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(54) Title: HYDROXYQUINOLIN-2(1H)-ONES AND DERIVATIVES THEREOF

(57) Abstract: This invention relates to known and novel hydroxyquinolin-2(1*H*)-ones and derivatives thereof which are useful for the treatment of cognitive-related disorders and neuropathic pain disorders in a mammal, e.g., a human. The invention also relates to pharmaceutical compositions containing such compounds.

HYDROXYQUINOLIN-2(1H)-ONES AND DERIVATIVES THEREOF

Field of the Invention

This invention relates to novel compounds useful for the treatment of cognitive-related disorders and neuropathic pain disorders in a mammal, e.g., a human. The invention also relates to pharmaceutical compositions containing such compounds.

Background of the Invention

The enzyme D-amino acid oxidase (DAAO) metabolizes D-amino acids, and in particular, metabolizes D-serine in vitro at physiological pH. DAAO is expressed in the mammalian brain and periphery. D-Serine's role as a neurotransmitter is important in the activation of the N-methyl-D-aspartate (NMDA) selective subtype of the glutamate receptor, an ion channel expressed in neurons, here denoted as NMDA receptor. Small organic molecules, which inhibit the enzymatic cycle of DAAO, may control the levels of D-serine, and thus influence the activity of the NMDA receptor in the brain. NMDA receptor activity is important in a variety of disease states, such as schizophrenia, psychosis, ataxias, ischemia, several forms of pain including neuropathic pain, and deficits in memory and cognition.

Small organic molecules that inhibit the enzymatic cycle of DAAO may also control production of toxic metabolites of D-serine oxidation, such as hydrogen peroxide and ammonia. Thus, these molecules may influence the progression of cell loss in neurodegenerative disorders. Neurodegenerative diseases are diseases in which central nervous system (CNS) neurons and/or peripheral neurons undergo a progressive loss of function, usually accompanied by (and perhaps caused by) a physical deterioration of the structure of either the neuron itself or its interface with other neurons. Such conditions include Parkinson's disease, Alzheimer's disease, Huntington's disease and neuropathic pain. N-methyl-D-aspartate (NMDA)-glutamate receptors are expressed at excitatory synapses throughout the CNS. These receptors mediate a wide range of brain processes, including synaptic plasticity, that are associated with certain types of memory formation and

learning. NMDA-glutamate receptors require binding of two agonists to effect neurotransmission. One of these agonists is the excitatory amino acid L-glutamate, while the second agonist, at the so-called "strychnine-insensitive glycine site", is now thought to be D-serine. In animals, D-serine is synthesized from L-serine by serine racemase and degraded to its corresponding ketoacid by DAAO. Together, serine racemase and DAAO are thought to play a crucial role in modulating NMDA neurotransmission by regulating CNS concentrations of D-serine.

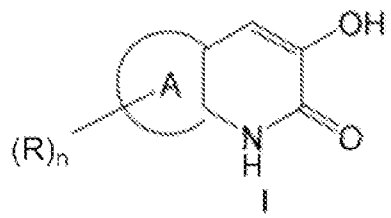
Several DAAO inhibitors are known in the literature including aminopyrazolines such as WO 2007/093829, fused bicyclics such as WO 2008/089453, WO 2008/005456, WO2007/039773 and US 7,166,725.

Certain fused bicyclic glycine receptor antagonists have also been disclosed including WO 96/04288 and US 5,597,922.

The present inventors have now discovered a group of very potent small molecules with selective DAAO inhibitory activity.

Summary of the Invention

The present invention relates to a method of treating a disorder or condition that can be treated by inhibiting D-amino acid oxidase (DAAO) activity in a mammal, preferably a human, in need of such treatment comprising administering to said mammal an effective amount of a compound of formula



I

wherein ring "A" is a 6 membered aryl or 5 or 6 membered heteroaryl ring; wherein said 6 membered heteroaryl ring has one nitrogen heteroatom and wherein said 5 membered heteroaryl ring has one or two heteroatoms selected from N, O or S;

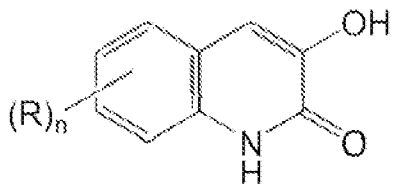
each R is independently selected from the group consisting of hydrogen, chloro, fluoro, bromo, methyl, ethyl, methoxy, ethoxy,

trifluoromethyl, and cyano (wherein R is a substituent on either ring of the hydroxy quinolinone nucleus);

n is an integer selected from the group consisting of zero, one, two or three; or a pharmaceutically acceptable salt thereof.

The present invention further relates to a method of enhancing cognition in a mammal, preferably a human, comprising administering to said mammal an effective amount of a compound of formula I

One embodiment of the methods of the invention relates to compounds of formula



Ia

Another embodiment of the methods of the invention relates to compounds of the formula I wherein ring "A" is a 6 membered heteroaryl ring; containing one nitrogen heteroatom.

Another embodiment of the methods of the invention relates to compounds of the formula I wherein ring "A" is a 5 membered heteroaryl ring; containing one heteroatom selected from N, O or S.

Another embodiment of the methods of the invention relates to compounds of the formula I wherein ring "A" is a 5 membered heteroaryl ring; containing two heteroatoms wherein the first heteroatom is selected from N, O or S and the second heteroatom is N.

The present methods also relates to a group of compounds of formula I wherein said compound is selected from the group consisting of:

6-chloro-3-hydroxyquinolin-2(1H)-one;

3-hydroxy-6,8-dimethylquinolin-2(1H)-one;

3-hydroxy-6-methylquinolin-2(1H)-one;

3-hydroxy-8-methylquinolin-2(1H)-one;

6-fluoro-3-hydroxyquinolin-2(1H)-one;

7-chloro-3-hydroxyquinolin-2(1H)-one;

3-hydroxyquinolin-2(1H)-one;

8-chloro-3-hydroxyquinolin-2(1H)-one;

3-hydroxy-1,8-naphthyridin-2(1H)-one;

3-hydroxy-4-methylquinolin-2(1H)-one;

3-hydroxy-6-methoxyquinolin-2(1H)-one;

5,7-dichloro-3-hydroxyquinolin-2(1H)-one; and

5,6-dichloro-3-hydroxyquinolin-2(1H)-one;

and the pharmaceutically acceptable salts of such compounds.

The present invention also relates to the following compounds *per se* and to the method of using said compounds for the treatment of a disorder or condition that can be treated by inhibiting D-amino acid oxidase (DAAO) activity in a mammal, perferably a human, in need of such treatment:

7-fluoro-3-hydroxyquinolin-2(1*H*)-one;

5-chloro-6-fluoro-3-hydroxyquinolin-2(1*H*)-one;

7-ethyl-3-hydroxyquinolin-2(1*H*)-one;

4-fluoro-3-hydroxyquinolin-2(1*H*)-one;

4,8-difluoro-3-hydroxyquinolin-2(1*H*)-one;

3-hydroxy-1,5-naphthyridin-2(1*H*)-one;

3-hydroxy-1,7-naphthyridin-2(1*H*)-one;

3-hydroxy-1,6-naphthyridin-2(1*H*)-one;

5-hydroxy-1-methyl-1,7-dihydro-6*H*-pyrazolo[3,4-*b*]pyridin-6-one;

6-hydroxythieno[3,2-*b*]pyridin-5(4*H*)-one;

8-fluoro-3-hydroxyquinolin-2(1*H*)-one;

3-hydroxy-7-methylquinolin-2(1*H*)-one;

4-bromo-7-chloro-3-hydroxyquinolin-2(1*H*)-one;

6,7-dichloro-3-hydroxyquinolin-2(1*H*)-one;

7,8-dichloro-3-hydroxyquinolin-2(1*H*)-one;

7-chloro-3-hydroxy-8-methylquinolin-2(1*H*)-one;

3-hydroxy-4-methyl-1,8-naphthyridin-2(1*H*)-one;

6-hydroxyfuro[3,2-b]pyridin-5(4*H*)-one;

5-fluoro-3-hydroxyquinolin-2(1*H*)-one;

3-hydroxy-5-methylquinolin-2(1*H*)-one;
5-chloro-3-hydroxyquinolin-2(1*H*)-one;
3-hydroxypyrrolo[1,2-b]pyridazin-2(1H)-one;
5-hydroxyfuro[2,3-b]pyridin-6(7H)-one;
5-hydroxyisoxazolo[5,4-b]pyridin-6(7H)-one;
6-hydroxyisoxazolo[4,5-b]pyridin-5(4H)-one;
5-hydroxyisoxazolo[3,4-b]pyridin-6(7H)-one;
6-hydroxyisoxazolo[4,3-b]pyridin-5(4H)-one;
6-hydroxy[1,3]oxazolo[4,5-b]pyridin-5(4H)-one;
6-hydroxy[1,3]oxazolo[5,4-b]pyridin-5(4H)-one;
5-hydroxy-2-methylfuro[2,3-b]pyridin-6(7H)-one;
6-hydroxy-2-methylfuro[3,2-b]pyridin-5(4H)-one;
6-hydroxy-2-methyl[1,3]oxazolo[4,5-b]pyridin-5(4H)-one;
5-hydroxy-3-methylisoxazolo[3,4-b]pyridin-6(7H)-one;
6-hydroxy-2-methyl[1,3]oxazolo[5,4-b]pyridin-5(4H)-one;
6-hydroxy-3-methylisoxazolo[4,5-b]pyridin-5(4H)-one;
5-hydroxy-3-methylisoxazolo[5,4-b]pyridin-6(7H)-one;
5-hydroxythieno[2,3-b]pyridin-6(7H)-one;
6-hydroxy[1,3]thiazolo[5,4-b]pyridin-5(4H)-one;
6-hydroxy[1,3]thiazolo[4,5-b]pyridin-5(4H)-one;
2-fluoro-5-hydroxyfuro[2,3-b]pyridin-6(7H)-one;
2-fluoro-6-hydroxyfuro[3,2-b]pyridin-5(4H)-one;
6-hydroxy-2-methylthieno[3,2-b]pyridin-5(4H)-one;
5-hydroxy-2-methylthieno[2,3-b]pyridin-6(7H)-one;
2-fluoro-6-hydroxythieno[3,2-b]pyridin-5(4H)-one;
2-fluoro-5-hydroxythieno[2,3-b]pyridin-6(7H)-one;
2-chloro-6-hydroxyfuro[3,2-b]pyridin-5(4H)-one;
2-chloro-5-hydroxyfuro[2,3-b]pyridin-6(7H)-one;
2-chloro-6-hydroxythieno[3,2-b]pyridin-5(4H)-one;
7-fluoro-3-hydroxy-1,5-naphthyridin-2(1H)-one;
8-fluoro-3-hydroxy-1,6-naphthyridin-2(1H)-one;

6-fluoro-3-hydroxy-1,8-naphthyridin-2(1H)-one;
8-fluoro-3-hydroxy-1,5-naphthyridin-2(1H)-one;
5-fluoro-3-hydroxy-1,8-naphthyridin-2(1H)-one;
6-chloro-3-hydroxy-1,8-naphthyridin-2(1H)-one;
8-chloro-3-hydroxy-1,5-naphthyridin-2(1H)-one;
7-chloro-3-hydroxy-1,5-naphthyridin-2(1H)-one;
5-chloro-3-hydroxy-1,8-naphthyridin-2(1H)-one;
8-chloro-3-hydroxy-1,6-naphthyridin-2(1H)-one;
5-chloro-6-fluoro-3-hydroxy-1,8-naphthyridin-2(1H)-one;
4-fluoro-3-hydroxy-1,8-naphthyridin-2(1H)-one;
4-fluoro-3-hydroxy-1,5-naphthyridin-2(1H)-one;
4-fluoro-3-hydroxy-1,6-naphthyridin-2(1H)-one;
4-fluoro-3-hydroxy-5-methylquinolin-2(1H)-one;
4-fluoro-3-hydroxy-8-methylquinolin-2(1H)-one;
4,7-difluoro-3-hydroxyquinolin-2(1H)-one;
4,5-difluoro-3-hydroxyquinolin-2(1H)-one;
4,6-difluoro-3-hydroxyquinolin-2(1H)-one;
4,7-difluoro-3-hydroxy-1,5-naphthyridin-2(1H)-one;
4,8-difluoro-3-hydroxy-1,5-naphthyridin-2(1H)-one;
4,5-difluoro-3-hydroxy-1,8-naphthyridin-2(1H)-one;
4,8-difluoro-3-hydroxy-1,6-naphthyridin-2(1H)-one;
4-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-5-carbonitrile;
4-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-8-carbonitrile;
5-ethyl-4-fluoro-3-hydroxyquinolin-2(1H)-one;
8-ethyl-4-fluoro-3-hydroxyquinolin-2(1H)-one;
4,5-difluoro-3-hydroxy-8-methylquinolin-2(1H)-one;
4,8-difluoro-3-hydroxy-5-methylquinolin-2(1H)-one;
4,6-difluoro-3-hydroxy-5-methylquinolin-2(1H)-one;
4,7-difluoro-3-hydroxy-8-methylquinolin-2(1H)-one;
8-chloro-4-fluoro-3-hydroxyquinolin-2(1H)-one;
5-chloro-4-fluoro-3-hydroxyquinolin-2(1H)-one;

8-chloro-4-fluoro-3-hydroxy-1,5-naphthyridin-2(1H)-one;
8-chloro-4-fluoro-3-hydroxy-1,6-naphthyridin-2(1H)-one;
4,5,6-trifluoro-3-hydroxyquinolin-2(1H)-one;
4,5,8-trifluoro-3-hydroxyquinolin-2(1H)-one;
4,7,8-trifluoro-3-hydroxyquinolin-2(1H)-one;
4,6,7-trifluoro-3-hydroxyquinolin-2(1H)-one;
5-ethyl-4,7-difluoro-3-hydroxyquinolin-2(1H)-one;
8-ethyl-4,6-difluoro-3-hydroxyquinolin-2(1H)-one;
5-ethyl-4,8-difluoro-3-hydroxyquinolin-2(1H)-one;
5-chloro-4-fluoro-3-hydroxy-8-methylquinolin-2(1H)-one;
8-chloro-4-fluoro-3-hydroxy-5-methylquinolin-2(1H)-one;
5-chloro-4,7-difluoro-3-hydroxyquinolin-2(1H)-one;
5-chloro-4,6-difluoro-3-hydroxyquinolin-2(1H)-one;
8-chloro-4,6-difluoro-3-hydroxyquinolin-2(1H)-one;
8-chloro-4,5-difluoro-3-hydroxyquinolin-2(1H)-one;
8-chloro-5-ethyl-4-fluoro-3-hydroxyquinolin-2(1H)-one;
6-chloro-8-ethyl-4-fluoro-3-hydroxyquinolin-2(1H)-one;
4-fluoro-3-hydroxy-5-(trifluoromethyl)quinolin-2(1H)-one;
4-fluoro-3-hydroxy-8-(trifluoromethyl)quinolin-2(1H)-one;
5,8-dichloro-4-fluoro-3-hydroxyquinolin-2(1H)-one;
7-fluoro-3-hydroxy-8-methylquinolin-2(1H)-one;
8-fluoro-3-hydroxy-5-methylquinolin-2(1H)-one;
6-fluoro-3-hydroxy-8-methylquinolin-2(1H)-one;
6-fluoro-3-hydroxy-5-methylquinolin-2(1H)-one;
7-fluoro-3-hydroxy-5-methylquinolin-2(1H)-one;
5-fluoro-3-hydroxy-8-methylquinolin-2(1H)-one;
6,7-difluoro-3-hydroxyquinolin-2(1H)-one;
5,8-difluoro-3-hydroxyquinolin-2(1H)-one;
7,8-difluoro-3-hydroxyquinolin-2(1H)-one;
5,6-difluoro-3-hydroxyquinolin-2(1H)-one;
5,7-difluoro-3-hydroxyquinolin-2(1H)-one;

