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above.

The compounds of formula 1, and the pharmaceutically acceptable salts of these
20 compounds are referred to herein, collectively, as the "novel compounds of this invention" and the "active compounds of this invention".

DETAILED DESCRIPTION OF THE INVENTION

Examples of preferred embodiments of this invention are compounds of the formula 1, and their pharmaceutically acceptable salts, wherein AA is a 6-membered
25 unsaturated carbocyclic ring.

Other preferred embodiments of this invention are compounds of the formula 1, and their pharmaceutically acceptable salts, wherein J is N.

Other preferred embodiments of this invention are compounds of the formula 1, and their pharmaceutically acceptable salts, wherein A is $-(CH_2)_4O-$.

30 Other preferred embodiments of this invention are compounds of the formula 1, and their pharmaceutically acceptable salts, wherein Q is N.

Other preferred embodiments of this invention are compounds of the formula **1**, and their pharmaceutically acceptable salts, wherein $-X---Y-$ is $-\text{CH}_2\text{-NH}-$.

Other preferred embodiments of this invention are compounds of the formula **1**, and their pharmaceutically acceptable salts, wherein $-X---Y-$ is $-\text{CH}_2\text{-CH}_2-$ or
5 $-\text{CH=CH}-$.

Other preferred embodiments of this invention are compounds of the formula **1**, and their pharmaceutically acceptable salts, wherein R^1 is hydrogen.

Other preferred embodiments of this invention are compounds of formula **1** and their pharmaceutically acceptable salts, wherein each of R^{10} and R^{11} is, independently,
10 hydrogen or fluoro.

Other preferred embodiments of this invention are compounds of formula **1** and their pharmaceutically acceptable salts, wherein D is N, Q is N, Z is CH, $-X---Y-$ is $-\text{CH}_2\text{-CH}_2-$ or $-\text{CH=CH}-$, and R^1 , R^4 , and R^5 are hydrogen.

Other preferred embodiments of this invention are compounds of formula **1** and
15 their pharmaceutically acceptable salts, wherein Q and Z are both N.

Other preferred embodiments of this invention are compounds of the formula **1**, and their pharmaceutically acceptable salts, wherein R^4 and R^5 are hydrogen.

Other preferred embodiments of this invention are compounds of the formula **1**, and their pharmaceutically acceptable salts, wherein D is N.

20 Other preferred embodiments of this invention are compounds of the formula **1**, and their pharmaceutically acceptable salts, wherein Q is N and Z is C or CH.

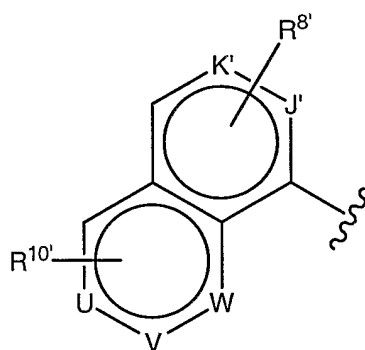
Other preferred embodiments of this invention are compounds of the formula **1**, and their pharmaceutically acceptable salts, wherein Q is N and Z is N.

25 Other embodiments of this invention are compounds of the formula **1**, and their pharmaceutically acceptable salts, wherein Q is C or CH, and Z is N.

Other embodiments of this invention relates to compounds of the formula **1**, and their pharmaceutically acceptable salts, wherein $-X---Y-$ is $-\text{O-CH}_2-$.

Other embodiments of this invention relates to compounds of the formula **1**, and their pharmaceutically acceptable salts, wherein $-X---Y-$ is $-\text{CH}_2\text{-NH}-$.

30 In another preferred embodiment, the invention relates to compounds of formula **1**, and their pharmaceutically acceptable salts, wherein G has a structure shown in formula (ii), below:



(ii)

wherein K' and J' are independently selected from N, CH, and C, provided that at least one of K' and J' is N;

R^{8'} is H, (C₁-C₄) alkyl, or (C₁-C₄) alkoxy;

5 R^{10'} is H, (C₁-C₄) alkyl, (C₁-C₄) alkoxy, or halo; and

U, V, and W are independently selected from N, CH, and C, provided that no more than two of U, V, and W are N.

R^{8'} is preferably attached to K'.

R^{8'} is preferably H or methyl.

10 R^{10'} is preferably attached to U or V.

R^{10'} is preferably H, methyl, or fluoro.

G is preferably an isoquinoline of formula (ii), more preferably an isoquinoline selected from the group consisting of 1-isoquinoliny, 7-fluoro-1-isoquinoliny, 6-fluoro-1-isoquinoliny, 3-methyl-1-isoquinoliny, and 7-fluoro-3-methyl-1-isoquinoliny.

Specific preferred embodiments of this invention are the following compounds and their pharmaceutically acceptable salts:

7-[4-(4-Isoquinolin-1-yl-piperazin-1-yl)-butoxy]-3,4-dihydro-1H-[1,8]naphthyridin-2-one;

20 7-[4-(4-Isoquinolin-4-yl-piperazin-1-yl)-butoxy]-3,4-dihydro-1H-[1,8]naphthyridin-2-one;

7-[4-(4-Isoquinolin-1-yl-piperazin-1-yl)-butoxy]-1H-[1,8]naphthyridin-2-one;

7-{4-[4-(6-Fluoro-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-3,4-dihydro-1H-[1,8]naphthyridin-2-one;

25 7-{4-[4-(6-Fluoro-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-1H-[1,8]naphthyridin-2-one;

7-{4-[4-(7-Fluoro-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-3,4-dihydro-1H-[1,8]naphthyridin-2-one;

7-{4-[4-(7-Fluoro-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-1H-[1,8]naphthyridin-2-one;

5 7-{4-[4-(7-Fluoro-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-4,4-dimethyl-3,4-dihydro-1H-[1,8]naphthyridin-2-one;

2-{4-[4-(7-Fluoro-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-8H-pyrido[2,3-d]pyrimidin-7-one;

10 2-{4-[4-(7-Fluoro-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-4-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;

7-[4-(4-[2,7]Naphthyridin-1-yl)-piperazin-1-yl]-butoxy]-1H-[1,8]naphthyridin-2-one;

7-[4-(4-[2,7]Naphthyridin-1-yl)-piperazin-1-yl]-butoxy]-3,4-dihydro-1H-[1,8]naphthyridin-2-one;

15 7-{4-[4-(3-Methyl-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-3,4-dihydro-1H-[1,8]naphthyridin-2-one;

7-{4-[4-(3-Methyl-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-1H-[1,8]naphthyridin-2-one.

Specific embodiments of this invention further relate to the following
20 compounds and their pharmaceutically acceptable salts:

7-[4-(4-[1,6]Naphthyridin-8-yl)-piperazin-1-yl]-butoxy]-3,4-dihydro-1H-[1,8]naphthyridin-2-one;

7-[4-(4-[1,6]Naphthyridin-8-yl)-piperazin-1-yl]-butoxy]-1H-[1,8]naphthyridin-2-one;

25 7-{4-[4-(7-Fluoro-3-methyl-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-3,4-dihydro-1H-[1,8]naphthyridin-2-one;

7-{4-[4-(7-Fluoro-3-methyl-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-1H-[1,8]naphthyridin-2-one;

30 7-{4-[4-(6-Fluoro-3-methyl-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-3,4-dihydro-1H-[1,8]naphthyridin-2-one;

7-{4-[4-(6-Fluoro-3-methyl-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-1H-[1,8]naphthyridin-2-one;

7-[4-(4-[1,7]Naphthyridin-8-yl-piperazin-1-yl)-butoxy]-3,4-dihydro-1H-[1,8]naphthyridin-2-one

7-[4-(4-[1,7]Naphthyridin-8-yl-piperazin-1-yl)-butoxy]-1H-[1,8]naphthyridin-2-one;

5 7-[4-(4-Thieno[2,3-c]pyridin-7-yl-piperazin-1-yl)-butoxy]-3,4-dihydro-1H-[1,8]naphthyridin-2-one; and

7-[4-(4-Thieno[2,3-c]pyridin-7-yl-piperazin-1-yl)-butoxy]-1H-[1,8]naphthyridin-2-one.

Compounds of the formula **1** may contain chiral centers and therefore may exist
10 in different enantiomeric and diastereomeric forms. This invention relates to all optical isomers and all stereoisomers of compounds of the formula **1**, both as racemic mixtures and as individual enantiomers and diastereoisomers of such compounds, and mixtures thereof, and to all pharmaceutical compositions and methods of treatment defined above that contain or employ them, respectively. Individual isomers can be obtained by
15 known methods, such as optical resolution, fractional crystallization, optically selective reaction, or chromatographic separation in the preparation of the final product or its intermediate. Individual enantiomers of the compounds of formula **1** may have advantages, as compared with the racemic mixtures of these compounds, in the treatment of various disorders or conditions.

20 In so far as the compounds of formula **1** are basic compounds, they are all capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate the base compound from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert to the
25 free base compound by treatment with an alkaline reagent and thereafter convert the free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent or in a suitable organic solvent, such as methanol or ethanol.
30 Upon careful evaporation of the solvent, the desired solid salt is readily obtained. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, *i.e.*, salts containing pharmaceutically acceptable anions, such as the

hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bi-tartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate (*i.e.*, 1,1'-methylene-bis-(2-hydroxy-
5 3-naphthoate)) salts.

The present invention also includes isotopically labeled compounds, which are identical to those of formula **1**, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into
10 compounds of the present invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine and chlorine, such as ^2H , ^3H , ^{13}C , ^{11}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. Compounds of the present invention, prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other
15 atoms are within the scope of this invention. Certain isotopically labeled compounds of the present invention, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, *i.e.*, ^3H , and carbon-14, *i.e.*, ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as
20 deuterium, *i.e.*, ^2H , can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds of formula **1** and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by
25 substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

The pharmaceutical compositions and methods of the present invention are suitable for use in treatment of a disease or disorder selected from single episodic or recurrent major depressive disorders, dysthymic disorders, depressive neurosis and
30 neurotic depression, melancholic depression including anorexia, weight loss, insomnia, early morning waking or psychomotor retardation; atypical depression (or reactive depression) including increased appetite, hypersomnia, psychomotor agitation or irritability, seasonal affective disorder and pediatric depression; bipolar disorders or

manic depression, for example, bipolar I disorder, bipolar II disorder and cyclothymic disorder; conduct disorder; disruptive behavior disorder; attention deficit hyperactivity disorder (ADHD); behavioral disturbances associated with mental retardation, autistic disorder, and conduct disorder; anxiety disorders such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, specific phobias, for example, specific animal phobias, social anxiety, social phobia, obsessive-compulsive disorder, stress disorders including post-traumatic stress disorder and acute stress disorder, and generalized anxiety disorders; borderline personality disorder; schizophrenia and other psychotic disorders, for example, schizophreniform disorders, schizoaffective disorders, delusional disorders brief psychotic disorders, shared psychotic disorders, psychotic disorders with delusions or hallucinations, psychotic episodes of anxiety, anxiety associated with psychosis, psychotic mood disorders such as severe major depressive disorder; mood disorders associated with psychotic disorders such as acute mania and depression associated with bipolar disorder; mood disorders associated with schizophrenia; delirium, dementia, and amnestic and other cognitive or neurodegenerative disorders, such as Parkinson's disease (PD), Huntington's disease (HD), Alzheimer's disease, senile dementia, dementia of the Alzheimer's type, memory disorders, loss of executive function, vascular dementia, and other dementias, for example, due to HIV disease, head trauma, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeldt-Jakob disease, or due to multiple etiologies; movement disorders such as akinesias, dyskinesias, including familial paroxysmal dyskinesias, spasticities, Tourette's syndrome, Scott syndrome, PALSYS and akinetic-rigid syndrome; extra-pyramidal movement disorders such as medication-induced movement disorders, for example, neuroleptic-induced Parkinsonism, neuroleptic malignant syndrome, neuroleptic-induced acute dystonia, neuroleptic-induced acute akathisia, neuroleptic-induced tardive dyskinesia and medication-induced postural tremor; chemical dependencies and addictions (e.g., dependencies on, or addictions to, alcohol, heroin, cocaine, benzodiazepines, nicotine, or phenobarbital) and behavioral addictions such as an addiction to gambling; and ocular disorders such as glaucoma and ischemic retinopathy in a mammal in need of such treatment, including a human, comprising an amount of a compound of the formula 1, or a pharmaceutically acceptable salt thereof, that is effective in treating such disorder or condition, and a pharmaceutically acceptable carrier.

In a specific embodiment of the methods or pharmaceutical compositions of the present invention, the disorder or condition treated is selected from major depression, single episode depression, recurrent depression, child abuse induced depression, postpartum depression, dysthymia, cyclothymia and bipolar disorder.

5 In another, more specific, embodiment of the methods or pharmaceutical compositions of the present invention, the disorder or condition treated is selected from schizophrenia, schizoaffective disorder, delusional disorder, substance-induced psychotic disorder, brief psychotic disorder, shared psychotic disorder, psychotic disorder due to a general medical condition, and schizophreniform disorder.

10 In another more specific embodiment of the methods or pharmaceutical compositions of the present invention, the disorder or condition that is being treated is selected from autism, pervasive development disorder, speech impediments such as stuttering, and attention deficit hyperactivity disorder.

In another more specific embodiment of the methods or pharmaceutical
15 compositions of this invention, the disorder or condition that is being treated is selected from generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, and phobias, including social phobia, agoraphobia, and specific phobias.

In another more specific embodiment of the methods or pharmaceutical
20 compositions of this invention, the disorder or condition that is being treated is selected from movement disorders such as akinesias, dyskinesias, including familial paroxysmal dyskinesias, spasticities, Tourette's syndrome, Scott syndrome, PALSYS and akinetic-rigid syndrome; and extra-pyramidal movement disorders such as medication-induced movement disorders, for example, neuroleptic-induced Parkinsonism, neuroleptic
25 malignant syndrome, neuroleptic-induced acute dystonia, neuroleptic-induced acute akathisia, neuroleptic-induced tardive dyskinesia and medication-induced postural tremor.

In another more specific embodiment of the methods or pharmaceutical
compositions of this invention, the disorder or condition that is being treated is selected
30 from delirium, dementia, and amnestic and other cognitive or neurodegenerative disorders, such as Parkinson's disease (PD), Huntington's disease (HD), Alzheimer's disease, senile dementia, dementia of the Alzheimer's type, memory disorder, vascular dementia, and other dementias, for example, due to HIV disease, head trauma,

Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeldt-Jakob disease, or due to multiple etiologies.

In another more specific embodiment of the methods of the present invention, the compound of formula 1 is administered to a human for the treatment of any two or
5 more comorbid disorders or conditions selected from those disorders and conditions referred to in any of the above methods.