6,8-difluoro-3-hydroxyquinolin-2(1H)-one;
3-hydroxy-2-oxo-1,2-dihydroquinoline-8-carbonitrile;
3-hydroxy-2-oxo-1,2-dihydroquinoline-6-carbonitrile;
3-hydroxy-2-oxo-1,2-dihydroquinoline-5-carbonitrile;
3-hydroxy-2-oxo-1,2-dihydroquinoline-7-carbonitrile;
7-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-6-carbonitrile;
7-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-8-carbonitrile;
7-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-5-carbonitrile;
6-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-7-carbonitrile;
5-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-7-carbonitrile;
8-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-5-carbonitrile;
8-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-6-carbonitrile;
6-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-5-carbonitrile;
6-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-8-carbonitrile;
5-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-8-carbonitrile;
5-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-6-carbonitrile;
8-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-7-carbonitrile;
6-chloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-8-carbonitrile;
5-chloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-7-carbonitrile;
7-chloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-5-carbonitrile;
5-chloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-8-carbonitrile;
7-chloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-8-carbonitrile;
8-chloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-7-carbonitrile;
5-chloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-6-carbonitrile;
8-chloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-5-carbonitrile;
6-chloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-5-carbonitrile;
8-chloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-6-carbonitrile;
8-ethyl-7-fluoro-3-hydroxyquinolin-2(1H)-one;
5-ethyl-8-fluoro-3-hydroxyquinolin-2(1H)-one;
5-ethyl-6-fluoro-3-hydroxyquinolin-2(1H)-one;
5-ethyl-7-fluoro-3-hydroxyquinolin-2(1H)-one;

8-ethyl-6-fluoro-3-hydroxyquinolin-2(1H)-one;
6-chloro-3-hydroxy-8-methylquinolin-2(1H)-one;
5-chloro-3-hydroxy-8-methylquinolin-2(1H)-one;
5-chloro-3-hydroxy-7-methylquinolin-2(1H)-one;
8-chloro-3-hydroxy-5-methylquinolin-2(1H)-one;
6-chloro-3-hydroxy-5-methylquinolin-2(1H)-one;
7-chloro-3-hydroxy-5-methylquinolin-2(1H)-one;
8-chloro-7-fluoro-3-hydroxyquinolin-2(1H)-one;
8-chloro-6-fluoro-3-hydroxyquinolin-2(1H)-one;
6-chloro-5-fluoro-3-hydroxyquinolin-2(1H)-one;
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5-chloro-8-fluoro-3-hydroxyquinolin-2(1H)-one;
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7-chloro-5-ethyl-3-hydroxyquinolin-2(1H)-one;
5-chloro-8-ethyl-3-hydroxyquinolin-2(1H)-one;
6-chloro-8-ethyl-3-hydroxyquinolin-2(1H)-one;
8-chloro-5-ethyl-3-hydroxyquinolin-2(1H)-one;
6-chloro-5-ethyl-3-hydroxyquinolin-2(1H)-one;
3-hydroxy-5-(trifluoromethyl)quinolin-2(1H)-one;
3-hydroxy-8-(trifluoromethyl)quinolin-2(1H)-one;
5,8-dichloro-3-hydroxyquinolin-2(1H)-one;
6,8-dichloro-3-hydroxyquinolin-2(1H)-one;
6-fluoro-3-hydroxy-8-(trifluoromethyl)quinolin-2(1H)-one;
8-fluoro-3-hydroxy-5-(trifluoromethyl)quinolin-2(1H)-one;
5-fluoro-3-hydroxy-8-(trifluoromethyl)quinolin-2(1H)-one;
6-fluoro-3-hydroxy-5-(trifluoromethyl)quinolin-2(1H)-one;
7-fluoro-3-hydroxy-5-(trifluoromethyl)quinolin-2(1H)-one;
7-fluoro-3-hydroxy-8-(trifluoromethyl)quinolin-2(1H)-one;

6-chloro-3-hydroxy-8-(trifluoromethyl)quinolin-2(1H)-one;
5-chloro-3-hydroxy-6-(trifluoromethyl)quinolin-2(1H)-one;
5-chloro-3-hydroxy-8-(trifluoromethyl)quinolin-2(1H)-one;
8-chloro-3-hydroxy-5-(trifluoromethyl)quinolin-2(1H)-one;
8-chloro-3-hydroxy-6-(trifluoromethyl)quinolin-2(1H)-one; and
7-chloro-3-hydroxy-5-(trifluoromethyl)quinolin-2(1H)-one;
5,6,7-trifluoro-3-hydroxyquinolin-2(1H)-one;
5,7,8-trifluoro-3-hydroxyquinolin-2(1H)-one; and
5,6,7,8-tetrafluoro-3-hydroxyquinolin-2(1H)-one; or
pharmaceutically acceptable salts of said compounds.

An embodiment of the present invention of particular interest relates to the 3-hydroxyquinolin-2(1*H*)-one compounds:

7-fluoro-3-hydroxyquinolin-2(1*H*)-one;
5-chloro-6-fluoro-3-hydroxyquinolin-2(1*H*)-one;
7-ethyl-3-hydroxyquinolin-2(1*H*)-one;
4-fluoro-3-hydroxyquinolin-2(1*H*)-one;
4,8-difluoro-3-hydroxyquinolin-2(1*H*)-one;
8-fluoro-3-hydroxyquinolin-2(1*H*)-one;
3-hydroxy-7-methylquinolin-2(1*H*)-one;
4-bromo-7-chloro-3-hydroxyquinolin-2(1*H*)-one;
6,7-dichloro-3-hydroxyquinolin-2(1*H*)-one;
7,8-dichloro-3-hydroxyquinolin-2(1*H*)-one;
7-chloro-3-hydroxy-8-methylquinolin-2(1*H*)-one;
5-fluoro-3-hydroxyquinolin-2(1*H*)-one;
3-hydroxy-5-methylquinolin-2(1*H*)-one; or
5-chloro-3-hydroxyquinolin-2(1*H*)-one; including the pharmaceutically acceptable salts thereof.

Another embodiment of the present invention of particular interest relates to a group of 6-membered heteroarylfused-pyridin-2(1H)-one compounds selected from the group consisting of:

3-hydroxy-1,5-naphthyridin-2(1*H*)-one;

3-hydroxy-1,7-naphthyridin-2(1*H*)-one;

3-hydroxy-1,6-naphthyridin-2(1*H*)-one; and

3-hydroxy-4-methyl-1,8-naphthyridin-2(1*H*)-one; or pharmaceutically acceptable salts of each of the foregoing.

Another embodiment of the present invention of particular interest relates to the 5-membered heteroarylfused-pyridin-2(1H)-ones:

5-hydroxy-1-methyl-1,7-dihydro-6*H*-pyrazolo[3,4-*b*]pyridin-6-one;

6-hydroxythieno[3,2-*b*]pyridin-5(4*H*)-one; or

6-hydroxyfuro[3,2-b]pyridin-5(4*H*)-one;

including pharmaceutically acceptable salts of each of the foregoing.

Another embodiment of the present invention of interest to the inventors relates to a group of (5-membered heteroarylfused)-pyridin-2(1H)-ones selected from the group consisting of:

3-hydroxypyrrolo[1,2-b]pyridazin-2(1H)-one;

5-hydroxyfuro[2,3-b]pyridin-6(7H)-one;

5-hydroxyisoxazolo[5,4-b]pyridin-6(7H)-one;

6-hydroxyisoxazolo[4,5-b]pyridin-5(4H)-one;

5-hydroxyisoxazolo[3,4-b]pyridin-6(7H)-one;

6-hydroxyisoxazolo[4,3-b]pyridin-5(4H)-one;

6-hydroxy[1,3]oxazolo[4,5-b]pyridin-5(4H)-one;

6-hydroxy[1,3]oxazolo[5,4-b]pyridin-5(4H)-one;

5-hydroxy-2-methylfuro[2,3-b]pyridin-6(7H)-one;

6-hydroxy-2-methylfuro[3,2-b]pyridin-5(4H)-one;

6-hydroxy-2-methyl[1,3]oxazolo[4,5-b]pyridin-5(4H)-one;

5-hydroxy-3-methylisoxazolo[3,4-b]pyridin-6(7H)-one;

6-hydroxy-2-methyl[1,3]oxazolo[5,4-b]pyridin-5(4H)-one;

6-hydroxy-3-methylisoxazolo[4,5-b]pyridin-5(4H)-one;

5-hydroxy-3-methylisoxazolo[5,4-b]pyridin-6(7H)-one;

5-hydroxythieno[2,3-b]pyridin-6(7H)-one;

6-hydroxy[1,3]thiazolo[5,4-b]pyridin-5(4H)-one;

6-hydroxy[1,3]thiazolo[4,5-b]pyridin-5(4H)-one;

2-fluoro-5-hydroxyfuro[2,3-b]pyridin-6(7H)-one;
2-fluoro-6-hydroxyfuro[3,2-b]pyridin-5(4H)-one;
6-hydroxy-2-methylthieno[3,2-b]pyridin-5(4H)-one;
5-hydroxy-2-methylthieno[2,3-b]pyridin-6(7H)-one;
2-fluoro-6-hydroxythieno[3,2-b]pyridin-5(4H)-one;
2-fluoro-5-hydroxythieno[2,3-b]pyridin-6(7H)-one;
2-chloro-6-hydroxyfuro[3,2-b]pyridin-5(4H)-one;
2-chloro-5-hydroxyfuro[2,3-b]pyridin-6(7H)-one; and
2-chloro-6-hydroxythieno[3,2-b]pyridin-5(4H)-one; or
pharmaceutically acceptable salts of each of the foregoing.

Another embodiment of the present invention of interest to the inventors relates to a group of (6-membered heteroaryl fused)-pyridin-2(1H)-ones selected from:

7-fluoro-3-hydroxy-1,5-naphthyridin-2(1H)-one;
8-fluoro-3-hydroxy-1,6-naphthyridin-2(1H)-one;
6-fluoro-3-hydroxy-1,8-naphthyridin-2(1H)-one;
8-fluoro-3-hydroxy-1,5-naphthyridin-2(1H)-one;
5-fluoro-3-hydroxy-1,8-naphthyridin-2(1H)-one;
6-chloro-3-hydroxy-1,8-naphthyridin-2(1H)-one;
8-chloro-3-hydroxy-1,5-naphthyridin-2(1H)-one;
7-chloro-3-hydroxy-1,5-naphthyridin-2(1H)-one;
5-chloro-3-hydroxy-1,8-naphthyridin-2(1H)-one;
8-chloro-3-hydroxy-1,6-naphthyridin-2(1H)-one; and
5-chloro-6-fluoro-3-hydroxy-1,8-naphthyridin-2(1H)-one; or
pharmaceutically acceptable salts of each of the foregoing.

A group of particularly interesting 4-fluoro-(6-membered heteroaryl fused)-pyridin-2(1H)-ones include:

4-fluoro-3-hydroxy-1,8-naphthyridin-2(1H)-one;
4-fluoro-3-hydroxy-1,5-naphthyridin-2(1H)-one;
4-fluoro-3-hydroxy-1,6-naphthyridin-2(1H)-one; and
pharmaceutically acceptable salts of each of the foregoing.

Another group of 4-fluoro-(aryl fused)-pyridin-2(1H)-ones (i.e. quinolin-2(1H)-ones) of particular interest includes:

4-fluoro-3-hydroxy-5-methylquinolin-2(1H)-one;

4-fluoro-3-hydroxy-8-methylquinolin-2(1H)-one;

4,7-difluoro-3-hydroxyquinolin-2(1H)-one;

4,5-difluoro-3-hydroxyquinolin-2(1H)-one;

4,6-difluoro-3-hydroxyquinolin-2(1H)-one;

4-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-5-carbonitrile;

4-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-8-carbonitrile;

5-ethyl-4-fluoro-3-hydroxyquinolin-2(1H)-one;

8-ethyl-4-fluoro-3-hydroxyquinolin-2(1H)-one;

4,5-difluoro-3-hydroxy-8-methylquinolin-2(1H)-one;

4,8-difluoro-3-hydroxy-5-methylquinolin-2(1H)-one;

4,6-difluoro-3-hydroxy-5-methylquinolin-2(1H)-one;

4,7-difluoro-3-hydroxy-8-methylquinolin-2(1H)-one;

8-chloro-4-fluoro-3-hydroxyquinolin-2(1H)-one;

5-chloro-4-fluoro-3-hydroxyquinolin-2(1H)-one; and

pharmaceutically acceptable salts thereof.

Other 4-fluoro-(aryl fused)-pyridin-2(1H)-ones (i.e. quinolin-2(1H)-ones) of interest include:

4,5,6-trifluoro-3-hydroxyquinolin-2(1H)-one;

4,5,8-trifluoro-3-hydroxyquinolin-2(1H)-one;

4,7,8-trifluoro-3-hydroxyquinolin-2(1H)-one;

4,6,7-trifluoro-3-hydroxyquinolin-2(1H)-one;

5-ethyl-4,7-difluoro-3-hydroxyquinolin-2(1H)-one;

8-ethyl-4,6-difluoro-3-hydroxyquinolin-2(1H)-one;

5-ethyl-4,8-difluoro-3-hydroxyquinolin-2(1H)-one;

5-chloro-4-fluoro-3-hydroxy-8-methylquinolin-2(1H)-one;

8-chloro-4-fluoro-3-hydroxy-5-methylquinolin-2(1H)-one;

5-chloro-4,7-difluoro-3-hydroxyquinolin-2(1H)-one;

5-chloro-4,6-difluoro-3-hydroxyquinolin-2(1H)-one;

8-chloro-4,6-difluoro-3-hydroxyquinolin-2(1H)-one;
8-chloro-4,5-difluoro-3-hydroxyquinolin-2(1H)-one;
8-chloro-5-ethyl-4-fluoro-3-hydroxyquinolin-2(1H)-one;
6-chloro-8-ethyl-4-fluoro-3-hydroxyquinolin-2(1H)-one;
4-fluoro-3-hydroxy-5-(trifluoromethyl)quinolin-2(1H)-one;
4-fluoro-3-hydroxy-8-(trifluoromethyl)quinolin-2(1H)-one;
5,8-dichloro-4-fluoro-3-hydroxyquinolin-2(1H)-one; and
pharmaceutically acceptable salts thereof.

A group of 4-fluoro-6-membered-heteroaryl fused pyridin-2(1H)-ones of particular interest include:

4,7-difluoro-3-hydroxy-1,5-naphthyridin-2(1H)-one;
4,8-difluoro-3-hydroxy-1,5-naphthyridin-2(1H)-one;
4,5-difluoro-3-hydroxy-1,8-naphthyridin-2(1H)-one;
4,8-difluoro-3-hydroxy-1,6-naphthyridin-2(1H)-one;
8-chloro-4-fluoro-3-hydroxy-1,5-naphthyridin-2(1H)-one;
8-chloro-4-fluoro-3-hydroxy-1,6-naphthyridin-2(1H)-one; and
pharmaceutically acceptable salts of each of the foregoing.

Other fluoroquinolin-2(1H)-ones of interest to the inventors include:

7-fluoro-3-hydroxy-8-methylquinolin-2(1H)-one;
8-fluoro-3-hydroxy-5-methylquinolin-2(1H)-one;
6-fluoro-3-hydroxy-8-methylquinolin-2(1H)-one;
6-fluoro-3-hydroxy-5-methylquinolin-2(1H)-one;
7-fluoro-3-hydroxy-5-methylquinolin-2(1H)-one;
5-fluoro-3-hydroxy-8-methylquinolin-2(1H)-one;
6,7-difluoro-3-hydroxyquinolin-2(1H)-one;
5,8-difluoro-3-hydroxyquinolin-2(1H)-one;
7,8-difluoro-3-hydroxyquinolin-2(1H)-one;
5,6-difluoro-3-hydroxyquinolin-2(1H)-one;
5,7-difluoro-3-hydroxyquinolin-2(1H)-one;
6,8-difluoro-3-hydroxyquinolin-2(1H)-one;
8-ethyl-7-fluoro-3-hydroxyquinolin-2(1H)-one;

5-ethyl-8-fluoro-3-hydroxyquinolin-2(1H)-one;
5-ethyl-6-fluoro-3-hydroxyquinolin-2(1H)-one;
5-ethyl-7-fluoro-3-hydroxyquinolin-2(1H)-one;
8-ethyl-6-fluoro-3-hydroxyquinolin-2(1H)-one; and
pharmaceutically acceptable salts of each of the foregoing.