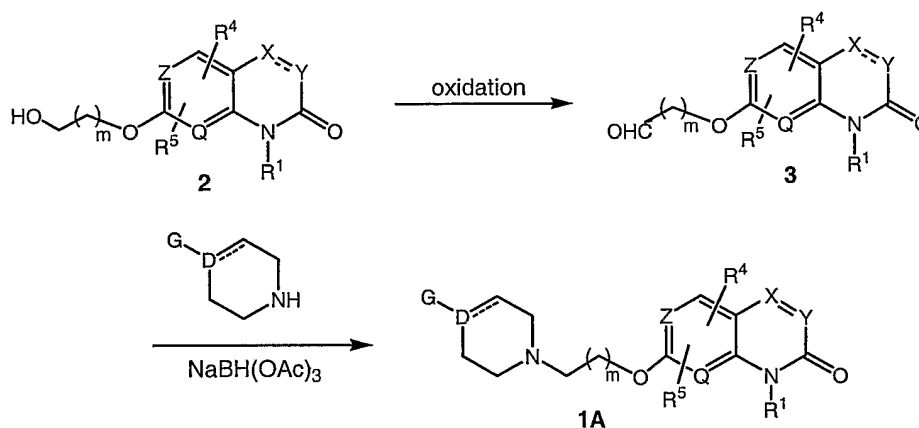
In embodiments of the pharmaceutical compositions of the present invention, comprising (a) a compound of formula 1, or a pharmaceutically acceptable salt thereof, and (b) an antidepressant or an anti-anxiety agent, as described above, or in methods of
10 the present invention comprising administering active agents (a) and (b), examples of classes antidepressants suitable for use in the invention include norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors (SSRIs), NK-1 receptor antagonists, monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase (RIMAs), serotonin and noradrenaline reuptake inhibitors (SNRIs),
15 corticotropin releasing factor (CRF) antagonists, α -adrenoreceptor antagonists, and atypical antidepressants. Suitable norepinephrine reuptake inhibitors include tertiary amine tricyclics and secondary amine tricyclics. Suitable tertiary amine tricyclics and secondary amine tricyclics include amitriptyline, clomipramine, doxepin, imipramine, trimipramine, dothiepin, butripyline, iprindole, lofepramine, nortriptyline, protriptyline,
20 amoxapine, desipramine and maprotiline. Suitable selective serotonin reuptake inhibitors include fluoxetine, fluvoxamine, paroxetine and sertraline. Examples of monoamine oxidase inhibitors include isocarboxazid, phenelzine, and tranylcyclopramine. Suitable reversible inhibitors of monoamine oxidase include moclobemide. Suitable serotonin and noradrenaline reuptake inhibitors of use in the
25 present invention include venlafaxine. Suitable CRF antagonists include those compounds described in International Patent Application Nos. WO 94/13643, WO 94/13644, WO 94/13661, WO 94/13676 and WO 94/13677. Suitable atypical anti-depressants include bupropion, lithium, nefazodone, trazodone and viloxazine. Suitable NK-1 receptor antagonists include those referred to in World Patent Publication WO
30 01/77100.

Suitable classes of anti-anxiety agents that can be used in combination with the compounds of formula 1 in the pharmaceutical compositions and methods of this invention include benzodiazepines and serotonin 1A (5-HT_{1A}) agonists or antagonists,

especially 5-HT_{1A} partial agonists, and corticotropin releasing factor (CRF) antagonists. Suitable benzodiazepines include alprazolam, chlordiazepoxide, clonazepam, chlorazepate, diazepam, halazepam, lorazepam, oxazepam, and prazepam. Suitable 5-HT_{1A} receptor agonists or antagonists include buspirone, flesinoxan, gepirone and ipsapirone.

The active compounds of this invention may be prepared as described below. Unless otherwise indicated, in the reaction schemes and discussion that follow, A, Z, D, Q, ring AA, G, X, Y, R¹ through R¹¹, formula 1, the dotted line connecting X and Y, and groups of formulas (i) and (ii) are defined as above. m is 3 or 4 in each of the reaction schemes, below.

Scheme A

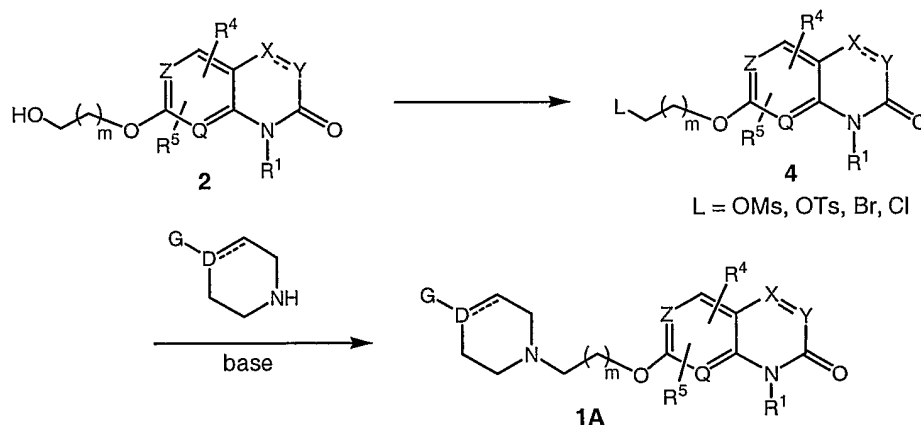


Scheme A illustrates a method for preparing compounds of the formula 1, optionally substituted as indicated in the definition of formula 1 above (also referred to as compounds of the formula 1A). This method involves oxidation of a compound of the formula 2 with Dess-Martin Periodinane or another suitable oxidizing agent such as IBX (o-iodoxybenzoic acid), oxalyl chloride in dimethyl sulfoxide (DMSO) (Swern oxidation) or PCC (pyridinium chlorochromate) to form the corresponding aldehyde of formula 3. This reaction may be carried out in dichloromethane (CH₂Cl₂), tetrahydrofuran (THF), DMSO, or a combination of two or more of these solvents. Reductive amination of a G-substituted piperidine or piperazine, as shown in Scheme A, using methods well known to those of skill in the art, with a compound of formula 3 yields the corresponding compound of formula 1A. The reductive amination can be performed, for example, utilizing catalytic hydrogenation methods or using a hydride reducing agent such as sodium triacetoxyborohydride (NaBH(OAc)₃) or sodium cyanoborohydride. The reaction solvent can be 1,2-dichloroethane, tetrahydrofuran,

acetonitrile, dimethylformamide or a combination of two or more of these solvents, with the optional addition of 1-10 equivalents of acetic acid. When the piperazine or piperidine hydrochloride or hydrobromide salt is used, a base such as triethylamine is typically added.

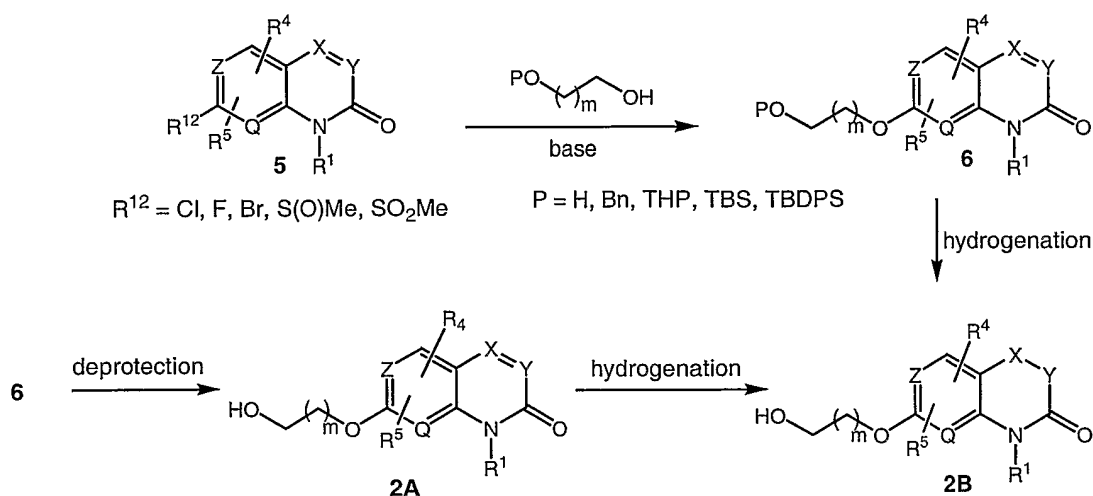
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Scheme B



Alternatively, compounds of the formula **1A** can be prepared according to Scheme B. The hydroxy group of the compound of formula **2** is converted into a leaving group (L) using conventional methods to provide the corresponding compound of formula **4** wherein L is mesylate (OMs), tosylate (OTs) or a halogen such as bromide, iodide or chloride. The resulting compound of formula **4** is then reacted with a G-substituted piperazine or piperidine, as depicted in Scheme B, to yield the desired compound of formula **1A**. This reaction is preferably run in the presence of a base such as potassium carbonate, sodium carbonate, cesium carbonate, triethylamine or diisopropylethylamine. The solvent used may be acetonitrile, water, tetrahydrofuran, dioxane, acetone, methyl isobutyl ketone, benzene or toluene, or a combination of two or more of these solvents. Inorganic salts such as sodium or potassium iodide may be employed as catalysts in the reaction. The temperature of the reaction may vary from about ambient temperature to about the reflux temperature of the solvent used. The reaction may also be conducted under microwave irradiation.

Scheme C



Scheme C illustrates a method for preparing compounds of the formula **2A** (wherein X is double bonded to Y) and **2B** (wherein X is single bonded to Y). Addition of 2 to 20 equivalents of a diol of the formula $\text{HOCH}_2(\text{CH}_2)_m\text{OH}$, where m is 3 or 4, or one to four equivalents of a suitably mono-protected diol of the formula $\text{POCH}_2(\text{CH}_2)_m\text{OH}$, wherein P is tetrahydropyranyl (THP), benzyl (Bn), *p*-methoxybenzyl, *tert*-butyldimethylsilyl (TBS), or *tert*-butyldiphenylsilyl (TBDPS), to a compound of the formula **5**, wherein R^{12} is chloro, fluoro, bromo, S(O)CH_3 or SO_2CH_3 , provides the corresponding compound of formula **6** (or **2A** when the unprotected diol reactant is used). R^{12} is most preferably fluoro. This reaction is conducted in the presence of a base such as potassium *tert*-butoxide, sodium *tert*-butoxide, sodium hydride, potassium hydride, lithium diisopropylamide, lithium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide, or sodium bis(trimethylsilyl)amide. Suitable solvents for this reaction include THF, dioxane, ethylene glycol dimethylether, DMF, N-methylpyrrolidinone (NMP), or DMSO, or a combination of two or more of these solvents. The temperature of the reaction may vary from about ambient temperature to about the reflux temperature of the solvent used.

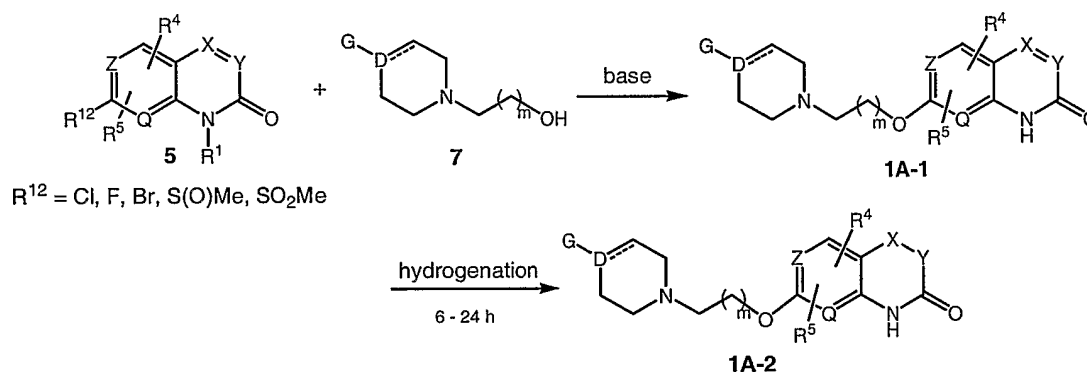
The reaction of the compound of formula **5** with the mono-protected diol of the formula $\text{POCH}_2(\text{CH}_2)_m\text{OH}$ to yield the compound of formula **6**, as described above, is preferably conducted in the presence of a catalytic amount of a phase transfer catalyst, such as tetrabutyl ammonium chloride or bromide. The use of a phase transfer catalyst accelerates the rate of the coupling, and allows one to carry out the reaction at a lower

temperature than would be possible without the catalyst. Use of the phase transfer catalyst also significantly reduces the formation of dimeric by-products.

Compounds of the formula **6** where, P is tetrahydropyranyl (THP), can be deprotected using conventional methods such as treatment with PPTS (pyridinium p-toluenesulfonate) or *p*-toluenesulfonic acid in ethanol to give the corresponding compounds of formula **2A**. Compounds of the formula **6** wherein P is *tert*-butyldimethylsilyl or *tert*-butyldiphenylsilyl can be deprotected using conventional methods such as treatment with tetrabutylammonium fluoride in tetrahydrofuran to yield compounds of the formula **2A**.

Compounds of the formula **2A** or compounds of the formula **6** wherein P is H or benzyl can be reduced using catalytic hydrogenation methods to provide the corresponding compounds of formula **2B**. For example, the hydrogenation can be conducted using 5 to 20 % palladium on activated carbon in a solvent such as methanol, ethanol, tetrahydrofuran, acetic acid, dimethylformamide, or a combination of two or more of these solvents for a period of about 5 hours to about 48 hours, preferably for about 24 hours, under a hydrogen pressure from about 1 to about 5 atmosphere, preferably about 1 atmosphere.

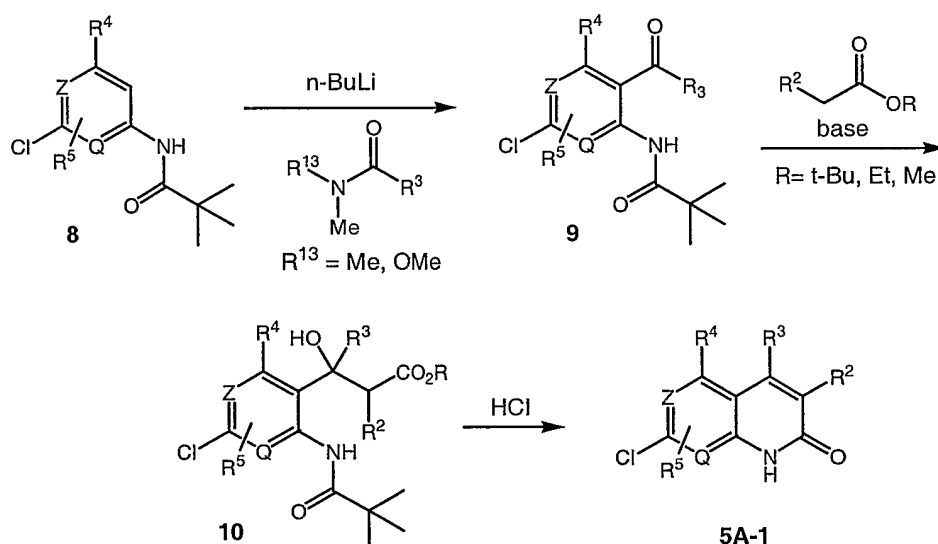
Scheme D



Scheme D illustrates another method for preparing compounds of the formula **1A**. Addition of a compound of the formula **5** to a compound of the formula **7** provides the corresponding compound of formula **1A-1**. Compounds of the formula (7) obtained from arylpiperazines and piperidines prepared per the general procedure of *Acta Physica et Chemica*, 28(3-4), 225-44; **1982**, can be reacted in the presence of a base such as potassium *tert*-butoxide, sodium *tert*-butoxide, sodium hydride, potassium hydride, lithium diisopropylamide, lithium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide, or sodium bis(trimethylsilyl)amide. Suitable solvents for this

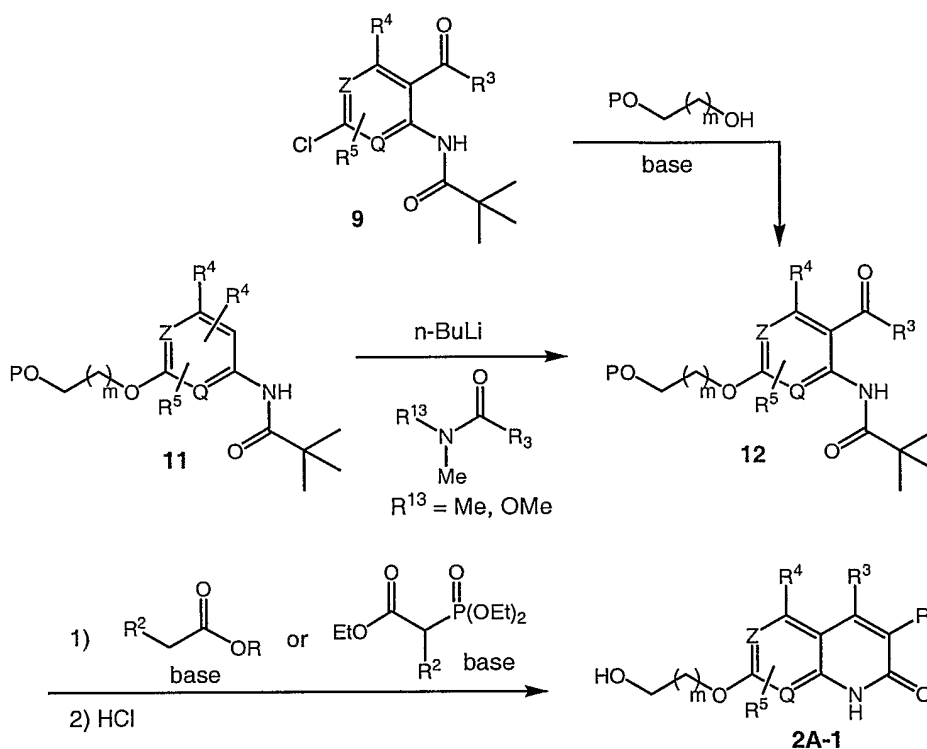
reaction include THF, dioxane, ethylene glycol dimethylether, DMF, NMP, and DMSO, or a combination of two or more of these solvents. The reaction temperature can range from about -78°C to about ambient temperature, and is preferably from about -20° to about 0°C . Catalytic hydrogenation of compounds of the formula **1A-1** (when G is compatible with the hydrogenation conditions) provides compounds of formula **1A-2**. For example, the hydrogenation can be conducted using 5 to 20% palladium on activated carbon in a solvent such as methanol, ethanol, THF, acetic acid, or DMF, or a combination of two or more of these solvents, for a period of about 5 hours to about 48 hours, preferably for about 12 to 24 hours.

Scheme E



Scheme E illustrates an alternative method for preparing compounds of the formula **5A-1**. (*J. Org. Chem.* **1990**, 55, 4744). (Compounds of the formula **5A-1** are compounds of the formula **5** wherein X is CR^3 , Y is CR^2 and there is a double bond between X and Y). In Scheme E, R^3 is ($\text{C}_1\text{-C}_4$) alkyl. Ortho metalation of compounds of the formula **8** and subsequent treatment with electrophiles having the formula shown in Scheme E results in compounds of the formula **9**. Condensation of compounds of the formula **9** with the enolates of the alkyl esters having the formula shown in Scheme E provides the corresponding compounds of formula **10**. Refluxing compounds of the formula **10** in aqueous acid such as 3N hydrochloric acid, with the optional use of a co-solvent such as dioxane, generates the corresponding compounds of formula **5A-1**.

Scheme F



Scheme F illustrates another method for preparing compounds of the formula **2A-1**. In Scheme F, R^3 is ($\text{C}_1\text{-C}_4$) alkyl. Addition of a suitably mono-protected diol, where n is 3 or 4 and P is tetrahydropyranyl (THP), benzyl, or *tert*-butyldimethylsilyl, to compounds of the formula **9** provides compounds of the formula **11**. The reaction is conducted in the presence of a base such as potassium *tert*-butoxide, sodium *tert*-butoxide, sodium hydride, potassium hydride, lithium diisopropylamide, lithium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide, or sodium bis(trimethylsilyl)amide. The solvents used may be THF, dioxane, ethylene glycol dimethylether, DMF, NMP, or DMSO or a combination of two or more of these solvents. The temperature of the reaction may vary from about 0°C to about the reflux temperature of the solvent.

Alternatively, compounds of the formula **12** can be prepared from compounds of the formula **11** according to the method described in Scheme E for the preparation of compounds of the formula **9**.

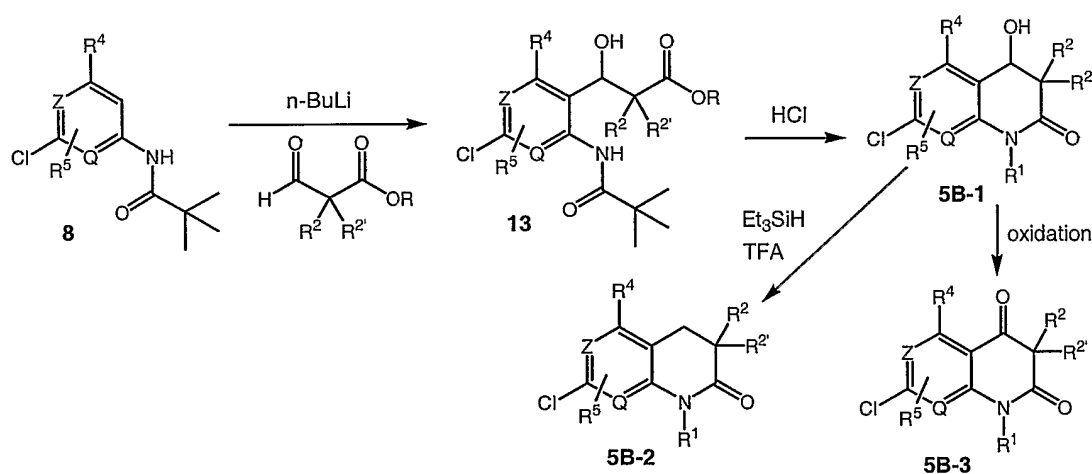
Condensation of compounds of the formula **12** with the enolates of the esters having the formula shown in Scheme F provides α -hydroxy ester intermediates, which are treated with an aqueous acid such as 3N hydrochloric acid, with the optional use of a co-solvent such as dioxane, at temperatures varying from about ambient temperature

to about the reflux temperature of the solvent, to generate compounds of the formula **2A-1**.

Alternatively, Horner-Wadsworth-Emmons reaction of compounds of the formula **12** with ketophosphonates having the formula shown in Scheme F, in the presence of a base such as sodium hydride, sodium ethoxide, or butyl lithium, in a solvent such as THF, DMSO, dioxane, ethylene glycol dimethylether, ethanol, or benzene, or a combination of two or more of these solvents, to give the corresponding intermediate α,β -unsaturated esters. This reaction can also be conducted using lithium chloride and a base, such as DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) or triethylamine, in a solvent such as acetonitrile or THF. The intermediate α,β -unsaturated esters are then treated with aqueous hydrochloric acid with the optional use of a co-solvent such as dioxane to provide the desired compounds of the formula **2A-1**. The temperature of this reaction may vary from about ambient temperature to about the reflux temperature of the solvent.

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Scheme G

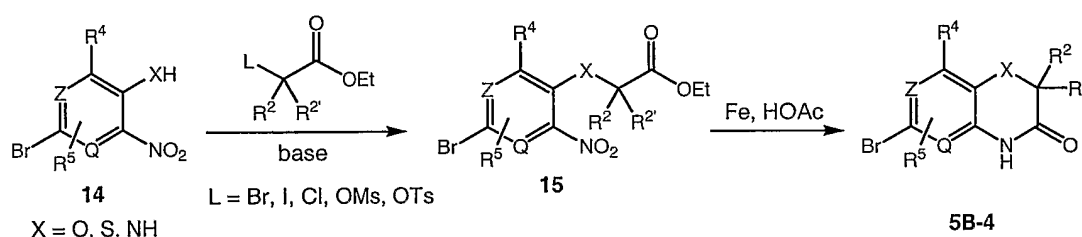


Scheme G illustrates a method for preparing compounds of the formula **5B-1**, **5B-2** and **5B-3**. Ortho metalation of compounds of the formula **8**, as described in Scheme E, and subsequent treatment with 3-oxopropionic acid esters of the formula shown in Scheme G above provides the corresponding compounds of formula **13**. The reaction can be conducted in a solvent such as tetrahydrofuran at temperatures ranging from about -78°C to about ambient temperature, preferably from about -78°C to about -0°C . Refluxing compounds of the formula **13** in an aqueous acid such as 3N hydrochloric acid, with the optional use of a co-solvent such as dioxane, generates the corresponding compounds of formula **5B-1**. Compounds of the formula **5B-2** can be

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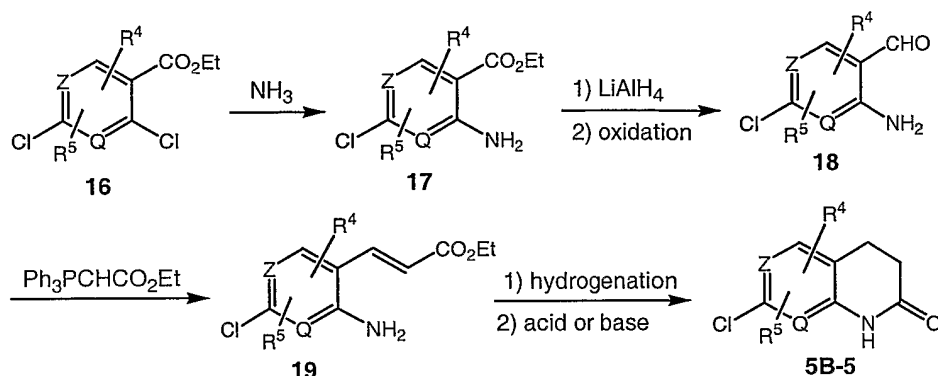
prepared by treating the corresponding compounds of the formula **5B-1** with triethylsilane in trifluoroacetic acid at a temperature from about room temperature to the reflux temperature of the solvent. Compounds of the formula **5B-3** can be prepared by treating compounds of the formula **5B-1** with an oxidizing agent such as Dess Martin periodinane, IBX or PCC at about ambient temperature in a solvent such as dichloromethane, dichloroethane, THF or DMSO, or a combination of two or more of these solvents.

Scheme H



Scheme H illustrates a method for preparing compounds of the formula **5B-4** (see PCT Patent Application WO 02/056882). Alkylation of compounds of the formula **14** with an ester of the formula shown in Scheme I ($\text{L} = \text{Br, I, Cl, OMs, OTs}$) yields the corresponding compounds of formula **15**. This reaction is typically run in the presence of a base such as potassium carbonate or sodium hydride, in a solvent such as acetonitrile, THF, dioxane, acetone, methyl isobutyl ketone, benzene, toluene or DMF, or a combination of two or more of these solvents. The temperature of the reaction may vary from about ambient temperature to about the reflux temperature of the solvent. The nitro group of compounds of the formula **15** can be reduced with iron powder and acetic acid, with or without the addition of a solvent such methanol or water, at temperatures from about room temperature to about the reflux temperature of the solvent mixture used. These conditions also result in ring closure to yield compounds of the formula **5B-4**.

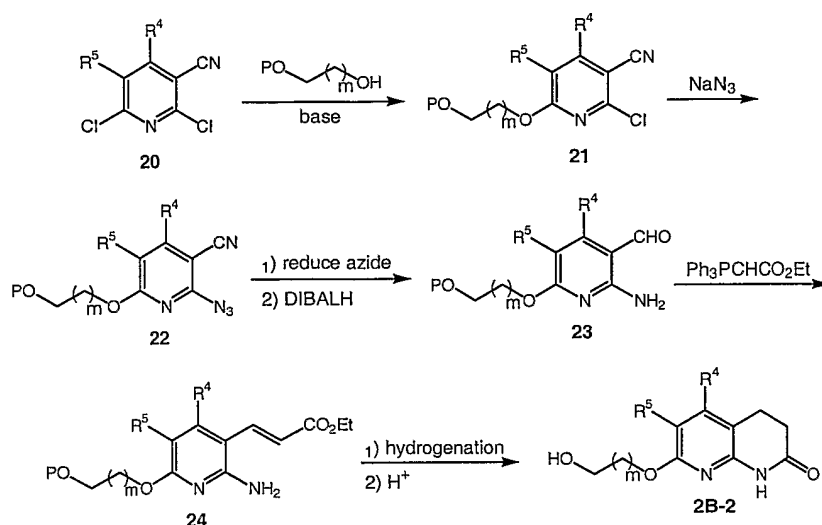
Scheme I



Scheme I illustrates a method for preparing compounds of the formula **5B-5**.