Nitrile quinolin-2(1H)-ones of interest to the inventors include:
3-hydroxy-2-oxo-1,2-dihydroquinoline-8-carbonitrile;
3-hydroxy-2-oxo-1,2-dihydroquinoline-6-carbonitrile;
3-hydroxy-2-oxo-1,2-dihydroquinoline-5-carbonitrile;
3-hydroxy-2-oxo-1,2-dihydroquinoline-7-carbonitrile;
7-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-6-carbonitrile;
7-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-8-carbonitrile;
7-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-5-carbonitrile;
6-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-7-carbonitrile;
5-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-7-carbonitrile;
8-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-5-carbonitrile;
8-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-6-carbonitrile;
6-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-5-carbonitrile;
6-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-8-carbonitrile;
5-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-8-carbonitrile;
5-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-6-carbonitrile;
8-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-7-carbonitrile;
6-chloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-8-carbonitrile;
5-chloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-7-carbonitrile;
7-chloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-5-carbonitrile;
5-chloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-8-carbonitrile;
7-chloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-8-carbonitrile;
8-chloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-7-carbonitrile;
5-chloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-6-carbonitrile;
8-chloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-5-carbonitrile;
6-chloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-5-carbonitrile; and

8-chloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-6-carbonitrile; and

pharmaceutically acceptable salts thereof.

A group of chloro-quinolin-2(1H)-ones of interest to the present inventors includes:

6-chloro-3-hydroxy-8-methylquinolin-2(1H)-one;

5-chloro-3-hydroxy-8-methylquinolin-2(1H)-one;

5-chloro-3-hydroxy-7-methylquinolin-2(1H)-one;

8-chloro-3-hydroxy-5-methylquinolin-2(1H)-one;

6-chloro-3-hydroxy-5-methylquinolin-2(1H)-one;

7-chloro-3-hydroxy-5-methylquinolin-2(1H)-one;

8-chloro-7-fluoro-3-hydroxyquinolin-2(1H)-one;

8-chloro-6-fluoro-3-hydroxyquinolin-2(1H)-one;

6-chloro-5-fluoro-3-hydroxyquinolin-2(1H)-one;

8-chloro-5-fluoro-3-hydroxyquinolin-2(1H)-one;

5-chloro-8-fluoro-3-hydroxyquinolin-2(1H)-one;

7-chloro-8-fluoro-3-hydroxyquinolin-2(1H)-one;

7-chloro-5-fluoro-3-hydroxyquinolin-2(1H)-one;

6-chloro-8-fluoro-3-hydroxyquinolin-2(1H)-one;

5-chloro-7-fluoro-3-hydroxyquinolin-2(1H)-one;

7-chloro-5-ethyl-3-hydroxyquinolin-2(1H)-one;

5-chloro-8-ethyl-3-hydroxyquinolin-2(1H)-one;

6-chloro-8-ethyl-3-hydroxyquinolin-2(1H)-one;

8-chloro-5-ethyl-3-hydroxyquinolin-2(1H)-one;

6-chloro-5-ethyl-3-hydroxyquinolin-2(1H)-one;

5,8-dichloro-3-hydroxyquinolin-2(1H)-one;

6,8-dichloro-3-hydroxyquinolin-2(1H)-one; and

pharmaceutically acceptable salts thereof.

A group of trifluoro-quinolin-2(1H)-ones of interest to the present inventors includes:

3-hydroxy-5-(trifluoromethyl)quinolin-2(1H)-one;

3-hydroxy-8-(trifluoromethyl)quinolin-2(1H)-one;

6-fluoro-3-hydroxy-8-(trifluoromethyl)quinolin-2(1H)-one;
8-fluoro-3-hydroxy-5-(trifluoromethyl)quinolin-2(1H)-one;
5-fluoro-3-hydroxy-8-(trifluoromethyl)quinolin-2(1H)-one;
6-fluoro-3-hydroxy-5-(trifluoromethyl)quinolin-2(1H)-one;
7-fluoro-3-hydroxy-5-(trifluoromethyl)quinolin-2(1H)-one;
7-fluoro-3-hydroxy-8-(trifluoromethyl)quinolin-2(1H)-one;
6-chloro-3-hydroxy-8-(trifluoromethyl)quinolin-2(1H)-one;
5-chloro-3-hydroxy-6-(trifluoromethyl)quinolin-2(1H)-one;
5-chloro-3-hydroxy-8-(trifluoromethyl)quinolin-2(1H)-one;
8-chloro-3-hydroxy-5-(trifluoromethyl)quinolin-2(1H)-one;
8-chloro-3-hydroxy-6-(trifluoromethyl)quinolin-2(1H)-one; and
7-chloro-3-hydroxy-5-(trifluoromethyl)quinolin-2(1H)-one; and
pharmaceutically acceptable salts thereof.

As used herein, the phrase "the compounds of the invention" includes the general and specific compounds, including examples discussed herein and pharmaceutically acceptable salts thereof. It will also be understood that the phrase "compounds of the invention and pharmaceutically acceptable salt(s) thereof" also encompasses the pharmaceutically acceptable hydrates, solvates, and tautomers of the compounds described herein and below and pharmaceutically acceptable salts thereof.

The phrase "pharmaceutically acceptable salt(s)", as used herein, unless otherwise indicated, includes salts of acidic or basic groups which may be present in the compounds of the present invention. The compounds of the present invention that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, i.e., salts containing pharmaceutically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, acid citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate,

fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts. The compounds of the present invention that include a basic moiety, such as an amino group, may form pharmaceutically acceptable salts with various amino acids, in addition to the acids mentioned above.

The invention also relates to base addition salts of the compounds of the invention. The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of those compounds of the compounds of the invention that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to those derived from such pharmaceutically acceptable cations such as alkali metal cations (e.g., potassium and sodium) and alkaline earth metal cations (e.g., calcium and magnesium), ammonium or water-soluble amine addition salts such as N-methylglucamine-(meglumine), and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines.

Suitable base salts are formed from bases which form non-toxic salts. Non-limiting examples of suitable base salts include the aluminum, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts.

Hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium salts.

For a review on suitable salts, see Handbook of Pharmaceutical Salts: Properties, Selection, and Use by Stahl and Wermuth (Wiley-VCH, 2002). Methods for making pharmaceutically acceptable salts of compounds of the invention are known to one of skill in the art.

The compounds of the invention may also exist in unsolvated and solvated forms. Thus, it will be understood that the compounds of the invention (and pharmaceutically acceptable salts thereof) also include

hydrates and solvates of said compounds of the invention (and pharmaceutically acceptable salts thereof) as discussed below.

The term "solvate" is used herein to describe a noncovalent or easily reversible combination between solvent and solute, or dispersion means and disperse phase. It will be understood that the solvate can be in the form of a solid, slurry (e.g., a suspension or dispersion), or solution. Non-limiting examples of solvents include ethanol, methanol, propanol, acetonitrile, dimethyl ether, diethyl ether, tetrahydrofuran, methylene chloride, and water. The term 'hydrate' is employed when said solvent is water.

A currently accepted classification system for organic hydrates is one that defines isolated site, channel, or metal-ion coordinated hydrates - see Polymorphism in Pharmaceutical Solids by K. R. Morris (Ed. H. G. Brittain, Marcel Dekker, 1995). Isolated site hydrates are ones in which the water molecules are isolated from direct contact with each other by intervening organic molecules. In channel hydrates, the water molecules lie in lattice channels where they are next to other water molecules. In metal-ion coordinated hydrates, the water molecules are bonded to the metal ion.

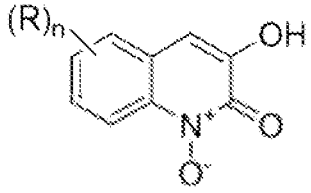
When the solvent or water is tightly bound, the complex will have a well-defined stoichiometry independent of humidity. When, however, the solvent or water is weakly bound, as in channel solvates and hygroscopic compounds, the water/solvent content will be dependent on humidity and drying conditions. In such cases, non-stoichiometry will be the norm.

Also included within the scope of the invention are metabolites of compounds of the invention, that is, compounds formed in vivo upon administration of the drug. Some examples of metabolites in accordance with the invention include:

(i) where the compound of the invention contains a methyl group, an hydroxymethyl derivative thereof (e.g., $-CH_3$ -> $-CH_2OH$);

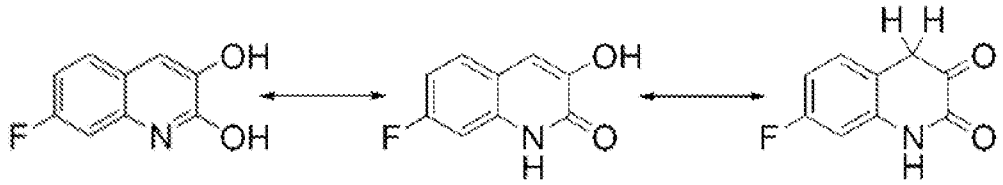
(ii) where the compound of the invention contains an alkoxy group, an hydroxy derivative thereof (e.g., -OR' -> -OH);

(iii) where the compound of the inventions is an N-oxide, e.g.;



wherein R is as defined above.

The compounds of the invention may exist in several tautomeric forms, including the enol and imine form, and the keto and enamine form and geometric isomers and mixtures thereof. All such tautomeric forms are included within the scope of the present invention. Tautomers exist as mixtures of a tautomeric set in solution. In solid form, usually one tautomer predominates. Even though one tautomer may be described, the present invention includes all tautomers of the present compounds. By way of example, the compound 7-fluoro-3-hydroxyquinolin-2(1*H*)-one (**1**), which is exemplified in Example 1, may exist in the following tautomeric forms:



The present invention also includes isotopically-labeled compounds, which are identical to those recited in formula I, 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 compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as, but not limited to, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{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 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 ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e.,

^{3}H, 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 deuterium, i.e., ^{2}H, 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 this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically-labeled reagent for a non-isotopically-labeled reagent.

In one embodiment, the invention relates to compositions comprising a compound of the invention and at least one additional ingredient (hereinafter "the compositions of the invention"). It will be understood that the compositions of the invention will encompass any combination of the compound of the invention and the at least one additional ingredient. Non-limiting examples of the at least one additional ingredient include impurities (e.g., intermediates present in the unrefined compounds of the invention), active ingredients as discussed herein (e.g., an additional drug or active agent), pharmaceutically acceptable excipients, or one or more solvents (e.g., a pharmaceutically acceptable carrier as discussed herein).

The term "solvent" as it relates to the compositions of the invention includes organic solvents (e.g., methanol, ethanol, isopropanol, ethyl acetate, methylene chloride, and tetrahydrofuran) and water. The one or more solvents may be present in a non-stoichiometric amount, e.g., as a trace impurity, or in sufficient excess to dissolve the compound of the invention. Alternatively, the one or more solvents may be present in a stoichiometric amount, e.g., 0.5:1, 1:1, or 2:1 molar ratio, based on the amount of compound of the invention.

In one embodiment, at least one additional ingredient that is present in the composition of the invention is an organic solvent.

In another embodiment, at least one additional ingredient that is present in the composition of the invention is water.

In one embodiment, at least one additional ingredient that is present in the composition of the invention is a pharmaceutically acceptable carrier.

In another embodiment, at least one additional ingredient that is present in the composition of the invention is a pharmaceutically acceptable excipient.

In one embodiment, the composition of the invention is a solution.

In another embodiment, the composition of the invention is a suspension.

In another embodiment, the composition of the invention is a solid.

In yet another embodiment, the invention relates to a composition comprising an effective amount of the compound of the invention, and a pharmaceutically acceptable carrier.

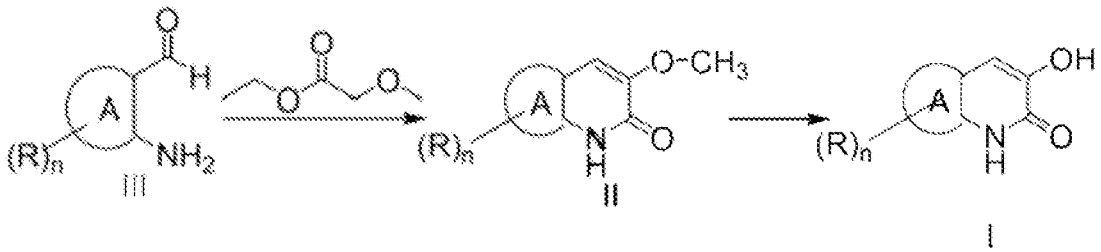
In another embodiment, the invention relates to a composition comprising a therapeutically effective amount of the compound the invention as defined above, a pharmaceutically acceptable carrier and, optionally, at least one additional medicinal or pharmaceutical agent.

Detailed Description of the Invention

The compounds of the invention can be prepared by one or more of the procedures generally described in Schemes 1 to 7 below and in the Examples section.

Compounds of formula **I**, wherein ring "A" is an optionally substituted fused phenyl radical or an optionally substituted 5 or 6 membered heteroaryl radical; R is hydrogen, (C_1-C_2)alkyl, (C_1-C_2)alkoxy, trifluoromethyl or halo; and n is an integer from zero to three; may be prepared from aromatic (i.e. ring "A" is optionally substituted phenyl) or heteroaromatic (i.e. ring "A" is optionally substituted heteroaryl) aminoaldehydes **III** as shown in Scheme 1.

Scheme 1

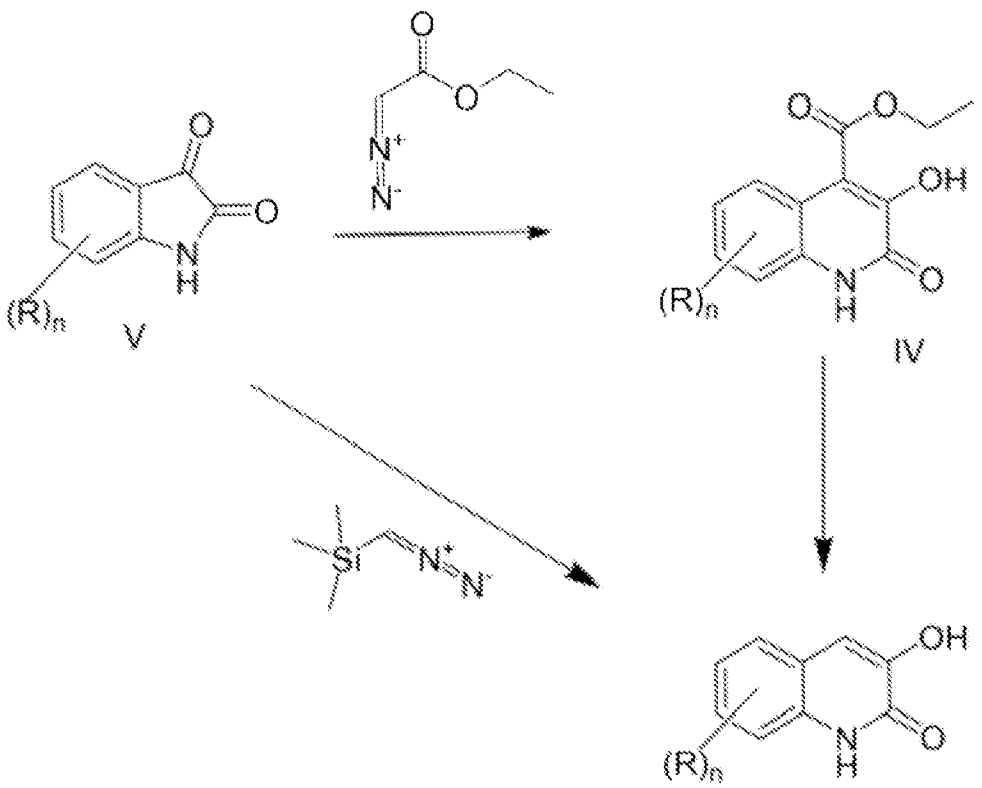


The anion of ethyl methoxyacetate, prepared by treatment with a base, for instance lithium bis(trimethylsilyl)amide or lithium diisopropylamide, can be reacted with a compound of Formula **III** to generate a compound of formula **II**. In some cases it is advantageous to treat the crude reaction product with acid, for example hydrochloric acid, at temperatures ranging from about 25°C to reflux. Demethylation of the compound of Formula **II** provides the compound of Formula **I**; this can be effected by a variety of methods familiar to those skilled in the art, and is frequently carried out through the action of boron tribromide.