- Compounds of the formula **16** can be heated with liquid ammonia in a sealed reaction vessel at temperatures of about 40°C to about 100°C, in a solvent such as THF, to yield compounds of the formula **17**. Reduction of the ester of compound **17** to the corresponding alcohol, using lithium aluminum hydride, under conventional conditions well known to those of skill in the art, followed by oxidation of the alcohol with an oxidizing agent such as barium manganate, manganese dioxide, IBX, Dess Martin periodinane, or PCC, in a solvent such as dichloromethane, THF, or DMSO, or a combination of two or more of these solvents, yields the corresponding aldehydes of formula **18**. Compounds of the formula **18** can then be reacted with (carbethoxymethylene)triphenylphosphorane or a similar Wittig reagent in a solvent such as dichloromethane, chloroform, THF, benzene or toluene, at a temperature from about room temperature to about the reflux temperature of the solvent, to give the corresponding compounds of formula **19**. In the case of barium manganate, the oxidation and the Wittig reaction can be carried out using a one-pot procedure (*J. Org. Chem.* **1998**, 63, 4489). Hydrogenation of compounds of the formula **19**, using methods known to those skilled in the art, for example, as described above, preferably using palladium on barium sulfate in a solvent such as THF, provides the corresponding amino esters. The resulting amino esters can be cyclized to give compounds of the formula **5B-5** by heating at a temperature from about 50°C to about the reflux temperature of the solvent, in a solvent such as ethanol, methanol or isopropanol, preferably with a catalytic amount of acid (*i.e.*, TsOH) or base (*i.e.*, DBU).

Scheme J



Scheme J illustrates an alternative method for preparing compounds of the formula **2B-2**. Addition of a suitably mono-protected diol, where *n* is 3 and *P* is THP, benzyl, or TBS, to compounds of the formula **20** provides the corresponding compounds of formula **21**. This reaction is typically conducted in the presence of a base such as potassium *tert*-butoxide, sodium *tert*-butoxide, sodium hydride, lithium diisopropylamide, lithium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide, or sodium bis(trimethylsilyl)amide, in a solvent such as THF, dioxane, or ethylene glycol dimethylether, preferably THF. The temperature of the reaction may vary from about -78 °C to about room temperature. Compounds of the formula **21** can be reacted with sodium azide in solvents such as DMF, NMP or DMSO, or a combination of two or more of these solvents, to provide compounds of the formula **22**. The temperature of the reaction may vary from about room temperature to about the reflux temperature of the solvent, and is preferably about 70°C. The azide of compounds of the formula **22** can be reduced to an amine using conventional reducing agents known to those skilled in the art, preferably using hexamethyldisilthiane [(Me₃Si)₂S] in a solvent such as methanol or ethanol. Subsequent reduction of the cyano group to an aldehyde using diisobutylaluminum hydride (DIBALH) in a solvent such as THF at about 0 °C provides compounds of the formula **23**. Compounds of the formula **23** can be reacted with (carbethoxymethylene)triphenylphosphorane or a similar Wittig reagent in a solvent such as dichloromethane, chloroform, THF, benzene or toluene, or a mixture of two or more of these solvents, at about room temperature to about the reflux

temperature of the solvent, to give compounds of the formula **24**. Compounds of the formula **24** can be hydrogenated using methods known to those skilled in the art, using, for example, palladium on activated carbon, palladium on barium sulfate, or Raney-nickel, in a solvent such as methanol, ethanol, THF, or a combination of two of the
5 formerly mentioned solvents. The resulting amino esters can be cyclized to give the corresponding compounds of the formula **2B-2** by heating at a temperature from about 50°C to about the reflux temperature of the solvent, in a solvent such as ethanol, methanol or isopropanol, or a mixture of two or more of these solvents. Preferably, a catalytic amount of acid (for example, toluene sulphonic acid) or base (for example,
10 1,8-diazabicyclo[5.4.0]undec-7-ene) is used.

The preparation of other compounds of the formula **1** not specifically described in the foregoing experimental section can be accomplished using combinations of the reactions described above that will be apparent to those skilled in the art.

In each of the reactions discussed or illustrated above, pressure is not critical
15 unless otherwise indicated. Pressures from about 0.5 atmospheres to about 5 atmospheres are generally acceptable, and ambient pressure, *i.e.*, about 1 atmosphere, is preferred as a matter of convenience.

The compounds of the formula **1** and the intermediates shown in the above reaction schemes can be isolated and purified by conventional procedures, such as
20 recrystallization or chromatographic separation.

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The compounds of the formula **1** and the intermediates shown in the above reaction schemes can be isolated and purified by conventional procedures, such as
30 recrystallization or chromatographic separation.

The compounds of the formula **1** and their pharmaceutically acceptable salts, can be administered to mammals via either the oral, parenteral (such as subcutaneous, intravenous, intramuscular, intrasternal and infusion techniques), rectal, buccal or

intranasal routes. In general, these compounds are most desirably administered in doses ranging from about 3 mg to about 600 mg per day, in single or divided doses (*i.e.*, from 1 to 4 doses per day), although variations will necessarily occur depending upon the species, weight and condition of the patient being treated and the patient's individual response to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out. However, a dosage level that is in the range of about 10 mg to about 100 mg per day is most desirably employed. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effects, provided that such higher dose levels are first divided into several small doses for administration throughout the day.

The novel compounds of the present invention may be administered alone or in combination with pharmaceutically acceptable carriers or diluents by any of the routes previously indicated, and such administration may be carried out in single or multiple doses. More particularly, the novel therapeutic agents of this invention can be administered in a wide variety of different dosage forms, *i.e.*, they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, suppositories, jellies, gels, pastes, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the weight ratio of the novel compounds of this invention to the pharmaceutically acceptable carrier will be in the range from about 1:6 to about 2:1, and preferably from about 1:4 to about 1:1.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tableting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight

polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For parenteral administration, solutions of a compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered (preferably pH greater than 8) if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intra-articular, intra-muscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

This invention relates to methods of treating anxiety, depression, schizophrenia and the other disorders referred to in the description of the methods of the present invention, wherein a novel compound of this invention and one or more of the other active agents referred to above (*e.g.*, an NK1 receptor antagonist, tricyclic antidepressant, 5HT1D receptor antagonist, or serotonin reuptake inhibitor) are administered together, as part of the same pharmaceutical composition, as well as to methods in which such active agents are administered separately as part of an appropriate dose regimen designed to obtain the benefits of the combination therapy. The appropriate dose regimen, the amount of each dose of an active agent administered, and the specific intervals between doses of each active agent will depend upon the subject being treated, the specific active agent being administered and the nature and severity of the specific disorder or condition being treated. In general, the novel compounds of this invention, when used as a single active agent or in combination with another active agent, will be administered to an adult human in an amount from about 3 mg to about 300 mg per day, in single or divided doses, preferably from about 10 to about 100 mg per day. Such compounds may be administered on a regimen of up to 6 times per day, preferably 1 to 4 times per day, especially 2 times per day and most especially once daily. Variations may nevertheless occur depending upon the species of animal being treated and its individual response to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval at which

such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several small doses for administration throughout the day.

A proposed daily dose of a 5HT reuptake inhibitor, preferably sertraline, in the combination methods and compositions of this invention, for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to above, is from about 0.1 mg to about 2000 mg, preferably from about 1 mg to about 200 mg of the 5HT reuptake inhibitor per unit dose, which could be administered, for example, 1 to 4 times per day. A proposed daily dose of a 5HT1D receptor antagonist in the combination methods and compositions of this invention, for oral, parenteral, rectal or buccal administration to the average adult human for the treatment of the conditions referred to above, is from about 0.01 mg to about 2000 mg, preferably from about 0.1 mg to about 200 mg of the 5HT1D receptor antagonist per unit dose, which could be administered, for example, 1 to 4 times per day.

For intranasal administration or administration by inhalation, the novel compounds of the invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch. Formulations of the active compounds of this invention for treatment of the conditions referred to above in the average adult human are preferably arranged so that each metered dose or "puff" of aerosol contains 20 μ g to 1000 μ g of active compound. The overall daily dose with an aerosol will be within the range 100 μ g to 10 mg. Administration may be several times daily, for example 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time.

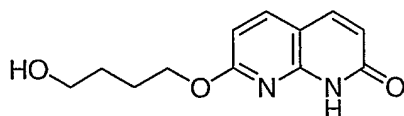
The ability of the novel compounds of this invention to bind to the dopamine D₂ receptor can be determined using conventional radioligand receptor binding assays. All receptors can be heterologously expressed in cell lines and binding assays can be conducted in membrane preparations from the cell lines using procedures outlined below. IC₅₀ concentrations can be determined by nonlinear regression of concentration-dependent reduction in specific binding. The Cheng-Prusoff equation can be used to convert the IC₅₀ to K_i concentrations. See Example 21, below, for a description of the assay used to determine the binding of the compounds of this invention to the dopamine D₂ receptor, and the binding data obtained for the assayed compounds.

Compounds of the present invention preferably exhibit K_i values of no more than 100 nM, more preferably no more than 50 nM, even more preferably no more than 25 nM, most preferably no more than 10 nM.

The following Examples illustrate the preparation of several compounds of the present invention. Melting points are uncorrected. NMR data are reported in parts per million and are referenced to the deuterium lock signal from the sample solvent. Any reference to a "title compound" in an example, below, refers to the compound named in the title of that particular example.

EXAMPLES

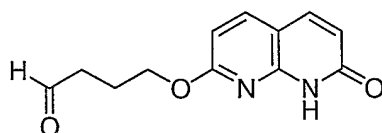
EXAMPLE 1



7-(4-Hydroxy-butoxy)-1H-[1,8]naphthyridin-2-one

To 1 liter (L) of n-methylpyrrolidinone was added 60% sodium hydride suspension (83.6g, 2.09moles). With external cooling to maintain 50°C, 1,4-butanediol (3.39 moles) was added dropwise, causing offgassing. The mixture was stirred for 15 minutes at 60°C, followed by addition of 7-Chloro-1H-[1,8]naphthyridin-2-one (Journal of Organic Chemistry, 55(15), 4744-50; 1990, 146g, 0.813 moles) while stirring at 68°C for 20 hours (h). To the mixture was added 5 liters of acetonitrile followed by filtration of a solid which was washed with a 50:50 mixture of acetonitrile and tetrahydrofuran. The solid was resuspended in 3 liters of tetrahydrofuran, to which was

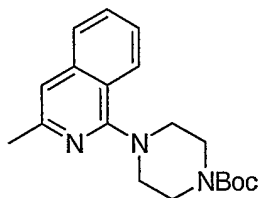
added 3N HCl in methanol (290ml, 0.870 moles). After heating for 1 hour at 60°C, the mixture was filtered thru celite, washed with 1 liter of tetrahydrofuran and concentrated to 500ml in volume. To the residue was added 1.5 liters of tetrahydrofuran, 10g Darco activated charcoal, and 100ml Magnesol. After stirring at 40°C for 30 minutes (min.), the mixture was filtered and washed with tetrahydrofuran and concentrated to 500ml in volume. To this residue was added 1 liter of acetonitrile followed by concentration of the mixture to 1 liter in volume. The resulting solid precipitate was filtered, washed with acetonitrile and ether, and dried at 50°C giving 7-(4-Hydroxy-butoxy)-1H-[1,8]naphthyridin-2-one, 101g, (53% yield).



4-(7-Oxo-7,8-dihydro-[1,8]naphthyridin-2-yloxy)-butyraldehyde

7-(4-Hydroxy-butoxy)-1H-[1,8]naphthyridin-2-one (69.44g, 296mmol) was dissolved in ethyl acetate (2.1L). IBX (232.42g, 828mmol) was added to make a slurry, and the reaction was heated to 75°C for three 8 hour periods over the course of two days. The reaction was cooled, filtered and the solids washed with dichloromethane. The filtrate was stripped to give a waxy solid which was triturated with methyl-t-butyl ether, from which was obtained 4-(7-Oxo-7,8-dihydro-[1,8]naphthyridin-2-yloxy)-butyraldehyde, as a solid (58.61g, 85% yield).

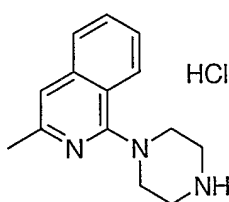
EXAMPLE 2



4-(3-Methyl-isoquinolin-1-yl)-piperazine-1-carboxylic acid tert-butyl ester

A solution of 1-boc-piperazine (1.179 g, 6.33 mmol) in tetrahydrofuran (15 mL) was cooled to -78 °C, then treated with n-butyllithium (2.5 M in hexanes, 2.5 mL, 6.25 mmol) dropwise. The colourless solution was stirred at -78°C for 30 minutes, then treated with 1-Chloro-3-methyl-isoquinoline (US 6,403,608 B1, 0.45g, 2.53 mmol) in tetrahydrofuran (5 mL) dropwise. The purple mixture was stirred at -78 °C for 2 hours,

then quenched with saturated NH_4Cl solution. The yellow mixture was diluted with saturated NaCl solution and extracted with ethyl acetate. The extracts were dried over anhydrous Na_2SO_4 , filtered and concentrated to a yellow oil. The oil was purified by column chromatography (chloroform/ethyl acetate, 2:3), to afford 4-(3-Methyl-
5 isoquinolin-1-yl)-piperazine-1-carboxylic acid tert-butyl ester (0.305 g, 37 %), as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 8.03 (d, 1H), 7.66 (d, 1H), 7.56 (t, 1H), 7.43 (t, 1H), 7.10 (s, 1H), 3.71-3.67 (m, 4H), 3.38-3.33 (m, 4H), 2.54 (s, 3H), 1.50 (s, 9H).

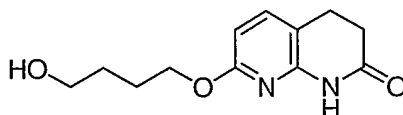


10 3-Methyl-1-piperazin-1-yl-isoquinoline Hydrochloride

An ice-cold solution of methanol (10 mL) was treated with acetyl chloride (0.8 mL, 11.3 mmol). After 15 minutes, this mixture was added to 4-(3-Methyl-
isoquinolin-1-yl)-piperazine-1-carboxylic acid tert-butyl ester (0.340 g, 1.04 mmol) and the resulting solution was stirred at room temperature for 2 hours. The mixture
15 was concentrated under vacuum, to afford 3-Methyl-1-piperazin-1-yl-isoquinoline Hydrochloride (0.274 g, quantitative), as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.51 (br s, 2H), 8.15 (d, 1H), 7.86 (d, 1H), 7.77 (t, 1H), 7.60 (t, 1H), 7.36 (s, 1H), 3.74-3.62 (m, 4H), 3.43-3.31 (m, 4H), 2.50 (s, 3H).

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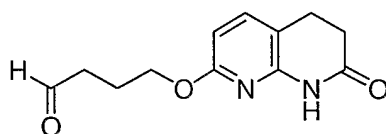
EXAMPLE 3



7-(4-Hydroxy-butoxy)-3,4-dihydro-1H-[1,8]naphthyridin-2-one

To 1.5 liters refluxing methanol was added 7-(4-Hydroxy-butoxy)-1H-[1,8]naphthyridin-2-one (87g). After 30 minutes, the mixture was allowed to cool to
25 22°C for 16 hours, followed by filtration through Celite to remove insoluble impurities. The pH of the filtrate was adjusted to 3 by addition of 2N HCl (2ml). This solution was added to a stainless steel hydrogenation vessel containing 10% palladium on carbon (PMC #1940C, 54% water, 30g) and hydrogenated at 34 psi for 48 hours. The catalyst

was removed by filtration through Celite, and the filtrate was concentrated to 100ml in volume under vacuum. The concentrate was diluted with a mixture of 1 liter of ethyl acetate and 200ml THF, and filtered again through Celite. The filtrate was washed sequentially with 20% potassium bicarbonate (800ml), brine, and dried over sodium sulfate. The suspension was filtered, concentrated to a crystalline solid and washed with a 50:50 mixture of ethyl acetate and hexane (100ml). The solid obtained from drying at 50°C under vacuum was 7-(4-Hydroxy-butoxy)-3,4-dihydro-1H-[1,8]naphthyridin-2-one, 75.8g, 87% yield, MP 103-106°C.



4-(7-Oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yloxy)-butyraldehyde

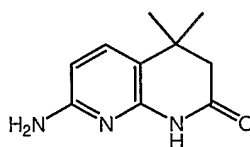
4-(7-Oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yloxy)-butyraldehyde, was produced using either a Dess-Martin oxidation reaction or a Swern oxidation reaction, as described below.

Dess-Martin oxidation: To a cloudy solution of the Dess-Martin periodinane (2.80 g, 6.60 mmol, 1.5 equiv) in CH₂Cl₂ (13 mL) was added a solution of 7-(4-hydroxy-butoxy)-3,4-dihydro-1H-[1,8]naphthyridin-2-one (1.04 g, 4.40 mmol) in CH₂Cl₂ (25 mL) via cannula. The reaction was stirred at room temperature for 5 h and stored in the freezer overnight. A 1:1 mixture of saturated Na₂S₂O₃ and saturated NaHCO₃ (50 mL) was added followed by ethyl ether (Et₂O). The mixture was stirred for 10 min and then extracted with Et₂O/EtOAc (2:1). The organic layer was washed with saturated NaHCO₃ and brine, dried over Na₂SO₄ and concentrated to give the title compound as a pale yellow oil (1.06 g, used crude in next reaction). MS: APCI: M+1: 235.1 (Exact Mass: 234.10).

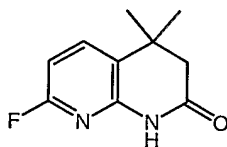
Swern oxidation: A solution of oxalyl chloride (9.97 mL, 112 mmol) in CH₂Cl₂ was cooled to -70 °C and DMSO (15.6 mL, 220 mmol) was carefully added. The solution was stirred at -60 °C for 10 min and then a solution of 7-(4-hydroxy-butoxy)-3,4-dihydro-1H-[1,8]naphthyridin-2-one (23 g, 97.5 mmol) in DMSO (70 mL) was added dropwise at -50~-60 °C. The reaction mixture was stirred at -60 °C for 20 min and then triethylamine (72 mL, 0.513 mol) was added dropwise. The reaction was warmed to room temp and stirred for 30 min. The mixture was poured into ice-water

and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 , combined with the organic phase, washed with brine, dried over Na_2SO_4 , and concentrated under vacuum to give the crude product. Purification by column chromatography (hexane:ethyl acetate 2:1) followed by recrystallization provided 4-(7-Oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yloxy)-butyraldehyde (12.7 g, 54.3 mmol, 56%).

EXAMPLE 4

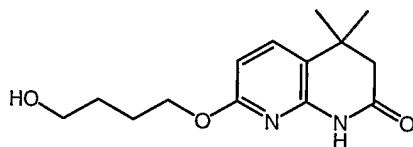
10 **7-Amino-4,4-dimethyl-3,4-dihydro-1H-[1,8]naphthyridin-2-one**

7-Amino-4,4-dimethyl-3,4-dihydro-1H-[1,8]naphthyridin-2-one, was produced as follows: 3-Methyl-but-3-enoic acid (6-amino-pyridin-2-yl)-amide (49.2 g, 0.26 mol) was dissolved in 500 mL CH_2Cl_2 in a 1000 mL 3-neck flask equipped with mechanical stirring, a 125 mL addition funnel and a thermal couple. While stirring, MeSO_3H (50 mL, 0.78 mol) was added to the flask dropwise. The exotherm upon addition was controlled to maintain a temperature $<20^\circ\text{C}$ by an ice/water bath. The mixture was allowed to stir for 15 minutes. AlCl_3 (274 g, 2.08 mol) was suspended in 1500 mL CH_2Cl_2 in a 5 L 4-neck flask equipped with mechanical stirring, 1000 mL addition funnel, N_2 line and a thermal couple. To this suspension, the amide solution was added dropwise. The exotherm from the addition was again controlled to maintain a temperature $<20^\circ\text{C}$ with an ice/water bath. The reaction was allowed to warm to room temperature and stir overnight. The reaction had consumed all the beta gamma unsaturated isomer and was deemed complete. The reaction mixture was slowly added to ice as an inverse quench. The quenched mixture was brought to pH 8-10 with 2 N KOH. The salts precipitated out of solution and saturated the aqueous phase. The suspension was transferred to a separatory funnel and extracted twice with 100:8:1 CH_2Cl_2 :EtOH: NH_4OH . The organic layers were combined, dried over Na_2SO_4 , filtered and concentrated to a crude solid. The solid was triturated with EtOAc and filtered. The resulting solid was 7-Amino-4,4-dimethyl-3,4-dihydro-1H-[1,8]naphthyridin-2-one (22.4 g, 0.117 mol, 46%). MS: APCI: $\text{M}+1$: 192.2 (Exact Mass: 191.11).



7-Fluoro-4,4-dimethyl-3,4-dihydro-1H-[1,8]naphthyridin-2-one

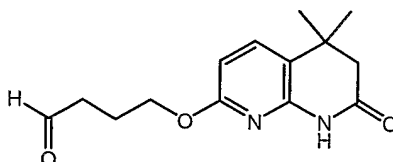
7-Fluoro-4,4-dimethyl-3,4-dihydro-1H-[1,8]naphthyridin-2-one, was produced as follows: HF-pyridine (100 mL) was cooled to -42°C in a 1000 mL HDPE bottle using an CH_3CN dry ice bath. While stirring vigorously, 7-amino-4,4-dimethyl-3,4-dihydro-1H-[1,8]naphthyridin-2-one (24.6 g, 0.129 mol) was added portionwise to control the exotherm. After the addition, NaNO_2 (8.9 g, 0.1291 mol) was added portionwise. Significant exotherms were observed for both additions. The reaction mixture was then allowed to warm to 0°C and stir for 2 h. The reaction mixture was quenched into a 4 L high density polyethylene (HDPE) bottle full of ice. The aqueous slurry was then neutralized using 2 N KOH. The resulting aqueous solution was extracted 3 times with CH_2Cl_2 . The organic layers were dried over Na_2SO_4 , filtered and concentrated to dryness. Excess pyridine was azeotroped with heptane. The product was dried under vacuum (2 mm Hg) for 3 h. The resulting product, 7-fluoro-4,4-dimethyl-3,4-dihydro-1H-[1,8]naphthyridin-2-one, was in the form of a white powder (23.06 g, 0.119 mol, 92%). MS: APCI: $\text{M}+1$: 195.1 (Exact Mass: 194.09).



7-(4-Hydroxy-butoxy)-4,4-dimethyl-3,4-dihydro-1H-[1,8]naphthyridin-2-one

7-(4-Hydroxy-butoxy)-4,4-dimethyl-3,4-dihydro-1H-[1,8]naphthyridin-2-one, was produced as follows: The 7-fluoro-4,4-dimethyl-3,4-dihydro-1H-[1,8]naphthyridin-2-one (5.09 g, 26.2 mmol) and butane-1,4-diol (11.81 g, 131.0 mmol) were combined in a dried 2-necked flask under N_2 . NMP (50 mL) was added and the solution was heated in an oil bath to 70°C overnight. The reaction was cooled to room temperature and poured into ice water. The solid that formed was collected and triturated in acetonitrile to give the title compound as a tan powder (1.72 g). The mother liquor was extracted with CH_2Cl_2 , dried over Na_2SO_4 , filtered and purified by medium pressure liquid chromatography (MPLC) (gradient of 100% CH_2Cl_2 to 100% ethyl acetate). The compound was isolated as a mixture with diol byproducts. 7-(4-

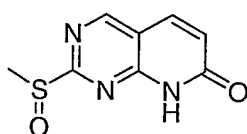
Hydroxy-butoxy)-4,4-dimethyl-3,4-dihydro-1H-[1,8]naphthyridin-2-one was formed as clear crystals for a total of 3.15 g (11.9 mmol, 45.5%). MS: APCI: M+1: 265.1 (Exact Mass: 264.15).



4-(5,5-Dimethyl-7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yloxy)-butyraldehyde

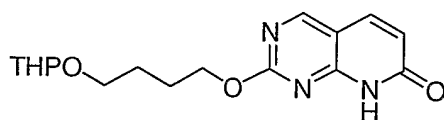
4-(5,5-Dimethyl-7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yloxy)-butyraldehyde, was produced as follows: 7-(4-Hydroxy-butoxy)-4,4-dimethyl-3,4-dihydro-1H-[1,8]naphthyridin-2-one (1.72 g, 6.51 mmol) was dissolved in ethyl acetate (50 mL, 0.14 M solution) and IBX (13 g, 46.4 mmol) was added. The suspension was immersed in an oil bath set at 80 °C and stirred vigorously with a condenser. After 1.5 h, the reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated to give 4-(5,5-Dimethyl-7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yloxy)-butyraldehyde as a tan solid (1.62 g, 6.18 mmol, 95%). MS: APCI: M+1: 263.1 (Exact Mass: 262.13).

EXAMPLE 5



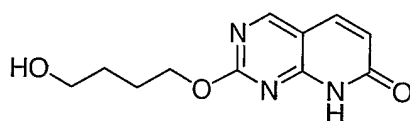
2-Methanesulfinyl-8H-pyrido[2,3-d]pyrimidin-7-one

To a suspension of 2-methylsulfonyl-8H-pyrido[2,3-d]pyrimidin-7-one (WO 9833798 A2, 5.0 g, 25.9 mmol) in CH₂Cl₂ (100 mL), CHCl₃ (50 mL) and MeOH (10 mL, the starting material still did not dissolve) was added the oxaziridine (8.11 g, 31.05 mmol, 1.2 equiv) as a solid. The reaction became homogenous after 3 h and was stirred overnight at RT. The reaction was concentrated and CH₂Cl₂/MeOH was added to dissolve the residue. Much of the solid did not dissolve so the mixture was filtered to give 2-Methanesulfinyl-8H-pyrido[2,3-d]pyrimidin-7-one, as an off-white solid (2.31 g, 11.04 mmol, 43%). MS: APCI: M+1: 210.1 (Exact Mass: 209.03).



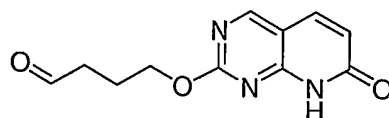
2-[4-(Tetrahydro-pyran-2-yloxy)-butoxy]-8H-pyrido[2,3-d]pyrimidin-7-one

To a solution of 4-(Tetrahydro-pyran-2-yloxy)-butan-1-ol (4.45 g, 25.3 mmol, 2.5 equiv) in THF (20 mL) cooled to 0 °C was added 1M potassium *tert*-butoxide (KO^tBu) in THF (25 mL, 25 mmol). The solution was stirred at 0 °C for 20 min and then added to a suspension of 2-methanesulfinyl-8H-pyrido[2,3-d]pyrimidin-7-one (2.12 g, 10.13 mmol) in DMF (30 mL) at RT. The reaction became homogenous and was stirred at RT for 1 h. Saturated NH₄Cl and H₂O were added to quench the reaction. The mixture was extracted with EtOAc. The organic layer was washed with H₂O and brine, dried over Na₂SO₄ and concentrated. Purification by liquid chromatography (70% EtOAc/Hexanes to 100% EtOAc) gave 2-[4-(Tetrahydro-pyran-2-yloxy)-butoxy]-8H-pyrido[2,3-d]pyrimidin-7-one, as a white solid (1.95 g, 6.11 mmol, 60%). MS: APCI: M+1: 320.2 (Exact Mass: 319.15).



2-(4-Hydroxy-butoxy)-8H-pyrido[2,3-d]pyrimidin-7-one

To a suspension of 2-[4-(tetrahydro-pyran-2-yloxy)-butoxy]-8H-pyrido[2,3-d]pyrimidin-7-one (1.95 g, 6.11 mmol) in EtOH (30 mL) and CH₂Cl₂ (2 mL, added to help dissolve the starting material) was added PPTS (151 mg, 0.6 mmol). The solution was stirred overnight at RT and then heated at 60 °C for 5 h. The reaction was concentrated to give a white solid. Purification by liquid chromatography (6% MeOH/CH₂Cl₂) gave 2-(4-Hydroxy-butoxy)-8H-pyrido[2,3-d]pyrimidin-7-one, as a white solid (1.22 g, 5.19 mmol, 85%). MS: APCI: M+1: 236.1 (Exact Mass: 235.10).

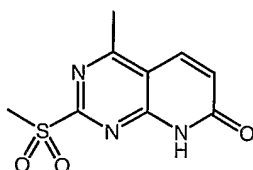


4-(7-Oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-yloxy)-butyraldehyde

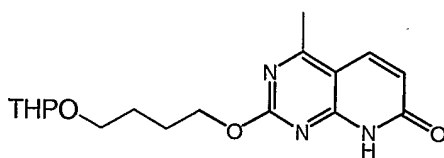
To a solution of 2-(4-hydroxy-butoxy)-8H-pyrido[2,3-d]pyrimidin-7-one (251 mg, 1.07 mmol) in DMSO (3 mL) was added a solution of IBX (597 mg, 2.13 mmol) in DMSO (7 mL, 0.3 M). The reaction was stirred at RT for 90 min, cooled to 0 °C and

quenched with 5% NaHCO₃. The mixture was extracted with CH₂Cl₂ (4x). The organic layer was washed with 5% NaHCO₃ and brine, dried over Na₂SO₄ and concentrated to give 4-(7-Oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-yloxy)-butyraldehyde, as a white solid (171 mg, 0.733 mmol, 69%). MS: APCI: M+1: 234.1
5 (Exact Mass: 233.08).