The requisite aminoaldehydes **III** are often commercially available, or can be prepared in a straightforward manner from related materials such as the corresponding carboxylic acid, carboxylic ester or alcohol as shown in Scheme 3 below.

Substituted isatins can also be used to prepare certain compounds of formula **I** (i.e. I(a) wherein ring "A" is the fused optionally substituted phenyl radical), as depicted in Scheme 2.

Scheme 2



Ia

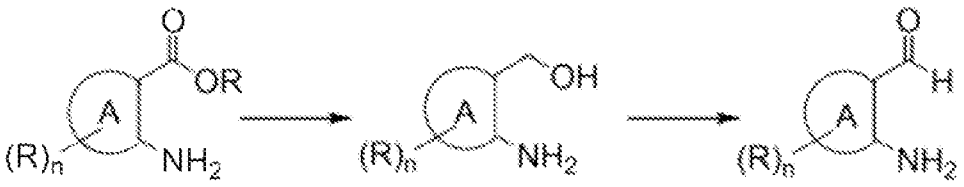
Treatment of isatin **V** (e.g., a substituted 1*H*-indole-2,3-dione wherein R is independently selected from hydrogen, chloro, fluoro, alkyl, trifluoromethyl or alkoxy and n is an integer from zero to three) with ethyl diazoacetate and an amine base, generally diethylamine, followed by subjection to acid, generally hydrochloric acid, provides a compound of formula **IV**, as described in S-Y. Sit et al., *Bioorganic Medicinal Chemistry Letters* **1996**, 6, 499-504. An alternative procedure employs ethyl diazoacetate and zinc chloride, as detailed in M.J. Fray et al., *Medicinal Chemistry Research* **1996**, 6, 581-592. Hydrolysis of the compound of formula **IV**, for instance with lithium hydroxide or sodium hydroxide, can be carried out under thermal or microwave conditions, resulting in decarboxylation and formation of a compound of Formula **I(a)**. See S-Y. Sit et al., *op. cit.* and M.J. Fray et al., *op. cit.* The compound of formula **V** can also be converted to a compound of Formula **I(a)**

through treatment with (trimethylsilyl)diazomethane, as described in Example 2 below.

Many isatins are commercially available. Those that are not may be prepared by literature methods. See P. Hewawasam and N.A. Meanwell, *Tetrahedron Letters* **1994**, *35*, 7303-7306, and references contained therein.

Scheme 3 refers to the preparation of certain intermediates useful in the preparation of compounds of Formula I in Scheme 1 above.

Scheme 3

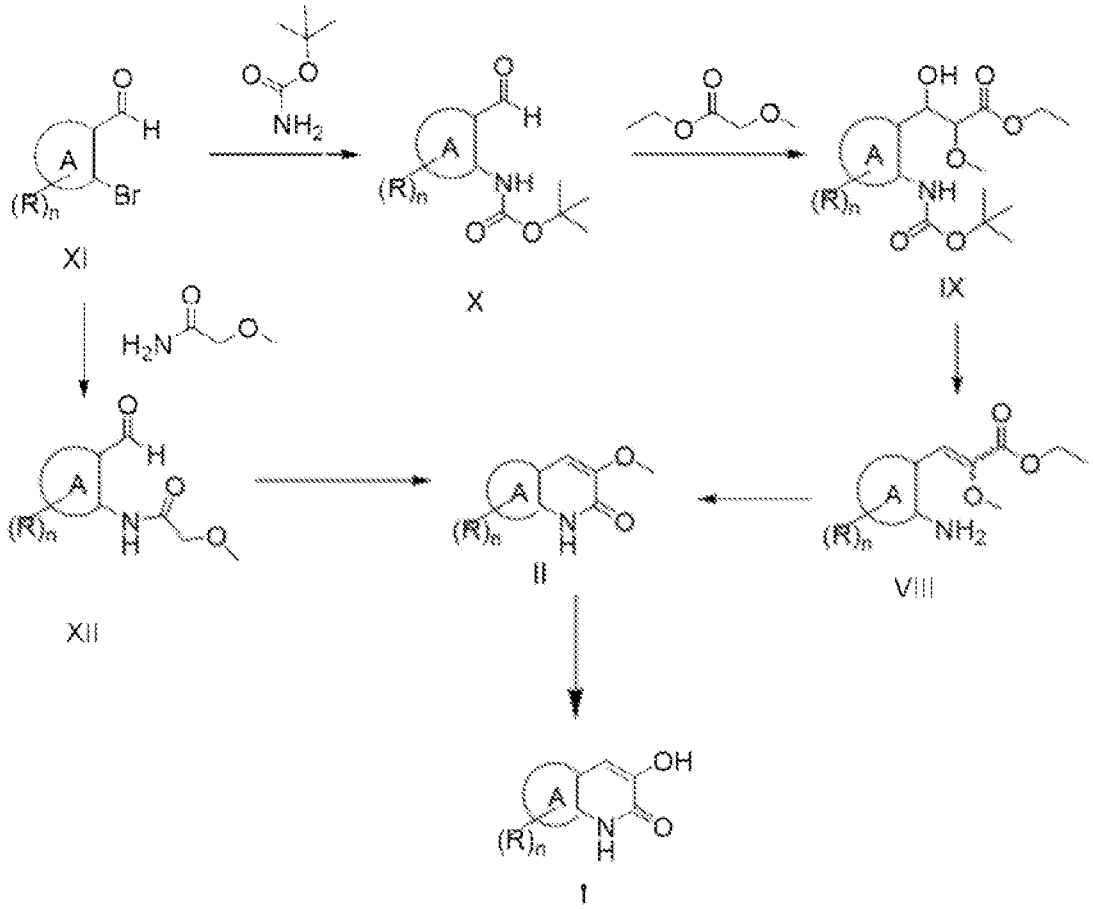


VII VI III

Referring to Scheme 3, reduction of a compound of Formula **VII**, wherein ring "A" is an optionally substituted phenyl radical or an optionally substituted 5 or 6 membered heteroaryl radical; R is hydrogen, $(C_1$-$C_2)$alkyl, $(C_1$-$C_2)$alkoxy, trifluoromethyl or halo; and n is an integer from zero to three to an alcohol of Formula **VI**, wherein ring "A" is an optionally substituted phenyl radical or an optionally substituted 5 or 6 membered heteroaryl radical; R is hydrogen, $(C_1$-$C_2)$alkyl, $(C_1$-$C_2)$alkoxy, trifluoromethyl or halo; and n is an integer from zero to three can be carried out with numerous reagents known to those skilled in the art; the choice of reagent depends on what other functionality is present in the molecule. One useful reagent for this transformation is lithium aluminum hydride. Oxidation of the alcohol of Formula **VI** to the aldehyde of Formula **III**, wherein ring "A" is an optionally substituted phenyl radical or an optionally substituted 5 or 6 membered heteroaryl radical; R is hydrogen, $(C_1$-$C_2)$alkyl, $(C_1$-$C_2)$alkoxy, trifluoromethyl or halo; and n is an integer from zero to three can also be carried out via a number of methods, for instance treatment with manganese(IV) oxide.

Aromatic or heteroaromatic *ortho*-bromo aldehydes can also be used to prepare compounds of Formula **I**, as outlined in Scheme 4.

Scheme 4



Referring to Scheme 4, replacement of the bromine atom in a compound of Formula **XI,** wherein ring "A" is an optionally substituted phenyl radical or an optionally substituted 5 or 6 membered heteroaryl radical; R is hydrogen, $(C_1$-$C_2)$alkyl, $(C_1$-$C_2)$alkoxy, trifluoromethyl or halo; and n is an integer from zero to three, by a protected amine equivalent, such as *tert*-butyl carbamate, can be carried out through a coupling reaction, for instance employing a palladium catalyst, such as tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct, and a ligand such as Xantphos. See, for example, J. Yin and S.L. Buchwald, *Organic Letters* **2000**, 2, 1101-1104. Reaction of the product aldehyde of Formula **X** with ethyl methoxyacetate, as described above for Scheme 2, affords a compound of Formula **IX**, which can be dehydrated and deprotected to form a compound of Formula **VIII**, for instance by mild treatment with boron

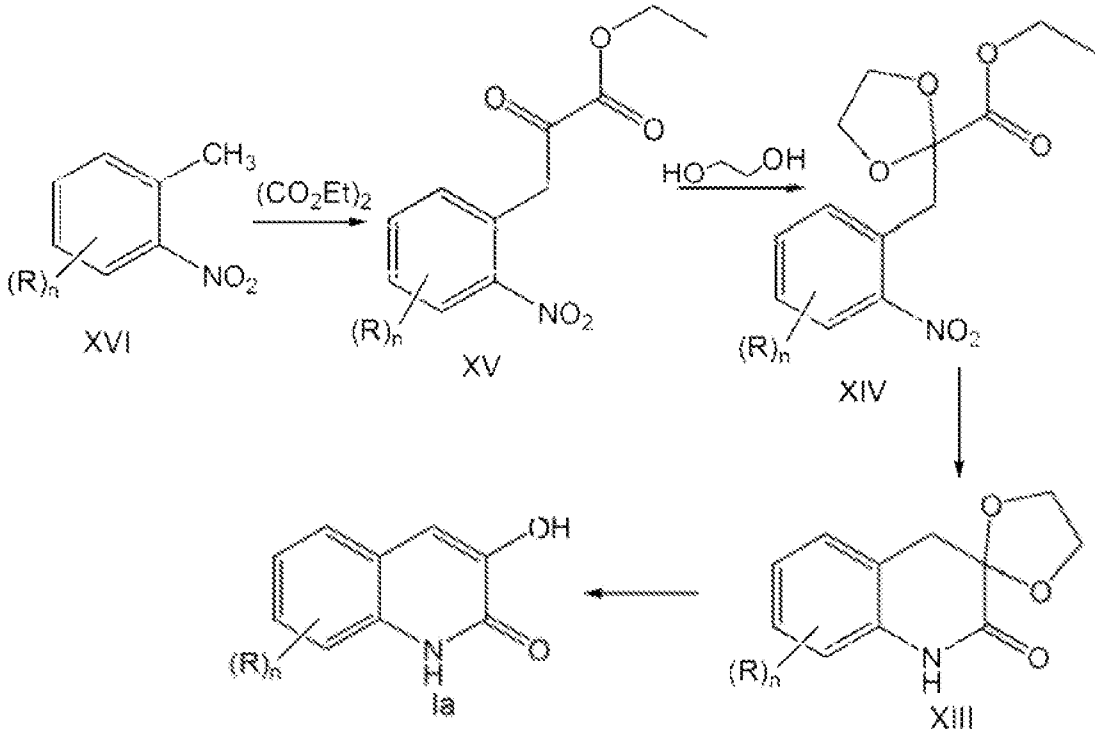
tribromide, as described in Example 19 below. Ring closure to the compound of Formula **II** occurs upon exposure to base, for example lithium bis(trimethylsilyl)amide.

Alternatively, a compound of Formula **XI**, wherein ring "A" is an optionally substituted phenyl radical or an optionally substituted 5 or 6 membered heteroaryl radical; R is hydrogen, (C_1-C_2)alkyl, (C_1-C_2)alkoxy, trifluoromethyl or halo; and n is an integer from zero to three, can be reacted with 2-methoxyacetamide under coupling conditions similar to those described for synthesis of Formula **X** above, to afford a compound of Formula **XII**; see also P.J. Manley and M.T. Bilodeau, *Organic Letters* **2004**, *6*, 2433-2435. Ring closure to a compound of Formula **II** is carried out through exposure to base, for instance use of potassium *tert*-butoxide at about 70°C. Conversion of a compound of formula **II** to a compound of formula **I** can be carried out as described above.

Bromoaldehydes of formula **XI** can be prepared from the corresponding carboxylic acid, ester or alcohol, in similar fashion to the chemistry depicted in Scheme 3.

Construction of compounds of Formula **Ia** (i.e. ring "A" is fused phenyl) can also be achieved from an *ortho*-nitro toluene starting material, as depicted in Scheme 5.

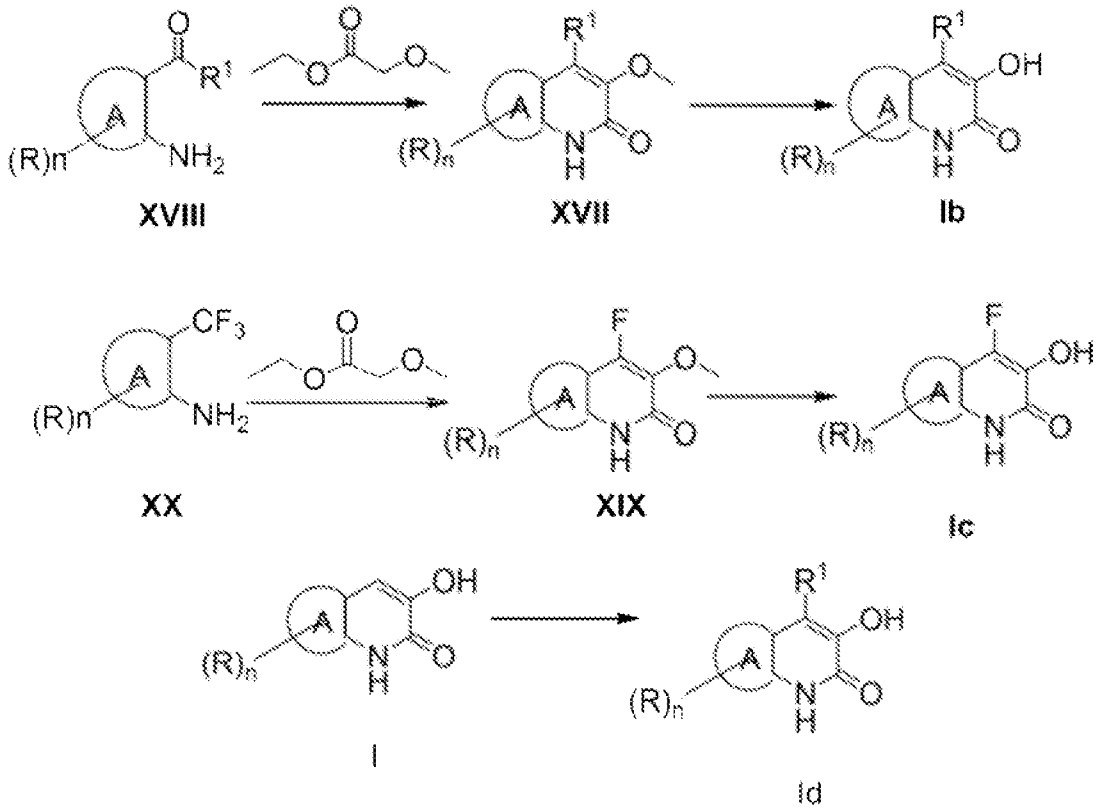
Scheme 5



Referring to Scheme 5, reaction of a nitrotoluene of Formula **XVI** with diethyl oxalate and sodium ethoxide provides a compound of Formula **XV**, which can be protected with ethylene glycol under acidic conditions, such as with *para*-toluenesulfonic acid, to give a compound of Formula **XIV**. Reduction of the nitro group, for instance with Raney nickel, tin(II) chloride or iron/hydrochloric acid, is followed by intramolecular cyclization to afford a compound of Formula **XIII**. Subjection of a compound of Formula **XIII** to acidic conditions, generally hydrochloric acid at temperatures of 60-90°C, then provides a compound of formula **Ia**.

Introduction of substituents at the 4-position of the hydroxypyridone ring into a compound of Formula **I** (i.e. wherein one of said R is a substituent on the pyridine ring) can be effected in several ways, depending on the identity of the 4-substituent, as shown in Scheme 6.

Scheme 6



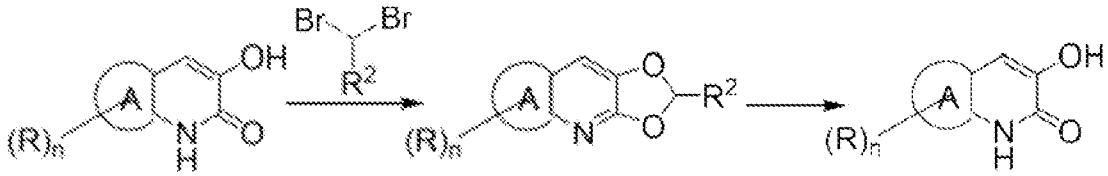
Referring to Scheme 6, where the desired 4-substituent is an alkyl group, a compound of Formula **I(b)** can be prepared from the aminoketone of Formula **XVIII**, in a manner analogous to preparation from aminoaldehyde of Formula **III** in Scheme 1. A compound of this type is exemplified in Example 18.

4-Fluoro compounds of the formula 1(c) can be generated from the corresponding trifluoromethyl starting material of Formula **XX**, following the general method of A.S. Kiselyov et al., *Organic Letters* **2004**, *6*, 4061-4063. Once again, as in Scheme 1, the anion of ethyl methoxyacetate is employed; reaction with a compound of Formula **XX** provides fluoro-substituted intermediate of Formula **XIX**, which is then transformed into a compound of Formula **I(c)**. Where a chlorine or bromine atom is desired at the 4-position, a different approach is employed, using the methodology of S-Y. Sit et al., *Bioorganic Medicinal Chem. Lett.* **1996**, *6*, 499-504. Treatment of a des-halo congener of Formula **I** (i.e. the pyridone ring is unsubstituted at the 4 position)

with *N*-chlorosuccinimide or *N*-bromosuccinimide provides the corresponding halogenated material **I(d),** wherein R^1 is chloro or bromo.

Introduction of substituents on the fused aryl or heteroaryl ring can be effected after preparation of compounds of formula I (and Ia, Ib, Ic and Id) as described herein above and in the Examples described herein below by using a protecting group for the alpha-hydroxy carbonyl system, as shown in Scheme 7.

Scheme 7



I XXI I

Compounds of formula **I**, wherein at least one R is bromine and the remaining R radicals are H, (C_1-C_2)alkyl, trifluoromethyl, chloro or (C_1-C_2)alkoxy; can be protected by reaction with dibromomethane or (dibromomethyl)benzene, in the presence of a base, for instance potassium carbonate or cesium fluoride, to provide a compound of formula **XXI**, wherein R^2 is hydrogen or phenyl. The bromine substituent of **XXI** can then be converted to a number of other functional groups through methods known to those skilled in the art. Replacement of bromine by a cyano group can be effected through palladium-catalyzed cyanation; see J. Ramnauth et al., Synlett **2003**, 2237-2239 and references cited therein. The bromine substituent can be replaced by methyl or ethyl through a Negishi-type coupling with dimethylzinc or diethylzinc, according to the general procedure of J.M. Herbert, *Tetrahedron Letters* **2004**, *45*, 817-819. Introduction of an aldehyde can be carried out by lithium-halogen exchange using an organolithium reagent such as *n*-butyllithium or *tert*-butyllithium, followed by reaction with dimethylformamide. Compounds of the Formula **XXI** can then be converted to the compound of Formula **I,** wherein one R is -CN, methyl,

Ethyl and -CHO by deprotection using, for example, boron tribromide or an acid such as hydrochloric acid.

Introduction of functional groups onto the phenyl ring of compound of Formula **I** can also be accomplished in the absence of a bromine. Nitration of the aryl or heteroaryl ring in a compound of Formula **XXI** is carried out, for instance through reaction with nitric acid and sulfuric acid. Conversion of the nitro group to a halogen atom can be effected through reduction of the nitro group to an amino group, followed by, for example, diazotization and subsequent Sandmeyer reaction to provide a compound of Formula **XXI**, wherein one of said R is chlorine or bromine. Diazotization in the presence of fluoroborate, followed by thermal decomposition (the Balz-Schiemann reaction) yields a compound of Formula **XXI** wherein one of said R is fluorine.

As noted above, the compounds of the invention are useful for treating disorders in a patient such as a mammal, preferably a human. Non-limiting examples of disorders that may be treated with a compound of the invention include cognitive-related disorders and disorders associated with neuropathic pain.

In one embodiment, the invention relates to a method of treating a cognitive-related disorder comprising administering a therapeutically effective amount of a compound of the invention to a patient in need thereof.

This invention also relates to a method of treating a disorder or condition selected from psychosis, schizophrenia, conduct disorder, disruptive behavior disorder, bipolar disorder, 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 or depression associated with bipolar disorder and mood disorders associated with schizophrenia, behavioral manifestations of mental retardation, conduct disorder and autistic disorder; movement disorders such as Tourette's syndrome, akinetic-rigid syndrome, movement disorders associated with Parkinson's disease, tardive dyskinesia and other drug induced and neurodegeneration based dyskinesias; attention deficit

hyperactivity disorder; cognitive disorders such as dementias (including age related dementia, and senile dementia of the Alzheimer's type) and memory disorders in a mammal, including a human, comprising administering to a mammal in need of such treatment an amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, that is effective in treating such condition or disorder.

In another embodiment, the invention relates to a method of treating a disorder or condition selected from psychosis, schizophrenia, bipolar disorder, 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 or depression associated with bipolar disorder and mood disorders associated with schizophrenia, cognitive disorders such as dementias (including age related dementia, and senile dementia of the Alzheimer's type), memory disorders and any combination thereof.

In another embodiment, the compounds of the invention are useful for a treating childhood learning disorders such as Developmental articulation disorder, Developmental expressive language disorder, Developmental receptive language disorder, Developmental reading disorder (such as dyslexia), Developmental writing disorder, Developmental arithmetic disorder and Attention disorders (such as ADHD).

In another embodiment, the compounds of the invention are useful for treating benign forgetfulness.

In another embodiment, the invention relates to a method of treating a disorder associated with neuropathic pain comprising administering a therapeutically effective amount of a compound of the invention to a patient in need thereof.

The term "treating", as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, unless otherwise

indicated, refers to the act of treating as "treating" is defined immediately above. The term "treating" also includes adjuvant and neo-adjuvant treatment of a subject.

As used herein, the phrase "neuropathic pain" refers to pain, typically chronic in duration, initiated or caused by a primary lesion or dysfunction in the nervous system. Nerve damage can be caused by trauma and disease and thus the term 'neuropathic pain' encompasses many disorders with diverse etiologies. These include, but are not limited to, peripheral neuropathy, diabetic neuropathy, post herpetic neuralgia, trigeminal neuralgia, back pain, cancer neuropathy, HIV neuropathy, phantom limb pain, carpal tunnel syndrome, central post-stroke pain and pain associated with chronic alcoholism, hypothyroidism, uremia, multiple sclerosis, spinal cord injury, Parkinson's disease, epilepsy and vitamin deficiency. Neuropathic pain is pathological as it has no protective role. It is often present well after the original cause has dissipated, commonly lasting for years, significantly decreasing a patient's quality of life. The symptoms of neuropathic pain include spontaneous pain, which can be continuous, and paroxysmal or abnormal evoked pain, such as hyperalgesia (increased sensitivity to a noxious stimulus), allodynia (sensitivity to a normally innocuous stimulus), shooting burning pain, and tingling and numbness. The diagnosis of neuropathic pain generally requires a complete medical history that includes a careful description of symptoms and a physical examination.

In Vitro Assays

The *in vitro* activity of the compounds of the invention may be determined by the following procedures.

DAAO:

DAAO assays are known in the literature. One DAAO assay that can be used to demonstrate the activity of the compounds of the invention is based on the measurement of H_2O_2, one of the products of the action of DAAO on the amino acid substrate of interest, serine. Amplex Red (Invitrogen Life Science # A-12222) is used in a coupled reaction along with

horseradish peroxidase (Sigma # P-8250) to produce a product, Resorufin, which can be monitored via fluorescence.

Inhibitor compounds are diluted in 100% DMSO starting at 4 mM in half log increments to create an 11-point dose response by the Pfizer Material Management Group. Each dilution is spotted in duplicate, 0.5 microliters/well, into black 384 well plates (Costar #3573). No inhibition control wells (ZPE) are spotted with 0.5 microliters of 100% DMSO and 100% inhibition control wells (HPE) are spotted with 0.5 microliters of 4 mM 3-hydroxyquinolin-2(1H)-one in 100% DMSO. Twenty microliters of assay buffer (100mM Tris-HCL, pH 8.5) containing 4 nM human DAAO enzyme expressed in sf9 insect cells (produced and purified in-house), 80 uM flavin adenine dinucleotide (Sigma #F6625), 0.8 units horseradish peroxidase (Sigma #P8250), and 100 uM Amplex Red (Molecular Probes #A12222) were added to each well of the plate using a Titertek MultiDrop-384 reagent addition device. Next, twenty microliters of assay buffer containing 200 uM D-Serine (Sigma #S4250) was added using the MultiDrop. The plates are spun at 1,000 rpm to ensure all liquid is coalesced to the bottom of the well. Exposure of Amplex Red to light must be kept to a minimum. The reaction is then incubated in the dark at ambient temperature for 30 – 60 minutes before reading the plates on a PerkinElmer Envision 2103 Multilabel Reader using the following settings: 10 flashes of the flash lamp, excitation filter 530 nm, emission filter 590 nm. The mean of the plate HPE and ZPE control values are used to calculate % inhibition values for each compound well in SIGHTS (an in-house data analysis software package) and non-linear curve fitting is used to calculate an IC50 value for each compound.

Applying the above assay to the compounds of the invention provides the data reported in Table 1.

TABLE 1

Example	DAAO IC50
1	9.87 nM

Example	DAAO IC50
2	6.50 nM
3	22600 nM
4	63.0 nM
5	160 nM
6	128 nM
7	784 nM
8	31.8 nM
9	1380 nM
10	23.8 nM
11	5.81 nM
12	197 nM
13	3290 nM
14	3660 nM
15	4930 nM
16	1840 nM
17	10600 nM
18	455 nM
19	10.9 nM
20	8.66 nM
21	5.06 nM
22	70.1 nM
23	11.5 nM
24	10.3 nM
25	61.9 nM
26	92.6 nM
27	5430 nM
28	41.1 nM
29	105 nM

Example	DAAO IC50
30	4.58 nM
31	11.3 nM
32	1.9 nM
33	40.9 nM
34	22.2 nM
35	2 nM
36	7 nM
37	36 nM

The compounds of this invention can be administered via either the oral, parenteral (such as subcutaneous, intravenous, intramuscular, intrasternal and infusion techniques), rectal, intranasal or topical routes to mammals. In general, these compounds are most desirably administered to humans in doses ranging from about 1mg to about 2000 mg per day, although variations will necessarily occur depending upon the weight and condition of the subject being treated and the particular route of administration chosen. However, a dosage level that is in the range of from about 0.1 mg to about 20 mg per kg of body weight per day is most desirably employed. Nevertheless, variations may still 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 effects provided that such higher dose levels are first divided into several small doses for administration throughout the day.

The pharmaceutical composition may, for example, be in a form suitable for oral administration such as a tablet, capsule, pill, powder, sustained release formulations, solution, or suspension; for parenteral injection such as a sterile solution, suspension or emulsion; for topical administration such as an ointment

or cream; or for rectal administration such as a suppository. The pharmaceutical composition may be in unit dosage forms suitable for single administration of precise dosages. The pharmaceutical composition will include a conventional pharmaceutical carrier or excipient and a compound according to the invention as an active ingredient. In addition, it may include other medicinal or pharmaceutical agents, carriers, adjuvants, etc.

In one embodiment, the pharmaceutical composition of the invention is in a form suitable for oral administration.

Exemplary parenteral administration forms include solutions or suspensions of active compounds in sterile aqueous solutions, for example, aqueous propylene glycol or dextrose solutions. Such dosage forms can be suitably buffered, if desired.

Suitable pharmaceutical carriers include inert diluents or fillers, water and various organic solvents. The pharmaceutical compositions may, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus for oral administration, tablets containing various excipients, such as citric acid may be employed together with various disintegrants such as starch, alginic acid and certain complex silicates and with binding agents such as sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tableting purposes. Solid compositions of a similar type may also be employed in soft and hard filled gelatin capsules. Preferred materials, therefore, include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration the active compound therein may be combined with various sweetening or flavoring agents, coloring matters or dyes and, if desired, emulsifying agents or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin, or combinations thereof.

Methods of preparing various pharmaceutical compositions with a specific amount of active compound are known, or will be apparent, to those

skilled in this art. For examples, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easter, Pa., 15th Edition (1975).

The compounds of the invention may be administered in combination with one or more additional medicinal or pharmaceutical agents ("the additional active agent"). Such use of compounds of the invention in combination with an additional active agent may be for simultaneous, separate or sequential use.

In one embodiment, the compounds of this invention are administered as adjunctive therapy with antipsychotics such as Ziprasidone (Geodon), molindone, loxapine, risperidone, olanzapine, quetiapine, aripiprazole, paliperidone, zyrrexa, bifeprunox, vabicaserin, ispronicline, sertindole, amisulpride, prochlorperazine, fluphenazine, trifluoroperazine, thioridazine, haloperidol, chloropromazine, flupentixol, pipotiazine, clozapine, and pimozide.

In another embodiment, the compounds of the present invention may also be used in combination with CNS agents such as antidepressants (such as sertraline), anti-Parkinsonian drugs (such as deprenyl, L-dopa, Requip, Mirapex, MAOB inhibitors such as selegine and rasagiline, comP inhibitors such as Tasmar, A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists, Nicotine agonists, Dopamine agonists and inhibitors of neuronal nitric oxide synthase), anti-Alzheimer's drugs such as donepezil, tacrine, $\alpha 2\delta$ inhibitors, COX-2 inhibitors, gaba pentenoids, propentofylline or metryfonate, and antipyschotics such as PDE10 inhibitors, 5HT2C agonists, alpha 7 nicotinic receptor agonists, CB1 antagonists and compounds having activity antagonizing dopamine D2 receptors.

In another embodiment, the compounds of the invention are administered as adjunctive therapy with Alzheimer's therapeutics including donepezil, rivastigmine, galantamine, memantine; dimebon, immunotherapeutics (such as bapineuzumab, LY 2062430, gammagard, ACC-001, R 1450, GSK 9337765 and CAD 106); secretase inhibitors (such as LY 450139, tarenflurbil, M-0752 (Merck); S-1953 (Wyeth)) and Rage inhibitors (such as PF-04499742 and PF-04494700).

In one embodiment, the one or more additional active agents, when used, are administered prior to administration of the compounds of the invention. In another embodiment, the one or more additional active agents, when used, are administered after administration of the compounds of the invention. In another embodiment, the one or more additional active agents, when used, are administered at about the same time as administration of the compounds of the invention.