EXAMPLE 6

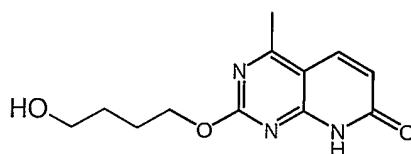
**2-Methanesulfonyl-4-methyl-8H-pyrido[2,3-d]pyrimidin-7-one**

10 A solution of 4-methyl-2-methylsulfanyl-8H-pyrido[2,3-d]pyrimidin-7-one (24 g, 0.1158 mol, US 6,498,163) in a mixture of CH₂Cl₂ (1.9 L) and methanol (300 mL) is treated with m-chloroperbenzoic acid (103 g, 60%, 0.345 mol) in portions at room temperature. The mixture is stirred for 24 h, cooled to ~5 °C and quenched with saturated sodium bicarbonate solution. The solids are filtered, washed thoroughly with
15 water followed by ether and dried in vacuum to give 2-Methanesulfonyl-4-methyl-8H-pyrido[2,3-d]pyrimidin-7-one, as a solid (10 g, 0.042 mol, 36%). MS: APCI: M+1: 240.0 (Exact Mass: 239.04).

**4-Methyl-2-[4-(tetrahydro-pyran-2-yloxy)-butoxy]-8H-pyrido[2,3-d]pyrimidin-7-one**

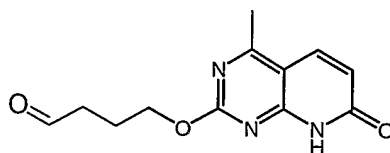
To an ice bath cooled solution of 4-(tetrahydro-pyran-2-yloxy)-butan-1-ol (27.3 g, 0.1567 mol) in dry THF (125 mL) is added drop wise a solution of KOtBu (1M, 155 mL, 0.155 mol) in THF within 15 min. The mixture is then stirred at 0 °C for 2 h. To
25 this mixture is added a suspension of 2-methanesulfonyl-4-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (15 g, 0.0627 mol) in DMF (225 mL) at RT within 15 min. The orange red colored reaction mixture is stirred at RT for 1.5 h, cooled and quenched with saturated NH₄Cl solution (150 mL) and water (2 L). The mixture is extracted with ethyl

acetate (2 x 0.75 L) and the organic layer is washed with brine (300 mL), dried over anhydrous sodium sulfate, filtered through a small bed of silica gel eluting with 5% methanol in ethyl acetate (750 mL) and concentrated. The residue is then triturated with hexane, filtered and dried to give 4-Methyl-2-[4-(tetrahydro-pyran-2-yloxy)-butoxy]-8H-pyrido[2,3-d]pyrimidin-7-one, as a white solid (16.5 g, 0.0495 mol 78%).
 MS: APCI: M+1: 334.0 (Exact Mass: 333.17).



2-(4-Hydroxy-butoxy)-4-methyl-8H-pyrido[2,3-d]pyrimidin-7-one

A mixture of 4-methyl-2-[4-(tetrahydro-pyran-2-yloxy)-butoxy]-8H-pyrido[2,3-d]pyrimidin-7-one (16.5 g, 0.049 mol) and PPTS (1.24 g, 0.0049 mol) in ethanol (250 mL) and CH₂Cl₂ (20 mL) is stirred at room temperature for 16 h, followed by heating at reflux (~90 °C) for 3 h. The cloudy reaction mixture is evaporated under vacuum and the residue is triturated in hexane-ethyl acetate (150 mL, 1:1) and dried to give 2-(4-Hydroxy-butoxy)-4-methyl-8H-pyrido[2,3-d]pyrimidin-7-one, as a yellow powder (12.5 g, 0.049 mol, 100%). MS: APCI: M+1: 250.0 (Exact Mass: 249.11).



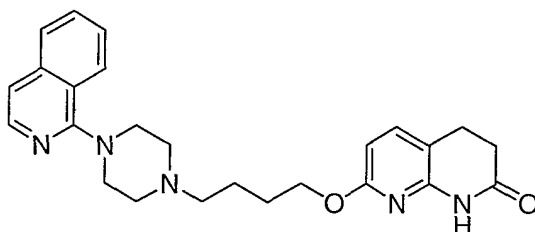
4-(4-Methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-yloxy)-butyraldehyde

A stirred solution of IBX (26 g, 0.092 mol) in DMSO (220 ml) is treated with 2-(4-hydroxy-butoxy)-4-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (11 g, 0.0467 mol) portion wise while stirring at RT during 30 min and the reaction is stirred at RT for an additional 2 h. The mixture is cooled and treated with saturated NaHCO₃ (150 mL) and extracted with chloroform (4 x 0.5 L). The combined organic layer is washed with brine/ice (2 x), dried over Na₂SO₄, filtered and concentrated. The residue is stirred with ether, filtered, washed with ether and dried to give 6 g of the crude, which shows it to be a mixture. The ether filtrate residue also shows some product, but mostly starting material. The residue from the filtrate and the crude (11 g) are subjected to re-oxidation as above using fresh IBX (15.5 g, 0.055 mol) in DMSO (150 mL), but stirred at 30 °C

for 3 h. Workup as above yielded 4-(4-Methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-yloxy)-butyraldehyde, as an off-white powder (8.3 g, 0.057 mol, 66.8%). MS: APCI: M+1: 248.0 (Exact Mass: 247.10).

5

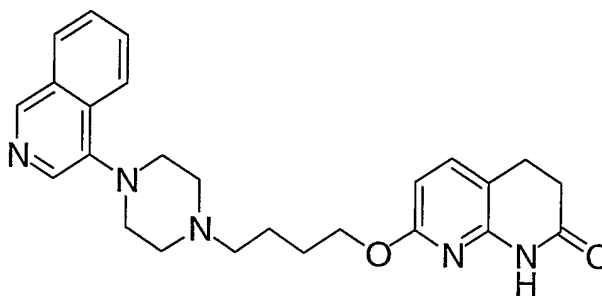
EXAMPLE 7



7-[4-(4-Isoquinolin-1-yl-piperazin-1-yl)-butoxy]-3,4-dihydro-1H-[1,8]naphthyridin-2-one

The dihydrochloride salt of 1-Piperazin-1-yl-isoquinoline (WO 98/42712),
10 (550mg, 1.92 mmol) was suspended in dichloroethane (10 mL). Triethylamine (1.04g, 10.3 mmol) was added and the mixture was stirred for 5 minutes. 4-(7-oxo-7,8-dihydro-[1,8]naphthyridin-2-yloxy)-butyraldehyde (665 mg, 2.84 mmol), produced as described in Example 1, above, was added, followed by addition of 0.3g 3 Angstrom molecular sieves. After stirring for 2 hours, Sodium triacetoxyborohydride (765mg, 3.61 mmol)
15 was added and the mixture was stirred for 18 hours. The mixture was quenched with water (20 mL), filtered, and the aqueous phase was adjusted to pH 6 by addition of 1N citric acid, agitated and decanted. The dichloromethane was again extracted with water adjusted to pH 3 by addition of 1N citric acid. The aqueous phase was adjusted to pH 13 by addition of 50% NaOH solution and extracted with dichloromethane. The
20 organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and evaporated. The crude solid was purified by column chromatography (dichloromethane / methanol / ethyl acetate) to yield the title compound (Yield: 520 mg, 46%) as a white foam, MS ES: m/z 432.3 (M+H)⁺ (Exact mass: 431.23).

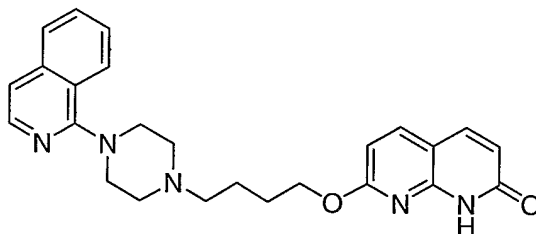
EXAMPLE 8



7-[4-(4-Isoquinolin-4-yl-piperazin-1-yl)-butoxy]-3,4-dihydro-1H-[1,8]naphthyridin-2-one

5 In a manner similar to Example 7, above, the dihydrochloride salt of 4-Piperazin-1-yl-isoquinoline (Chem. Pharm. Bull. **49**(10) 1313-1320 (2001)), and 4-(7-oxo-7,8-dihydro-[1,8]naphthyridin-2-yloxy)-butyraldehyde (Example 1, above) gave a crude solid that was purified by column chromatography (dichloromethane / methanol / ethyl acetate) to yield the title compound (Yield: 447mg, 64%) as a white solid, MS ES:
10 m/z 432.3 (M+H)⁺ (Exact mass: 431.23).

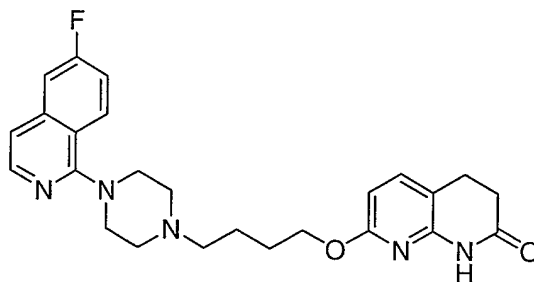
EXAMPLE 9



7-[4-(4-Isoquinolin-1-yl-piperazin-1-yl)-butoxy]-1H-[1,8]naphthyridin-2-one

15 In a similar manner, the dihydrochloride salt of 1-Piperazin-1-yl-isoquinoline (WO 98/42712), (700 mg, 2.4 mmol) and 4-(7-Oxo-7,8-dihydro-[1,8]naphthyridin-2-yloxy)-butyraldehyde (520 mg, 2.2 mmol) (Example 1, above) were dissolved in dichloroethane (10 mL). Triethylamine (1.0mg, 13 mmol) was added and the mixture was stirred for 5 minutes. Sodium triacetoxyborohydride (660 mg, 3.1 mmol) was
20 added and the mixture was stirred overnight. The mixture was quenched with water (20 mL) and extracted with dichloromethane (20 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated. The residue was purified by column chromatography. The crude residue was purified by column chromatography (dichloromethane/methanol/ethyl acetate) to yield the title compound (Yield: 443 mg,
25 46%) as a white solid, MS: APCI: M+1: 430.3 (Exact Mass: 429.22).

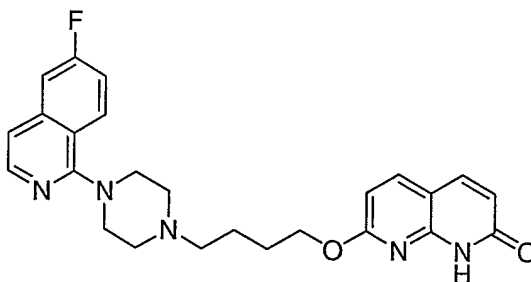
EXAMPLE 10



7-{4-[4-(6-Fluoro-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-3,4-dihydro-1H-[1,8]naphthyridin-2-one

- 5 6-Fluoro-1-piperazin-1-yl-isoquinoline trifluoroacetate salt (WO 98/42712), (515 mg, 1.28 mmol) and 4-(7-oxo-7,8-dihydro-[1,8]naphthyridin-2-yloxy)-butyraldehyde (300 mg, 1.28 mmol) were dissolved in dichloroethane (10 mL). Triethylamine (389 mg, 3.84 mmol) was added and the mixture was stirred for 5 minutes. Sodium triacetoxyborohydride (380 mg, 1.79 mmol) was added and the
- 10 mixture was stirred for 1.5 hours. The mixture was quenched with water (20 mL) and extracted with dichloromethane (20 mL). The organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and evaporated. The crude solid was purified by column chromatography (10:90 methanol / ethyl acetate) to yield the title compound (Yield: 410 mg, 71%) as a white solid, mp 57-59 °C, MS ES+ 450.22 (M+1)
- 15 ⁺ Exact Mass: 449.22.

EXAMPLE 11



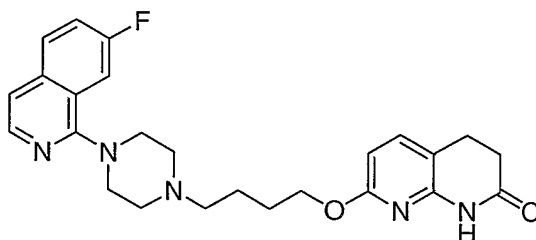
7-{4-[4-(6-Fluoro-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-1H-[1,8]naphthyridin-2-one

20

In a process similar to Example 10, above, 6-Fluoro-1-piperazin-1-yl-isoquinoline trifluoroacetate salt (WO 98/42712), (520 mg, 1.29 mmol) and 4-(7-Oxo-7,8-dihydro-[1,8]naphthyridin-2-yloxy)-butyraldehyde (300 mg, 1.29 mmol) (Example 1) were dissolved in dichloroethane (10 mL). Triethylamine (392 mg, 3.87 mmol) was

added and the mixture was stirred for 5 minutes. Sodium triacetoxyborohydride (383 mg, 1.81 mmol) was added and the mixture was stirred for 1.5 hours. The mixture was quenched with water (20 mL) and extracted with dichloromethane (20 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated. The residue was purified by column chromatography (10:90 methanol / ethyl acetate) to yield the title compound (Yield: 408 mg, 71%) as a beige solid, mp 79-181 °C MS ES+ 448.16 (M+1)⁺ Exact Mass: 447.2.

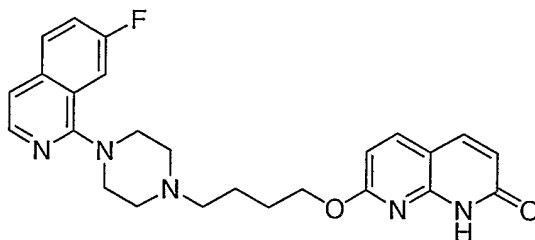
EXAMPLE 12



7-{4-[4-(7-Fluoro-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-3,4-dihydro-1H-[1,8]naphthyridin-2-one

7-Fluoro-1-piperazin-1-yl-isoquinoline trifluoroacetate salt (WO 98/42712), (250 mg, 1.08 mmol) and 4-(7-oxo-7,8-dihydro-[1,8]naphthyridin-2-yl)-butyraldehyde (253mg, 1.08 mmol) (Example 1) were dissolved in dichloroethane (10 mL). Triethylamine (219 mg, 2.16 mmol) was added and the mixture was stirred for 5 minutes. Sodium triacetoxyborohydride (321 mg, 1.51 mmol) was added and the mixture was stirred for 1.5 hours. The mixture was quenched with water (20 mL) and extracted with dichloromethane (20 mL). The organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and evaporated. The crude solid was purified by column chromatography (10:90 methanol / ethyl acetate) to yield the title compound (Yield: 402 mg, 83%) as a white solid, mp 63-65 °C, MS ES+ 450.19 (M+1)⁺, Exact Mass: 449.22.