The additional active agent may be administered by any route useful to administer said additional active agent.

In one embodiment, the one or more additional active agents are present in the pharmaceutical composition of the invention. Accordingly, in another embodiment, the invention relates to a method of treating a patient with a pharmaceutical composition of the invention further comprising one or more additional active agents.

The examples and preparations provided below further illustrate and exemplify the compounds of the present invention and methods of preparing such compounds. It is to be understood that the scope of the present invention is not limited in any way by the scope of the following examples and preparations.

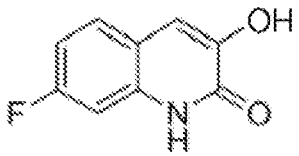
All patents, applications, publications, test methods, literature, and other materials cited herein are hereby incorporated by reference in their entireties.

Examples

Experiments were generally carried out under inert atmosphere (nitrogen or argon), particularly in cases where oxygen- or moisture-sensitive reagents or intermediates were employed. Commercial solvents and reagents were generally used without further purification. Chemical shifts for nuclear magnetic resonance (NMR) data are expressed in parts per million (ppm, δ) referenced to residual peaks from the deuterated solvents employed.

Example 1

7-fluoro-3-hydroxyquinolin-2(1*H*)-one



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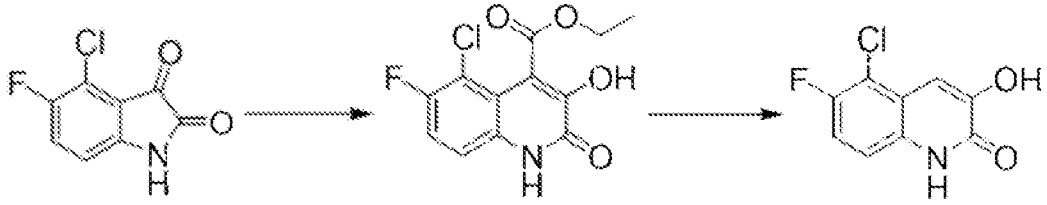
The title compound was prepared by the procedure depicted in Scheme 1 and described in detail below, using the general method of S-Y. Sit et al., Bioorganic Medicinal Chem. Lett. **1996**, *6*, 499.

Step 1. 6-Fluoro-1*H*-indole-2,3-dione (6-fluoroisatin, 200 mg, 1.2 mMol), diethylamine (0.24 mL, 2.3 mMol), and ethyl diazoacetate (0.24 mL, 2.3 mMol) were dissolved in ethanol (15 mL) and stirred at room temperature for 64 hours. Removal of solvent *in vacuo* then provided the diazo intermediate as an oil (LCMS *m/z* 278.0 [M-1]); this was treated with hydrochloric acid (1N, 75 mL), and allowed to react for 40 hours at room temperature. Filtration of the reaction mixture yielded ethyl 7-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-4-carboxylate as an orange solid (144 mg, 0.57 mMol). LCMS *m/z* 252.1 (M+1). ^{1}H NMR (400 MHz, CD_3OD) δ 1.42 (t, *J*=7.0 Hz, 3H), 4.48 (q, *J* =7.0 Hz, 2H), 7.02 (m, 2H), 7.67 (dd, *J* =5.6, 8.9 Hz, 1H).

Step 2. Methanol (7.5 mL), water (7.5 mL) and the compound from step 1 (100 mg, 0.4 mMol) were combined in a 30 mL microwave tube and treated with lithium hydroxide (86 mg, 3.6 mMol). The reaction was subjected to microwave conditions (Biotage Advancer, 150°C, high power) for 2 hours, with 30 seconds of prestirring. A white solid was removed via filtration, and the filtrate was acidified to pH 0 with 1N hydrochloric acid. Filtration of the resulting precipitate provided the title compound as a beige solid (70 mg, 0.39 mMol). MS (APCI) *m/z* 180.0 (M+1). ^{1}H NMR (400 MHz, CD_3OD) δ 6.98 (m, 2H), 7.13 (br s, 1H), 7.51 (dd, *J*=6.0, 8.5 Hz, 1H).

Example 2

5-chloro-6-fluoro-3-hydroxyquinolin-2(1*H*)-one

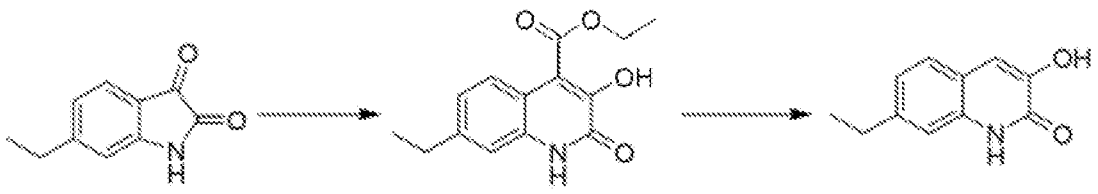


Step 1. Ethyl 5-chloro-6-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-4-carboxylate was prepared according to the general procedure for the synthesis of intermediate in Step 1 of Example 1, except that 4-chloro-5-fluoro-1*H*-indole-2,3-dione was used in place of 6-fluoro-1*H*-indole-2,3-dione, and that the aqueous filtrate after the hydrochloric acid treatment was extracted with dichloromethane (2 x 15 mL) and the combined organic layers concentrated *in vacuo* to provide additional aliquots of intermediate (total: 220 mg, 0.77 mMol, 77%). LCMS *m/z* 284.1 (M-1).

Step 2. The title compound was prepared according to the general procedure for the synthesis of Example 1, except the microwave reaction was carried out for 5 hours, to provide the title compound as a beige solid (9 mg, 0.042 mMol, 9%). LCMS *m/z* 212.1 (M-1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.19 (s, 1H), 7.24 (dd, *J*=4.6, 9.1 Hz, 1H), 7.35 (dd, *J*=9.1, 9.1 Hz, 1H), 10.27 (br s, 1H), 12.27 (br s, 1H).

Example 3

7-ethyl-3-hydroxyquinolin-2(1*H*)-one



Step 1. Preparation of ethyl 7-ethyl-3-hydroxy-2-oxo-1,2-dihydroquinoline-4-carboxylate.

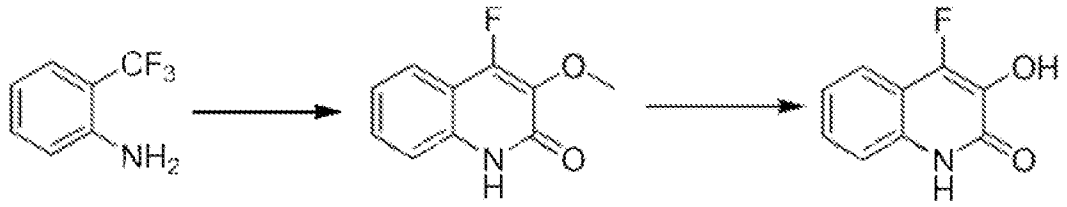
6-Ethyl-1*H*-indole-2,3-dione (200 mg, 1.1 mMol), diethylamine (0.24 mL, 2.3 mMol), and ethyl diazoacetate (0.24 mL, 2.3 mMol) were dissolved in ethanol (15 mL) and stirred at room temperature for 64 hours. Removal of

solvent *in vacuo* provided the diazo intermediate as an oil (LCMS *m/z* 288.2 [M-1]): this was treated with hydrochloric acid (1N, 75 mL), and allowed to react for 16 hours at room temperature. The reaction mixture was extracted twice with dichloromethane, and solvent was removed *in vacuo* to provide 0.27 g crude product. Purification was carried out via silica gel chromatography (Gradient: 50% ethyl acetate/heptane to 100% ethyl acetate) to provide ethyl 7-ethyl-3-hydroxy-2-oxo-1,2-dihydroquinoline-4-carboxylate (130 mg, <0.5 mMol), still contaminated with some of the indole-2,3-dione starting material. LCMS *m/z* 260.2 (M-1).

Step 2. Methanol (7.5 mL), water (7.5 mL) and the product from step 1 (130 mg, <0.5 mMol) were combined, treated with lithium hydroxide (100 mg, 4.7 mMol) and heated to reflux for 18 hours. The reaction was filtered, and the filtrate was acidified with 1N hydrochloric acid, then extracted twice with ethyl acetate, and twice with dichloromethane. The combined dichloromethane layers were concentrated *in vacuo*. The residue was purified by silica gel chromatography (Gradient: 5% ethyl acetate/heptane to 50% to 100% ethyl acetate), followed by two sequential preparative silica gel thin layer chromatographic separations (Eluant: 50% ethyl acetate/hexanes), providing the title compound as a brown solid (1.9 mg, 0.01 mMol). LCMS *m/z* 188.2 (M-1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, 3H, presumed - obscured by solvent), 2.74 (q, *J*=7.5 Hz, 2H), 6.87 (s, 1H), 7.11 (m, 2H), 7.20 (s, 1H), 7.43 (d, *J*=8.1 Hz, 1H), 11.15 (br s, 1H).

Example 4

4-fluoro-3-hydroxyquinolin-2(1*H*)-one



Step 1. Preparation of 4-fluoro-3-methoxyquinolin-2(1*H*)-one.

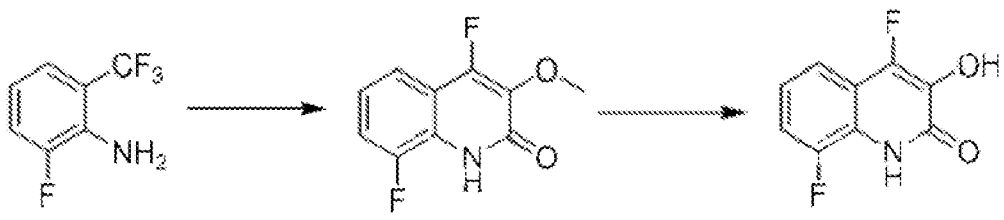
The general method of A.S. Kiselyov et al., *Organic Letters*, **2004**, 6, 4061 was employed to prepare the title compound. Ethyl methoxyacetate

(0.59 mL, 5.0 mMol) was added to a freshly prepared solution of lithium diisopropylamide (13 mMol) in tetrahydrofuran (5 mL) at -78°C. After 30 minutes, 2-(trifluoromethyl)aniline (0.15 mL, 1.2 mMol) was added and the reaction mixture was allowed to warm to room temperature and stir for 16 hours. Volatiles were removed *in vacuo*, and the remaining material was treated with saturated aqueous ammonium chloride solution. The resulting mixture was extracted twice with ethyl acetate, and the combined organic layers were washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Concentration *in vacuo* provided a residue that was purified by silica gel chromatography (Gradient: 100% heptane to 100% ethyl acetate). The resulting orange oil was triturated with diethyl ether to provide the title intermediate as a white solid (20 mg, 0.10 mMol). LCMS *m/z* 194.1 (M+1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (d, *J*=1.7 Hz, 3H), 7.30 (m, 1H), 7.35 (br d, *J*=8.3 Hz, 1H), 7.51 (m, 1H), 7.77 (dd, *J*=1.2, 7.9 Hz, 1H), 10.88 (br s, 1H).

Step 2. The product from Step 1 (18 mg, 0.093 mMol) was mixed with dichloromethane (0.5 mL) and the mixture was cooled to -78°C. Boron tribromide (1M in dichloromethane, 0.28 mL, 0.28 mMol) was added, and the reaction was allowed to stir for 1 hour at the same temperature. Methanol (3 mL) was then added to the cold reaction mixture, volatiles were removed *in vacuo*, and the residue was re-evaporated with dichloromethane. Addition of ether was followed by filtration to give the title compound as a yellow-white solid (5 mg, 0.028 mMol) LCMS *m/z* 180.1 (M+1). ^{1}H NMR (400 MHz, CD_3OD) δ 7.30 (m, 1H), 7.34 (br d, *J*=8.3 Hz, 1H), 7.45 (m, 1H), 7.71 (m, 1H).

Example 5

4,8-difluoro-3-hydroxyquinolin-2(1*H*)-one



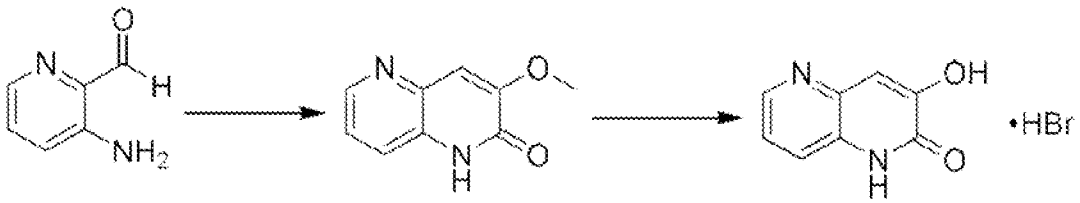
Step 1. Preparation of 4,8-difluoro-3-methoxyquinolin-2(1*H*)-one.

4,8-Difluoro-3-methoxyquinolin-2(1*H*)-one was prepared according to the general procedure for the synthesis of the intermediate in Step 1 of Example 4, except that 2-fluoro-6-(trifluoromethyl)aniline was used in place of 2-(trifluoromethyl)aniline. 4,8-Difluoro-3-methoxyquinolin-2(1*H*)-one was obtained as an off-white, fluffy solid (9 mg, 0.043 mMol, 8%). LCMS *m/z* 212.1 (M+1). ^{1}H NMR (400 MHz, CD_3OD) δ 4.04 (d, *J*=1.7 Hz, 3H), 7.30 (ddd, *J*=8.1, 8.1, 5.0, 1H), 7.37 (ddd, *J*=10.9, 8.3, 1.2 Hz, 1H), 7.59 (bd, *J*=7.9 Hz, 1H).

Step 2. The title compound was prepared according to the general procedure for the synthesis of product in Example 4, except that 4,8-difluoro-3-methoxyquinolin-2(1*H*)-one was used as the reactant to provide the title compound as a white/pinkish solid (3.5 mg, 0.018 mMol, 36%). LCMS *m/z* 198.0 (M+1). ^{1}H NMR (400 MHz, CD_3OD) δ 7.25 (m, 2H), 7.51 (m, 1H).

Example 6

3-hydroxy-1,5-naphthyridin-2(1*H*)-one hydrobromide



Step 1. Preparation of 3-methoxy-1,5-naphthyridin-2(1*H*)-one.

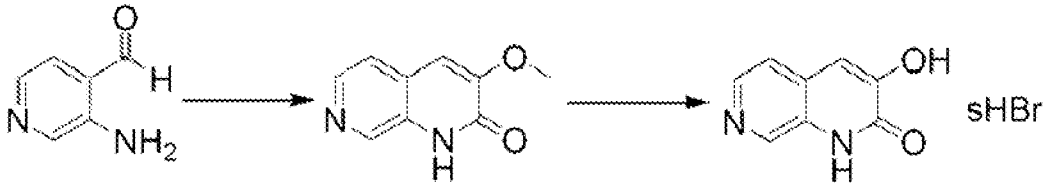
Ethyl methoxyacetate (0.71 mL, 6.0 mMol) was added to a -78°C solution of lithium bis(trimethylsilyl)amide (1.0 M solution in tetrahydrofuran, 6.0 mL, 6.0 mMol) in tetrahydrofuran (6 mL). After 20 minutes, a solution of 3-aminopyridine-2-carbaldehyde (244 mg, 2.00 mMol) in tetrahydrofuran (3 mL) was added drop-wise from a syringe. The resulting light orange solution was allowed to come slowly to room temperature as the dry ice/acetone bath warmed up. After 18 hours, the reaction was quenched with 6N hydrochloric acid (1.1 mL, 6.6 mMol), providing a precipitate; this mixture was heated to reflux for 2 hours. The reaction was then concentrated *in vacuo*, and the residue was dissolved in methanol. Product was precipitated out over time as

a light gray solid (18 mg). The mother liquor from this filtration was loaded onto dry silica gel and solvent was removed under reduced pressure. Additional product was then obtained through dry column vacuum chromatography [DCVC: See D.S. Pedersen and C. Rosenbohm, *Synthesis* **2001**, *16*, 2431] of this material (Eluant: 100% dichloromethane to 10:2 dichloromethane:methanol). The product obtained from the DCVC was triturated with methanol to yield product as an off-white solid (78 mg). A final DCVC of mixed fractions and the second mother liquor provided more product as a white solid (97 mg; total recovery: 193 mg, 1.1 mMol). LCMS *m/z* 175.1 (M-1). ^{1}H NMR (400 MHz, CD_3OD) δ 3.98 (s, 3H), 7.26 (s, 1H), 7.41 (dd, *J*=4.6, 8.3 Hz, 1H), 7.70 (br d, *J*=8.3 Hz, 1H), 8.45 (dd, *J*=1.2, 4.6 Hz, 1H).

Step 2. In a microwave vial equipped with a stir bar, finely ground product from Step 1 (10 mg, 0.06 mMol) was mixed with anhydrous dichloromethane (1 mL) and cooled in a dry ice/acetone bath. After addition of boron tribromide (1.0 M solution in dichloromethane, 0.38 mL, 0.38 mMol), the reaction was left in the cold bath for 5 minutes, then stirred at room temperature for 20 minutes, and finally heated in a microwave reactor for 10 minutes at 100°C. The tightly capped reaction was then subjected to conventional heating at 60°C for 65 hours. After being quenched with methanol (3 mL), approximately half of the reaction mixture was concentrated *in vacuo*, and the residue was triturated with dichloromethane to provide the title compound as a gray solid (5.4 mg, 0.022 mMol). LCMS *m/z* 161.0 (M-1). ^{1}H NMR (400 MHz, CD_3OD) δ 7.23 (s, 1H), 7.79 (dd, *J*=5.7, 8.4 Hz, 1H), 8.20 (d, *J*=8.0 Hz, 1H), 8.53 (dd, *J*=1.2, 5.7 Hz, 1H).

Example 7

3-hydroxy-1,7-naphthyridin-2(1*H*)-one hydrobromide



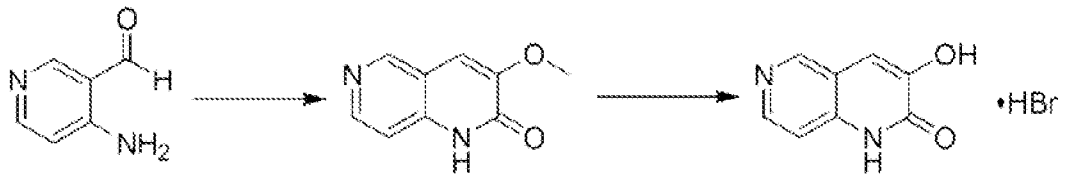
Step 1. Preparation of 3-methoxy-1,7-naphthyridin-2(1*H*)-one.

3-Methoxy-1,7-naphthyridin-2(1*H*)-one was prepared according to the general procedure for the synthesis of the intermediate from Step 1 of Example 6, except that 3-aminoisonicotinaldehyde was used in place of 3-aminopyridine-2-carbaldehyde. Product was obtained as white and light yellow solids (88 mg, 0.50 mMol, 25%). LCMS *m/z* 175.1 (M-1). ^{1}H NMR (400 MHz, CD_3OD) δ 3.97 (s, 3H), 7.25 (s, 1H), 7.60 (d, *J*=5.4 Hz, 1H), 8.27 (d, *J*=5.4 Hz, 1H), 8.54 (s, 1H).

Step 2. The product from Step 1 (10.9 mg, 0.062 mMol) was mixed with anhydrous dichloromethane (2 mL) and cooled in a dry ice/acetone bath. After addition of boron tribromide (1.0 M solution in dichloromethane, 0.32 mL, 0.32 mMol), the reaction was left in the cold bath for 30 minutes, then allowed to warm to room temperature and stir for 18 hours. The reaction was cooled to -78°C again, and additional boron tribromide (1 mL, 1 mMol) was added. The mixture was allowed to reach ambient temperature, and stirred for 7 days, after which it was cooled in an ice bath and quenched with methanol (4 mL). The mixture was warmed to room temperature, solvents were removed under reduced pressure, and the residue was triturated with dichloromethane, and then with 20:1 dichloromethane:methanol, to provide the title compound as a light gray solid (8 mg, 0.033 mMol). LCMS *m/z* 161.1 (M-1). ^{1}H NMR (400 MHz, CD_3OD) δ 7.28 (s, 1H), 8.02 (d, *J*=6.2 Hz, 1H), 8.36 (d, *J*=6.2 Hz, 1H), 8.61 (s, 1H).

Example 8

3-hydroxy-1,6-naphthyridin-2(1*H*)-one hydrobromide



Step 1. Preparation of 3-methoxy-1,6-naphthyridin-2(1*H*)-one.

Ethyl methoxyacetate (0.71 mL, 6.0 mMol) was added to a -78°C solution of lithium bis(trimethylsilyl)amide (1.0 M solution in tetrahydrofuran, 6.0 mL, 6.0 mMol) in tetrahydrofuran (6 mL). After 20 minutes, a solution of 4-aminonicotinaldehyde (244 mg, 2.00 mMol) in tetrahydrofuran (4 mL) was

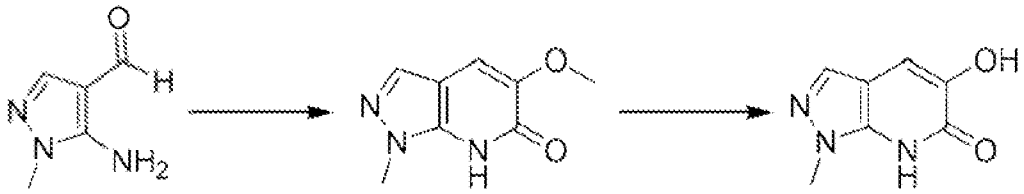
added drop-wise from a syringe. The resulting light orange solution was allowed to come slowly to room temperature as the dry ice/acetone bath warmed up. After 18 hours, the reaction was quenched with 6N hydrochloric acid (1.1 mL, 6.6 mMol), providing a precipitate; this mixture was heated to reflux for 2 hours. The reaction was then concentrated *in vacuo*, and the residue was triturated with dichloromethane, then methanol. A solid was removed via filtration, and the filtrate was concentrated *in vacuo*. The residue was triturated with ether to provide a tan solid; approximately one-third of this solid was subjected to DCVC over silica gel (Eluant: 100% dichloromethane to 100:10:1 dichloromethane:methanol:triethylamine), yielding 3-methoxy-1,6-naphthyridin-2(1*H*)-one as a white solid contaminated with triethylamine. A second DCVC was carried out on this material (Eluant: 100% dichloromethane to 10:1 dichloromethane:methanol) to provide additional intermediate as a white solid (65 mg, 0.37 mMol). APCI *m/z* 175.1 (M-1). ^{1}H NMR (400 MHz, CD_3OD) δ 3.96 (s, 3H), 7.37 (s, 1H), 7.39 (m, apparent br d, *J*=6.0 Hz, 1H), 8.40 (d, *J*=6.0 Hz, 1H), 8.86 (s, 1H).

Step 2. 3-Methoxy-1,6-naphthyridin-2(1*H*)-one from Step 1 (25 mg, 0.14 mMol) was mixed with anhydrous dichloromethane (2 mL) and cooled in a dry ice/acetone bath. After addition of boron tribromide (1.0 M solution in dichloromethane, 0.57 mL, 0.57 mMol), the reaction was left in the cold bath for 30 minutes, then allowed to warm to room temperature and stir for 18 hours. Additional dichloromethane (2 mL) was added, the reaction was cooled in a dry ice/acetone bath, and then treated with additional boron tribromide (0.57 mL, 0.57 mMol). The reaction mixture was allowed to come to ambient temperature and was stirred for 4 days, after which it was cooled to -78°C and quenched with methanol (5 mL). The mixture was warmed to room temperature, solvents were removed under reduced pressure, and the residue was triturated with dichloromethane, then with ethyl acetate, and finally with hot methanol to provide the title compound as an off-white solid (13.2 mg, 0.054 mMol). APCI *m/z* 161.1 (M-1). ^{1}H NMR (400 MHz, CD_3OD)

δ 7.27 (s, 1H), 7.62 (d, *J*=6.6 Hz, 1H), 8.46 (m, apparent br d, *J*=6.6Hz, 1H), 8.98 (s, 1H).

Example 9

5-hydroxy-1-methyl-1,7-dihydro-6*H*-pyrazolo[3,4-*b*]pyridin-6-one



Step 1. Preparation of 5-methoxy-1-methyl-1,7-dihydro-6*H*-pyrazolo[3,4-*b*]pyridin-6-one.

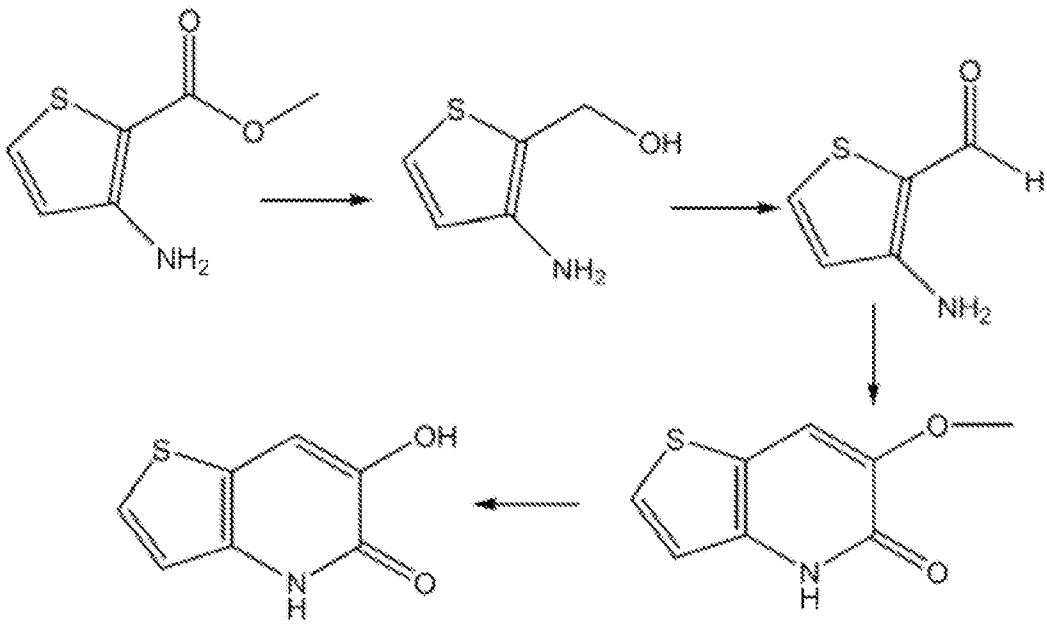
Ethyl methoxyacetate (0.35 mL, 3.0 mMol) was added to a -78°C solution of lithium bis(trimethylsilyl)amide (1.0 M solution in tetrahydrofuran, 3.0 mL, 3.0 mMol) in tetrahydrofuran (3 mL). After 20 minutes, a solution of 5-amino-1-methyl-1*H*-pyrazole-4-carbaldehyde (125 mg, 1.00 mMol) in tetrahydrofuran (3 mL, necessary to warm this to achieve a solution) was added drop-wise from a syringe. The resulting yellow solution was allowed to come slowly to room temperature as the dry ice/acetone bath warmed up. After 18 hours, the reaction was quenched with 6N hydrochloric acid (1 mL, 6 mMol), and the mixture was allowed to stir for 18 hours. The solids were collected by filtration and washed with ethyl acetate to provide 5-methoxy-1-methyl-1,7-dihydro-6*H*-pyrazolo[3,4-*b*]pyridin-6-one as an off-white solid (110 mg, 0.61 mMol). APCI *m/z* 178.1 (M-1). ^{1}H NMR (400 MHz, CD_3OD) δ 3.85 (s, 3H), 3.93 (s, 3H), 7.26 (s, 1H), 7.84 (s, 1H).

Step 2. 5-Methoxy-1-methyl-1,7-dihydro-6*H*-pyrazolo[3,4-*b*]pyridin-6-one from Step 1 (32 mg, 0.18 mMol) was mixed with anhydrous dichloromethane (2 mL) and cooled in a dry ice/acetone bath. After addition of boron tribromide (1.0 M solution in dichloromethane, 0.72 mL, 0.72 mMol), the reaction was left in the cold bath for 15 minutes, then allowed to warm to room temperature and stir for 18 hours. It was then cooled to -78°C and quenched with methanol (5 mL). The mixture was warmed to room temperature, solvents were removed under reduced pressure, and the residue

was triturated with dichloromethane, then with ethyl acetate to provide the title compound as a tan solid (20 mg, 0.12 mMol). LCMS *m/z* 164.1 (M-1). ^{1}H NMR (400 MHz, CD_3OD) δ 3.94 (s, 3H), 7.11 (s, 1H), 7.80 (s, 1H).

Example 10

6-hydroxythieno[3,2-*b*]pyridin-5(4*H*)-one



Step 1. Preparation of 3-aminothiophene-2-carbaldehyde.

A. Preparation of (3-amino-2-thienyl)methanol.

A solution of methyl 3-aminothiophene-2-carboxylate (4.0 g, 25 mMol) in tetrahydrofuran (10 mL) was added drop-wise to a 0°C solution of lithium aluminum hydride in tetrahydrofuran (1M, 51 mL, 51 mMol). After completion of the addition, the reaction was allowed to warm to room temperature, and then stirred for 1 hour. The reaction was carefully quenched with saturated aqueous sodium sulfate solution (40 mL); the resulting solid was removed by filtration and the filtrate was concentrated under reduced pressure to provide roughly 50 mL of an aqueous mixture. This was extracted with ethyl acetate (3 x 150 mL), and the combined organic layers were concentrated *in vacuo* to provide (3-amino-2-thienyl)methanol as a yellow solid (2.37 g, 18.3 mMol) which was carried on to the next step without purification. LCMS *m/z* 130.0 (M+1).

B. A solution of (3-amino-2-thienyl)methanol (2.37 g, 18.3 mMol) in dichloromethane (20 mL) was treated with activated manganese dioxide (8.0 g, 92 mMol) and stirred vigorously at room temperature for 18 hours. The mixture was then filtered through celite to provide an orange solution, which was concentrated *in vacuo* to yield 3-aminothiophene-2-carbaldehyde as a brown oil (1.58 g, 12.4 mMol) that was taken on to the next step without purification. LCMS *m/z* 128.0 (M+1).

Step 2. Preparation of 6-methoxythieno[3,2-*b*]pyridin-5(4*H*)-one.

Ethyl methoxyacetate (2.7 mL, 23 mMol) was added to a -78°C solution of lithium bis(trimethylsilyl)amide (1.0 M solution in tetrahydrofuran, 23.0 mL, 23.0 mMol). After 30 minutes, a solution of 3-aminothiophene-2-carbaldehyde (480 mg, 3.8 mMol) in tetrahydrofuran (10 mL) was added, and the resulting dark brown mixture was allowed to come slowly to room temperature. A portion of the reaction mixture was purified by silica gel chromatography (Eluant: ethyl acetate, then 10% methanol in ethyl acetate, then 15% methanol in ethyl acetate). The material obtained from this column was triturated with 10% methanol in DCM and then filtered to provide 6-methoxythieno[3,2-*b*]pyridin-5(4*H*)-one as a brown solid (12 mg, 0.066 mMol). LCMS *m/z* 180.1 (M-1). ^{1}H NMR (400 MHz, $CDCl_3$ with 2 drops CD_3OD) δ 3.88 (s, 3H), 7.03 (d, *J*=5.4 Hz, 1H), 7.14 (s, 1H), 7.33 (d, *J*=5.4 Hz, 1H).