EXAMPLE 13



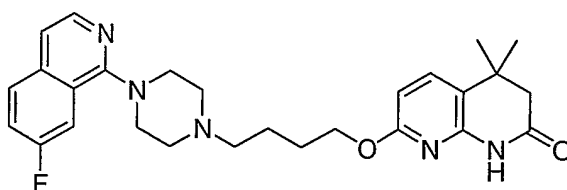
7-{4-[4-(7-Fluoro-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-1H-[1,8]naphthyridin-2-one

5 In a similar manner, 7-Fluoro-1-piperazin-1-yl-isoquinoline trifluoroacetate salt (WO 98/42712), (250 mg, 1.08 mmol) and 4-(7-Oxo-7,8-dihydro-[1,8]naphthyridin-2-yloxy)-butyraldehyde (251 mg, 1.08 mmol) (Example 1) were dissolved in dichloroethane (10 mL). Triethylamine (219 mg, 2.16 mmol) was added and the mixture was stirred for 5 minutes. Sodium triacetoxyborohydride (321 mg, 1.51 mmol)

10 was added and the mixture was stirred for 1.5 hours. The mixture was quenched with water (20 mL) and extracted with dichloromethane (20 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated. The residue was purified by column chromatography (10:90 methanol/ethyl acetate) to yield the title compound (Yield: 410 mg, 85%) as a white solid, mp 74-76 °C, MS ES+ 448.20 (M+1)⁺, Exact

15 Mass: 447.21.

EXAMPLE 14



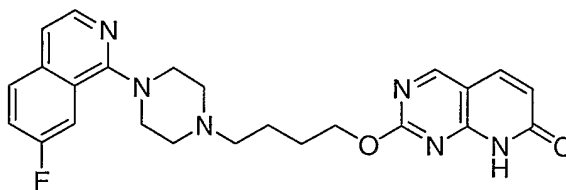
7-{4-[4-(7-Fluoro-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-4,4-dimethyl-3,4-dihydro-1H-[1,8]naphthyridin-2-one

20 7-Fluoro-1-piperazin-1-yl-isoquinoline trifluoroacetate salt (WO 98/42712), (263 mg, 0.82 mmol) and 4-(5,5-Dimethyl-7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yloxy)-butyraldehyde (210mg, 0.80mmol) (Example 4, above) were dissolved in dichloroethane (10 mL). Triethylamine (170 mg, 1.68 mmol) was added and the

25 mixture was stirred for 5 minutes. Sodium triacetoxyborohydride (237 mg, 1.12 mmol) was added and the mixture was stirred for 1.5 hours. The mixture was quenched with

water (20 mL) and extracted with dichloromethane (20 mL). The organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and evaporated. The crude solid was purified by column chromatography eluted with a gradient of dichloromethane to 10:90 methanol in ethyl acetate to yield the title compound (Yield: 148 mg, 39%, as a solid, mp 151 °C, MS: APCI: M+1: 478.4 (Exact mass: 477.25).

EXAMPLE 15

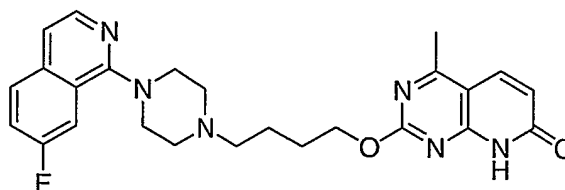


10 **2-{4-[4-(7-Fluoro-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-8H-pyrido[2,3-d]pyrimidin-7-one**

7-Fluoro-1-piperazin-1-yl-isoquinoline trifluoroacetate salt (WO 98/42712), (263 mg, 0.82 mmol) and 4-(7-Oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-yloxy)-butyraldehyde (187mg, 0.80mmol) (Example 5, above) were dissolved in dichloroethane (10 mL). Triethylamine (170 mg, 1.68 mmol) was added and the mixture was stirred for 5 minutes. Sodium triacetoxyborohydride (237 mg, 1.12 mmol) was added and the mixture was stirred for 1.5 hours. The mixture was quenched with water (20 mL) and extracted with dichloromethane (20 mL). The organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and evaporated. The crude solid was purified by column chromatography eluted with a gradient of dichloromethane to 100:8:1 dichloromethane:ethanol:concentrated ammonium hydroxide to yield the title compound (Yield: 280 mg, 78%, as a solid, mp 50 °C, MS: APCI: M+1: 449.2 (Exact mass: 448.20).

25

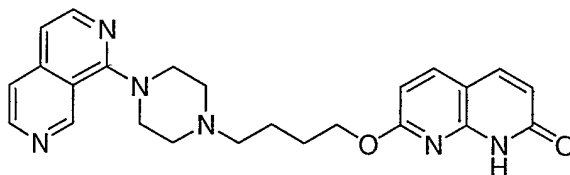
EXAMPLE 16



2-{4-[4-(7-Fluoro-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-4-methyl-8H-pyrido[2,3-d]pyrimidin-7-one

In a similar manner, 7-Fluoro-1-piperazin-1-yl-isoquinoline trifluoroacetate salt (WO 98/42712), (263 mg, 0.82 mmol) and 4-(4-Methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-yloxy)-butyraldehyde (197mg, 0.80mmol) (Example 6) were dissolved in dichloroethane (10 mL). Triethylamine (170 mg, 1.68 mmol) was added and the mixture was stirred for 5 minutes. Sodium triacetoxyborohydride (237 mg, 1.12 mmol) was added and the mixture was stirred for 1.5 hours. The mixture was quenched with water (20 mL) and extracted with dichloromethane (20 mL). The organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and evaporated. The crude solid was purified by column chromatography eluted with a gradient of dichloromethane to 100:8:1 dichloromethane: ethanol: concentrated ammonium hydroxide to yield the title compound (Yield: 261 mg, 71%, as a solid, MS: APCI: M+1: 463.1 (Exact mass: 462.22).

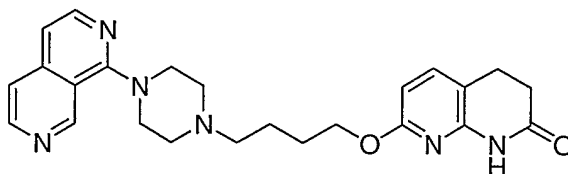
EXAMPLE 17



7-[4-(4-[2,7]Naphthyridin-1-yl)-piperazin-1-yl]-butoxy]-1H-[1,8]naphthyridin-2-one

To a mixture of 1-Piperazin-1-yl-[2,7]naphthyridine (U.S. Pat No 4,859,671, 0.29 g, 1.36 mmol), 4-(7-Oxo-7,8-dihydro-[1,8]naphthyridin-2-yloxy)-butyraldehyde (0.314 g, 1.36 mmol) (Example 1), and 1-methyl-2-pyrrolidinone (15 mL) was added NaBH(OAc)₃ (0.35 g, 1.63 mmol,) in portions, over 20 min. After the addition was over, the mixture was left stirring overnight. After quenching with H₂O (50 mL), the reaction mixture was extracted with CH₂Cl₂ (3 x 100 mL). The combined organic phases were washed with brine (100 mL), dried and concentrated. The residue was purified by chromatography on silica gel to give the title compound (310 mg) as a white solid. MS: 431 (M⁺+1), Exact Mass: 430.21.

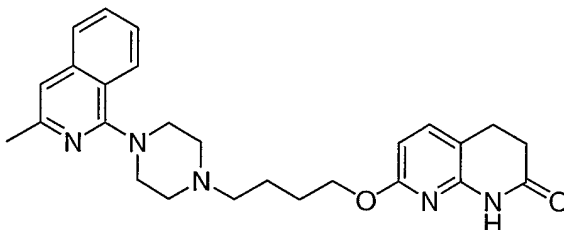
EXAMPLE 18



7-[4-(4-[2,7]Naphthyridin-1-yl-piperazin-1-yl)-butoxy]-3,4-dihydro-1H-[1,8]naphthyridin-2-one

5 In a manner similar to that above, 1-Piperazin-1-yl-[2,7]naphthyridine (U.S.4,859,671, 0.36 g) and 4-(7-Oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yloxy)-butyraldehyde (Example 3) gave the title compound, 0.60g.

EXAMPLE 19



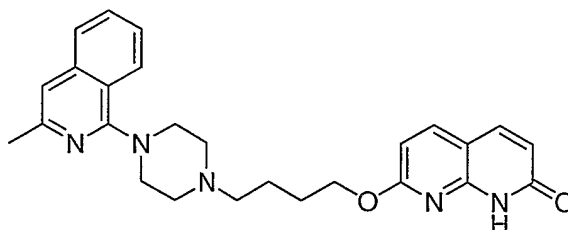
7-{4-[4-(3-Methyl-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-3,4-dihydro-1H-[1,8]naphthyridin-2-one

10 4-(7-oxo-7,8-dihydro-[1,8]naphthyridin-2-yloxy)-butyraldehyde (0.21g, 0.90 mmol) (Example 1) and the hydrochloride salt of 3-Methyl-1-piperazin-1-yl-isoquinoline (260mg, 0.99 mmol) (Example 2), were suspended in dichloroethane (20 mL). Triethylamine (0.25ml, 1.79 mmol) was added followed by sodium triacetoxyborohydride (0.266 g, 1.26 mmol). The yellow solution was stirred at room temperature for 1 hour, then quenched with water and extracted with dichloromethane. The extracts were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a yellow oil. The oil was purified by column chromatography (methanol:ethyl acetate, 3:97) to yield the title compound (0.351 g, 88%), as a light yellow solid, mp 65-68 °C. ES MS: 446.42 (M⁺).

15

20

EXAMPLE 20



7-{4-[4-(3-Methyl-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-1H-[1,8]naphthyridin-2-one

5 In a similar manner, the hydrochloride salt of 3-Methyl-1-piperazin-1-yl-isoquinoline, (0.250 g, 0.95 mmol) (Example 2) and 4-(7-Oxo-7,8-dihydro-[1,8]naphthyridin-2-yloxy)-butyraldehyde (0.200g, 0.86 mmol) (Example 1) were dissolved in dichloroethane (10 mL). Triethylamine (0.25mL, 1.79mmol) was added, followed by sodium triacetoxymethylborohydride (0.255g, 1.20mmol). The yellow mixture
10 was stirred at room temperature for 1 hour, then quenched with water and extracted with dichloromethane. The extracts were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a yellow oil. The oil was purified by column chromatography (1:9 methanol:ethyl acetate) to yield the title compound (0.235 g, 62 %), as a light yellow foam, mp 85-87 °C. ES MS: 444.37 (M⁺).

15

EXAMPLE 21

Dopamine D₂ Receptor Binding Assay:

The compounds produced as described in Examples 7-21, above were each tested in a Dopamine D₂ Receptor Binding Assay, as follows.

20 [³H]Spiperone binding to a membrane preparation from CHO-hD₂L cells was carried out in 250 μl of 50 mM Tris-HCl buffer containing 100 mM NaCl, 1 mM MgCl₂ and 1% DMSO at pH 7.4. Duplicate samples containing (in order of addition) the test compounds, 0.4 nM [³H]spiperone and approximately 12 μg protein were incubated for 120 minutes at room temperature. Bound radioligand was separated by
25 rapid filtration under reduced pressure through Whatman GF/B glass fiber filters previously treated with 0.3% polyethyleneimine. Radioactivity retained on the filter is determined by liquid scintillation spectrophotometry.

Specific binding was determined in the presence of 1 mM haloperidol was 95%. See Table 1, below, for results obtained from each of the compounds tested.

TABLE 1

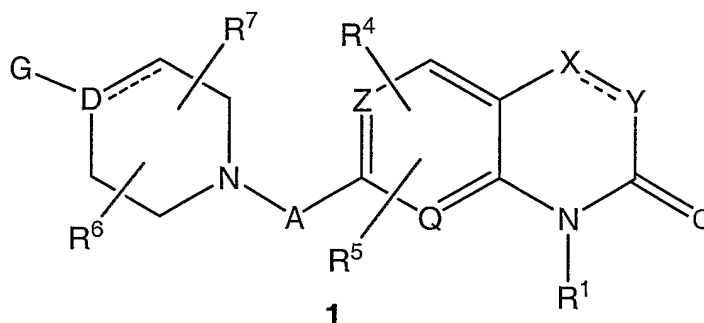
EXAMPLE	COMPOUND	D ₂ Ki (nM)
7	7-[4-(4-Isoquinolin-1-yl-piperazin-1-yl)-butoxy]-3,4-dihydro-1H-[1,8]naphthyridin-2-one	8.49
8	7-[4-(4-Isoquinolin-4-yl-piperazin-1-yl)-butoxy]-3,4-dihydro-1H-[1,8]naphthyridin-2-one	4.00
9	7-[4-(4-Isoquinolin-1-yl-piperazin-1-yl)-butoxy]-1H-[1,8]naphthyridin-2-one	1.00
10	7-{4-[4-(6-Fluoro-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-3,4-dihydro-1H-[1,8]naphthyridin-2-one	2.34
11	7-{4-[4-(6-Fluoro-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-1H-[1,8]naphthyridin-2-one	1.00
12	7-{4-[4-(7-Fluoro-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-3,4-dihydro-1H-[1,8]naphthyridin-2-one	2.49
13	7-{4-[4-(7-Fluoro-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-1H-[1,8]naphthyridin-2-one	2.45
14	7-{4-[4-(7-Fluoro-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-4,4-dimethyl-3,4-dihydro-1H-[1,8]naphthyridin-2-one	9.74
15	2-{4-[4-(7-Fluoro-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-8H-pyrido[2,3-d]pyrimidin-7-one	19.97
16	2-{4-[4-(7-Fluoro-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-4-methyl-8H-pyrido[2,3-d]pyrimidin-7-one	9.49
17	7-[4-(4-[2,7]Naphthyridin-1-yl-piperazin-1-yl)-butoxy]-1H-[1,8]naphthyridin-2-one	15.49
18	7-[4-(4-[2,7]Naphthyridin-1-yl-piperazin-1-yl)-butoxy]-3,4-dihydro-1H-[1,8]naphthyridin-2-one	10.95
19	7-{4-[4-(3-Methyl-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-3,4-dihydro-1H-[1,8]naphthyridin-2-one	17.70
20	7-{4-[4-(3-Methyl-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-1H-[1,8]naphthyridin-2-one	7.59

All of the compounds tested in this assay, as described above exhibited K_i values less 20 nM.

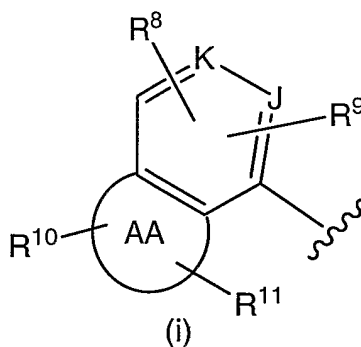
CLAIMS

What is claimed is:

1. A compound of formula **1**



- 5 wherein G is as shown in formula (i), below:



- A is $-(CH_2)_nO-$ wherein n is 4 or 5, and one or two of the carbon atoms of $-(CH_2)_nO-$ can be substituted, optionally and independently, with one or two substituents that are selected, independently, from fluoro and methyl, or with two substituents attached to the same carbon atom that form, together with the carbon to which they are attached, a spirocyclopropyl or spirocyclobutyl ring;

D is N, C, or CH, provided that when D is N, each carbon atom covalently attached to D is attached through a single bond;

- J and K are independently selected from N, CH, or C, provided that at least one of J and K is N;

Z and Q are independently selected from N or CH, provided that at least one of Z and Q is N;

R¹ is hydrogen, $-C(=O)CH_3$, or (C_1-C_3) alkyl;

- $-X-Y-$ is $-CH_2-CH_2-$, $-CH=CH-$, $-CH_2-NH-$, $-NH-CH_2-$, $-N=CH-$, $-CH=N-$, $-O-CH_2-$, or $-CH_2-O-$, wherein $-X-Y-$ can optionally be substituted, at any available bonding site, by one to four substituents R², R^{2'}, R³ and R^{3'};

R^2 , $R^{2'}$, R^3 and $R^{3'}$ are independently selected from hydrogen, halo, cyano, oxo, hydroxy, $-C(=O)CH_3$, (C_1-C_4) alkyl, and (C_1-C_4) alkoxy, wherein the alkyl moieties of the (C_1-C_4) alkyl, (C_1-C_4) alkoxy, and $-C(=O)CH_3$ groups can be optionally substituted with from one to three fluoro atoms and can also be optionally substituted with an

5 amino or hydroxy substituent;

R^4 and R^5 are independently selected from hydrogen, halo, cyano, hydroxy, $-C(=O)CH_3$, (C_1-C_4) alkyl, and (C_1-C_4) alkoxy, wherein the alkyl moieties of the (C_1-C_4) alkyl, (C_1-C_4) alkoxy, and $-C(=O)CH_3$ groups can be optionally substituted with from one to three fluoro atoms and can also be optionally substituted with an amino or

10 hydroxy substituent;

R^6 and R^7 are selected, independently, from hydrogen and methyl;

R^8 , R^9 , R^{10} and R^{11} are independently selected from hydrogen, halo, $-C(=O)CH_3$, (C_1-C_4) alkyl, and (C_1-C_4) alkoxy, wherein the alkyl moieties of the (C_1-C_4) alkyl, (C_1-C_4) alkoxy, and $-C(=O)CH_3$ groups can be optionally substituted with from one to three

15 fluoro atoms and can also be optionally substituted with an amino or hydroxy substituent;

ring AA is a saturated or unsaturated 5- 6- or 7-membered carbocyclic ring wherein one, two or three of the carbon atoms of ring AA that are not shared with the other fused ring of formula (i) can be replaced, optionally and independently, by a

20 nitrogen, oxygen or sulfur atom;

and the pharmaceutically acceptable salts thereof.

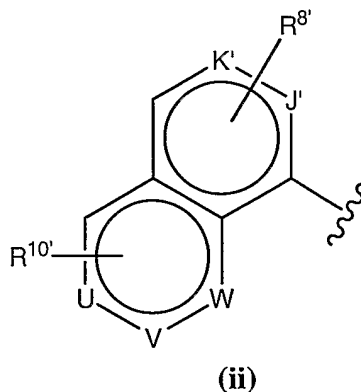
2. The compound or salt according to claim 1, wherein ring AA is a 6-membered unsaturated carbocyclic ring.

25 3. The compound or salt according to claim 1, wherein A is $-(CH_2)_4O-$.

4. The compound or salt according to claim 1, wherein $-X---Y-$ is $-CH_2NH-$, $-CH_2-CH_2-$ or $-CH=CH-$.

30 5. The compound or salt according to claim 1, wherein R^4 , R^5 , R^{10} , and R^{11} are independently hydrogen or fluoro.

6. The compound or salt according to claim 1, wherein G is as shown formula (ii):



where K' and J' are independently N, CH, or C, provided that at least one of K' or J' is N;

- 5 R^{8'} is H, (C₁-C₄) alkyl, or (C₁-C₄) alkoxy;

R^{10'} is H, (C₁-C₄) alkyl, or (C₁-C₄) alkoxy, or halo; and

U, V, and W are independently N, CH, or C, provided that no more than two of U, V, and W are N.

- 10 7. The compound or salt according to claim 1, selected from the group consisting of:

7-[4-(4-Isoquinolin-1-yl)-piperazin-1-yl]-butoxy]-3,4-dihydro-1H-[1,8]naphthyridin-2-one;

- 15 7-[4-(4-Isoquinolin-4-yl)-piperazin-1-yl]-butoxy]-3,4-dihydro-1H-[1,8]naphthyridin-2-one;

7-[4-(4-Isoquinolin-1-yl)-piperazin-1-yl]-butoxy]-1H-[1,8]naphthyridin-2-one;

7-{4-[4-(6-Fluoro-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-3,4-dihydro-1H-[1,8]naphthyridin-2-one;

- 20 7-{4-[4-(6-Fluoro-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-1H-[1,8]naphthyridin-2-one;

7-{4-[4-(7-Fluoro-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-3,4-dihydro-1H-[1,8]naphthyridin-2-one;

- 25 7-{4-[4-(7-Fluoro-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-1H-[1,8]naphthyridin-2-one;

7-{4-[4-(7-Fluoro-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-4,4-dimethyl-3,4-dihydro-1H-[1,8]naphthyridin-2-one;

- 2-{4-[4-(7-Fluoro-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-8H-pyrido[2,3-d]pyrimidin-7-one;
- 2-{4-[4-(7-Fluoro-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-4-methyl-8H-pyrido[2,3-d]pyrimidin-7-one;
- 5 7-[4-(4-[2,7]Naphthyridin-1-yl)-piperazin-1-yl]-butoxy]-1H-[1,8]naphthyridin-2-one;
- 7-[4-(4-[2,7]Naphthyridin-1-yl)-piperazin-1-yl]-butoxy]-3,4-dihydro-1H-[1,8]naphthyridin-2-one;
- 7-{4-[4-(3-Methyl-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-3,4-dihydro-1H-[1,8]naphthyridin-2-one;
- 10 7-[4-[4-(3-Methyl-isoquinolin-1-yl)-piperazin-1-yl]-butoxy]-1H-[1,8]naphthyridin-2-one;
- 7-[4-(4-[1,6]Naphthyridin-8-yl)-piperazin-1-yl]-butoxy]-3,4-dihydro-1H-[1,8]naphthyridin-2-one;
- 15 7-[4-(4-[1,6]Naphthyridin-8-yl)-piperazin-1-yl]-butoxy]-1H-[1,8]naphthyridin-2-one;
- 7-[4-(4-[1,6]Naphthyridin-8-yl)-piperazin-1-yl]-butoxy]-1H-[1,8]naphthyridin-2-one;
- 7-{4-[4-(7-Fluoro-3-methyl-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-3,4-dihydro-1H-[1,8]naphthyridin-2-one;
- 20 7-{4-[4-(7-Fluoro-3-methyl-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-1H-[1,8]naphthyridin-2-one;
- 7-{4-[4-(6-Fluoro-3-methyl-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-3,4-dihydro-1H-[1,8]naphthyridin-2-one;
- 25 7-{4-[4-(6-Fluoro-3-methyl-isoquinolin-1-yl)-piperazin-1-yl]-butoxy}-1H-[1,8]naphthyridin-2-one;
- 7-[4-(4-[1,7]Naphthyridin-8-yl)-piperazin-1-yl]-butoxy]-3,4-dihydro-1H-[1,8]naphthyridin-2-one
- 7-[4-(4-[1,7]Naphthyridin-8-yl)-piperazin-1-yl]-butoxy]-1H-[1,8]naphthyridin-2-one;
- 30 one;
- 7-[4-(4-Thieno[2,3-c]pyridin-7-yl)-piperazin-1-yl]-butoxy]-3,4-dihydro-1H-[1,8]naphthyridin-2-one; and

7-[4-(4-Thieno[2,3-c]pyridin-7-yl-piperazin-1-yl)-butoxy]-1H-[1,8]naphthyridin-2-one.

8. A pharmaceutical composition, comprising:
- 5 (a) a compound according to claim 1, or a pharmaceutically acceptable salt thereof, and
- (b) a pharmaceutically acceptable carrier.
9. A pharmaceutical composition useful for treating a disorder or condition in a
- 10 mammal, comprising:
- (a) a compound according to claim 1, or a pharmaceutically acceptable salt thereof; and
- (b) an antidepressant or an anti-anxiety agent, or a pharmaceutically acceptable salt thereof;
- 15 wherein the disorder or condition is selected from the group consisting of single episodic or recurrent major depressive disorders, dysthymic disorders, depressive neurosis and neurotic depression, melancholic depression; atypical depression; bipolar disorder; cyclothymic disorder; conduct disorder; disruptive behavior disorder; attention deficit hyperactivity disorder; behavioral disturbances associated with mental
- 20 retardation, autistic disorder, and conduct disorder; anxiety disorders; borderline personality disorder; schizophrenia and other psychotic disorders; delirium, dementia, and amnestic and other cognitive or neurodegenerative disorders; movement disorders, dyskinesias; extra-pyramidal movement disorders; chemical dependencies and
- additions; behavioral addictions; and ocular disorders, and wherein the compound and
- 25 the antidepressant or anti-anxiety agent, or pharmaceutically acceptable salts thereof, are present in amounts that render the combination effective in treating such disorder or condition.
10. A method for treating a disorder or condition in a mammal, comprising
- 30 administering to the mammal an effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein the disorder or condition is selected from the group consisting of single episodic or recurrent major depressive disorders, dysthymic disorders, depressive neurosis and neurotic depression,

- melancholic depression; atypical depression; bipolar disorder; cyclothymic disorder; conduct disorder; disruptive behavior disorder; attention deficit hyperactivity disorder; behavioral disturbances associated with mental retardation, autistic disorder, and conduct disorder; anxiety disorders; borderline personality disorder; schizophrenia and other psychotic disorders; delirium, dementia, and amnestic and other cognitive or neurodegenerative disorders; movement disorders, dyskinesias; extra-pyramidal movement disorders; chemical dependencies and additions; behavioral addictions; and ocular disorders.
11. The method according to claim 10, wherein the disorder or condition is selected from the group consisting of schizophrenia, schizoaffective disorder, delusional disorder, substance-induced psychotic disorder, brief psychotic disorder, shared psychotic disorder, psychotic disorder due to a general medical condition, and schizophreniform disorder.
12. A compound according to claim 1 for use as a medicament.
- 13, A compound according to claim 1 for use in the treatment of a disorder or condition selected from the group consisting of single episodic or recurrent major depressive disorders, dysthymic disorders, depressive neurosis and neurotic depression, melancholic depression; atypical depression; bipolar disorder; cyclothymic disorder; conduct disorder; disruptive behavior disorder; attention deficit hyperactivity disorder; behavioral disturbances associated with mental retardation, autistic disorder, and conduct disorder; anxiety disorders; borderline personality disorder; schizophrenia and other psychotic disorders; delirium, dementia, and amnestic and other cognitive or neurodegenerative disorders; movement disorders, dyskinesias; extra-pyramidal movement disorders; chemical dependencies and additions; behavioral addictions; and ocular disorders.
14. A composition comprising a compound according to claim 1 for use as a medicament.

15. A composition comprising a compound according to claim 1 for use in the treatment of a disorder or condition selected from the group consisting of single episodic or recurrent major depressive disorders, dysthymic disorders, depressive neurosis and neurotic depression, melancholic depression; atypical depression; bipolar disorder; cyclothymic disorder; conduct disorder; disruptive behavior disorder; attention deficit hyperactivity disorder; behavioral disturbances associated with mental retardation, autistic disorder, and conduct disorder; anxiety disorders; borderline personality disorder; schizophrenia and other psychotic disorders; delirium, dementia, and amnestic and other cognitive or neurodegenerative disorders; movement disorders, dyskinesias; extra-pyramidal movement disorders; chemical dependencies and additions; behavioral addictions; and ocular disorders.

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2006/000476

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D471/04 C07D519/00 A61K31/4375 A61P25/24 A61P25/16

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BIOSIS, EMBASE, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
A	KIKUCHI T ET AL: "PHARMACOLOGICAL PROFILE OF CPC-14597, A NOVEL ANTI-PSYCHOTIC DRUG (1): PRESYNAPTIC DOPAMINE AUTORECEPTOR AGONISTIC ACTIVITY AND POSTSYNAPTIC DOPAMINE D2 RECEPTOR ANTAGONISTIC ACTIVITY" JAPANESE JOURNAL OF PHARMACOLOGY, THE JAPANESE PHARMACOLOGICAL SOCIETY, KYOTO, JP, vol. 67, no. SUPPL 1, 1995, pages 144P, ANP1-235, XP008005977 ISSN: 0021-5198 the whole document	1-15
A	EP 0 367 141 A (OTSUKA PHARMACEUTICAL CO., LTD) 9 May 1990 (1990-05-09) claim 1 ----- -/-	1-15



Further documents are listed in the continuation of Box C



See patent family annex.

* Special categories of cited documents

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

19 July 2006

Date of mailing of the international search report

08/08/2006

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INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2006/000476

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ORJALES A ET AL: "New 3-benzisothiazolyl and 3-benzisoxazolylpiperazine derivatives with atypical antipsychotic binding profile" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, EDITIONS SCIENTIFIQUE ELSEVIER, PARIS, FR, vol. 37, no. 9, September 2002 (2002-09), pages 721-730, XP004383155 ISSN: 0223-5234 page 721, left-hand column, paragraph 2; figure 2; table 1; compound 19	1-15
A	MCCORT G ET AL: "Synthesis and SAR of 3- and 4-substituted quinolin-2-ones: discovery of mixed 5-HT(1B)/5-HT(2A) receptor antagonists." BIOORGANIC & MEDICINAL CHEMISTRY. AUG 2001, vol. 9, no. 8, August 2001 (2001-08), pages 2129-2137, XP002391169 ISSN: 0968-0896 page 2133, left-hand column, paragraph 2; tables 2,3	1-15
P,A	WO 2005/019215 A (WARNER-LAMBERT COMPANY LLC; CLARK, JERRY; DAVIS, JAMIE; FAVOR, DAVID;) 3 March 2005 (2005-03-03) claims; example A1	1-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2006/000476

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

Although claims 10,11 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6 4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2006/000476

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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			DE 68925405 T2	27-06-1996
			DE 122004000043 I1	03-02-2005
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			HK 1002706 A1	11-09-1998
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WO 2005019215	A	03-03-2005	AU 2004266191 A1	03-03-2005
			CA 2538915 A1	03-03-2005
			EP 1660497 A1	31-05-2006
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			NL 1026892 A1	28-02-2005