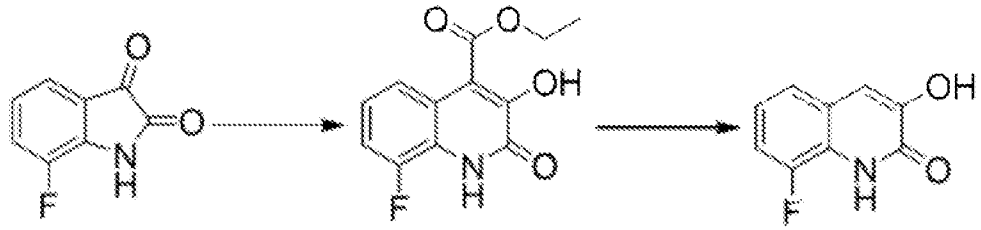
Step 3. Preparation of 6-hydroxythieno[3,2-*b*]pyridin-5(4*H*)-one.

The product from the previous step (10.5 mg, 0.058 mMol) was mixed with anhydrous dichloromethane (1.5 mL) and cooled in a dry ice/acetone bath. After addition of boron tribromide (1.0 M solution in dichloromethane, 0.174 mL, 0.174 mMol), the reaction was allowed to warm to room temperature and stirred for 3 hours. It was then carefully quenched with methanol (1 mL), and the reaction volume was brought to 10 mL with dichloromethane. This organic layer was washed with water (10 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to provide a light brown solid, which was resuspended in dichloromethane. Filtration of this mixture provided the title compound as a beige solid (2.3 mg, 0.014 mMol).

LCMS *m/z* 166.0 (M-1). ^{1}H NMR (400 MHz, CD_3OD) δ 7.00 (dd, *J*=0.6, 5.4 Hz, 1H), 7.33 (d, *J*=0.6 Hz, 1H), 7.47 (d, *J*=5.4 Hz, 1H).

Example 11

8-fluoro-3-hydroxyquinolin-2(1*H*)-one



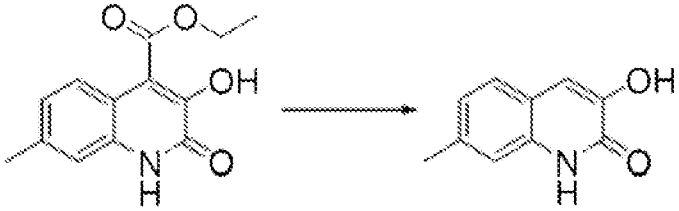
Step 1. Preparation of ethyl 8-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-4-carboxylate.

Ethyl 8-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-4-carboxylate was prepared according to the general procedure for the synthesis of the intermediate of Step 1 of Example 1, except that 7-fluoro-1*H*-indole-2,3-dione was used in place of 6-fluoro-1*H*-indole-2,3-dione. Ethyl 8-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-4-carboxylate was obtained as an orange solid (1.03 g, 4.1 mMol, 68%). LCMS *m/z* 250.1 (M-1). ^{1}H NMR (400 MHz, CD_3OD) δ 1.42 (t, *J*=7.1 Hz, 3H), 4.49 (q, *J*=7.1 Hz, 2H), 7.19 (m, 2H), 7.41 (m, 1H).

Step 2. Methanol (1 mL), water (1 mL) and compound ethyl 8-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-4-carboxylate (100 mg, 0.40 mMol) were combined in a microwave vial and treated with lithium hydroxide (20 mg, 0.84 mMol). The reaction was subjected to microwave conditions (150°C) for 15 minutes, then cautiously acidified with 1N hydrochloric acid (0.84 mL, 0.84 mMol), and filtered. The collected solid was rinsed with pH 7 buffer, then methanol, to provide the title compound as a tan solid (40 mg, 0.22 mMol). LCMS *m/z* 178.0 (M-1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.10 (ddd, *J*=8, 8, 5.2 Hz, 1H), 7.13 (d, *J*=1.6 Hz, 1H), 7.18 (ddd, *J*=10.3, 8.1, 1.4 Hz, 1H), 7.32 (br d, *J*=7.8 Hz, 1H), 9.74 (br s, 1H), 12.06 (br s, 1H).

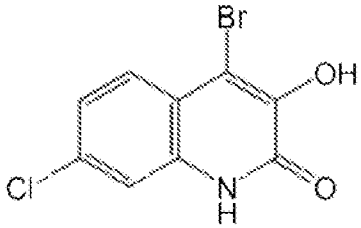
Example 12

3-hydroxy-7-methylquinolin-2(1*H*)-one



3-Hydroxy-7-methylquinolin-2(1*H*)-one was prepared according to the general procedure for the synthesis of the intermediate of Step 1 of Example 11, except that ethyl 3-hydroxy-7-methyl-2-oxo-1,2-dihydroquinoline-4-carboxylate [see M.J. Fray et al., *Medicinal Chem. Research* **1996**, *6*, 581] was used in place of ethyl 8-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-4-carboxylate. The title compound was obtained as a tan solid (49 mg, 0.28 mMol, 88%). LCMS *m/z* 174.1 (M-1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.32 (s, 3H), 6.94 (d, *J*=8.0 Hz, 1H), 6.98 (s, 1H), 7.04 (s, 1H), 7.34 (d, *J*=8.0 Hz, 1H).

Example 13

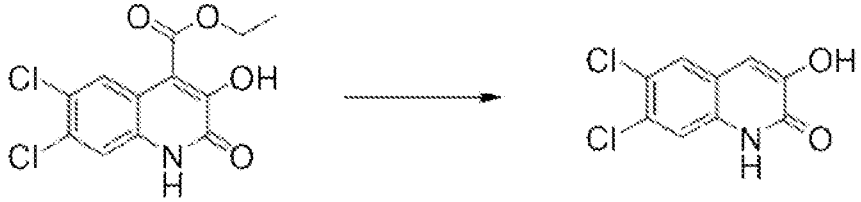


4-bromo-7-chloro-3-hydroxyquinolin-2(1*H*)-one

The title compound can be prepared according to the procedure of S-Y. Sit et al., *Bioorganic Medicinal Chem. Lett.* **1996**, *6*, 499. Specifically, 4-bromo-7-chloro-3-hydroxyquinolin-2(1*H*)-one was obtained as a white solid, LCMS *m/z* 274.2 (M-1, largest ion of halogen pattern). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.31 (dd, *J*=8.7, 2.1 Hz, 1H), 7.34 (d, *J*=2.2 Hz, 1H), 7.72 (d, *J*=8.8 Hz, 1H), 10.64 (br s, 1H), 12.4 (br s, 1H).

Example 14

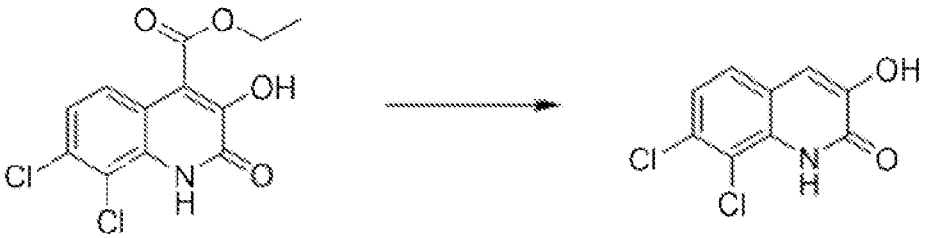
6,7-dichloro-3-hydroxyquinolin-2(1*H*)-one



6,7-Dichloro-3-hydroxyquinolin-2(1*H*)-one was prepared according to the general procedure for the synthesis of Example 12, except that ethyl 6,7-dichloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-4-carboxylate [see M.J. Fray et al., *Medicinal Chem. Research* **1996**, *6*, 581] was used as the starting material. The title compound was obtained as a tan solid. Yield: 36 mg, 0.16 mmol, 94%. LCMS *m/z* 230.0 (M+1). ^{1}H NMR (400 MHz, CD_3OD) δ 7.07 (s, 1H), 7.42 (s, 1H), 7.67 (s, 1H).

Example 15

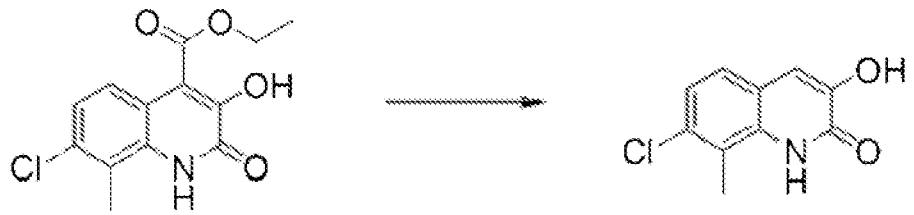
7,8-dichloro-3-hydroxyquinolin-2(1*H*)-one



7,8-dichloro-3-hydroxyquinolin-2(1*H*)-one was prepared according to the general procedure for the synthesis of Example 12, except that ethyl 7,8-dichloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-4-carboxylate [see M.J. Fray et al., *Medicinal Chem. Research* **1996**, *6*, 581] was used as the starting material. The title compound was obtained as an off-white solid. Yield: 34 mg, 0.15 mmol, 87%. LCMS *m/z* 230.0 (M+1). ^{1}H NMR (400 MHz, CD_3OD) δ 7.02 (s, 1H), 7.29 (d, *J*=8.4 Hz, 1H), 7.39 (d, *J*=8.6 Hz, 1H).

Example 16

7-chloro-3-hydroxy-8-methylquinolin-2(1*H*)-one



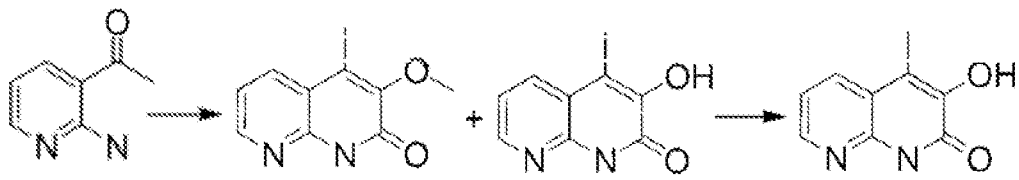
Step 1. Ethyl 7-chloro-3-hydroxy-8-methyl-2-oxo-1,2-dihydroquinoline-4-carboxylate.

Ethyl 7-chloro-3-hydroxy-8-methyl-2-oxo-1,2-dihydroquinoline-4-carboxylate can be prepared according to the procedure of M.J. Fray et al., *Medicinal Chem. Research* **1996**, *6*, 581 and was obtained as a beige solid. LCMS *m/z* * (M-1). ^{1}H NMR (400 MHz, CD_3OD) δ 1.42 (t, *J*=7.1 Hz, 3H), 2.54 (s, 3H), 4.48 (q, *J*=7.1 Hz, 2H), 7.26 (d, *J*=8.8 Hz, 1H), 7.39 (br d, *J*=8.7 Hz, 1H).

Step 2. The title compound was prepared according to the general procedure for the synthesis of Example 12, except that ethyl 7-chloro-3-hydroxy-8-methyl-2-oxo-1,2-dihydroquinoline-4-carboxylate was used as the starting material. The title compound was obtained as an off-white solid. Yield: 36 mg, 0.17 mmol, 94%. LCMS *m/z* 210.1 (M+1). ^{1}H NMR (400 MHz, CD_3OD) δ 2.49 (s, 3H), 6.76 (s, 1H), 7.09 (d, *J*=8.4 Hz, 1H), 7.16 (d, *J*=8.6 Hz, 1H).

Example 17

3-hydroxy-4-methyl-1,8-naphthyridin-2(1*H*)-one



Step 1. Preparation of 3-methoxy-4-methyl-1,8-naphthyridin-2(1*H*)-one.

3-methoxy-4-methyl-1,8-naphthyridin-2(1*H*)-one was prepared according to the general procedure for the synthesis of the intermediate of Step 1 of Example 7, except that 1-(2-aminopyridin-3-yl)ethanone [see T.J.

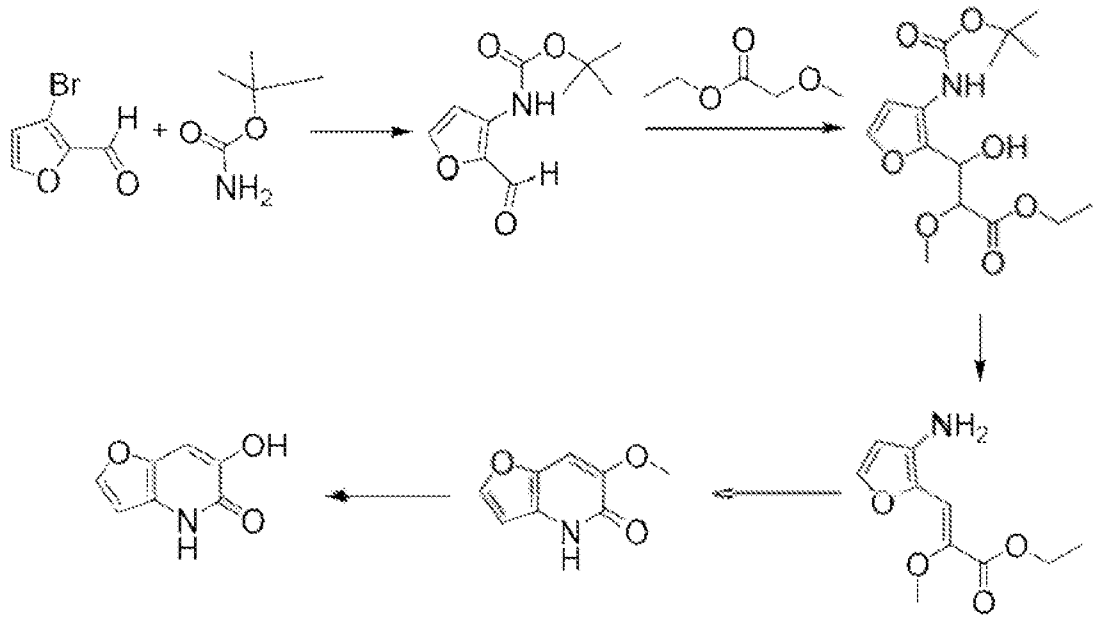
Murray et al., *Tetrahedron* **1995**, *51*, 635] was used in place of 3-aminopyridine-2-carbaldehyde. After the addition of hydrochloric acid, the beige precipitate was filtered, then resuspended in 1N hydrochloric acid and heated at reflux for about 66 hours. The cooled reaction mixture was extracted with ethyl acetate (3 x 50 mL), and the combined organic layers were washed with saturated aqueous sodium chloride solution and dried over sodium sulfate. Filtration and removal of solvent *in vacuo* provided a roughly 1:1 mixture of compound 3-methoxy-4-methyl-1,8-naphthyridin-2(1*H*)-one and desired final product, 3-hydroxy-4-methyl-1,8-naphthyridin-2(1*H*)-one, as a beige solid. Yield: 50 mg, about 0.136 mmol each compound, 25%. LCMS *m/z* 191.1 (M+1 for 3-methoxy-4-methyl-1,8-naphthyridin-2(1*H*)-one) and 175.2 (M-1 for 3-hydroxy-4-methyl-1,8-naphthyridin-2(1*H*)-one). ^{1}H NMR (400 MHz, CD_3OD) δ 2.39 (s, 3H), 2.46 (s, 3H), 3.90 (s, 3H), 7.28 (dd, *J*=8.0, 4.9 Hz, 1H), 7.31 (dd, *J*=7.9, 4.8 Hz, 1H), 8.08 (dd, *J*=8.0, 1.5 Hz, 1H), 8.17 (dd, *J*=8.1, 1.7 Hz, 1H), 8.37 (dd, *J*=4.7, 1.5 Hz, 1H), 8.47 (dd, *J*=4.6, 1.7 Hz, 1H).

Step 2. Preparation of compound 3-hydroxy-4-methyl-1,8-naphthyridin-2(1*H*)-one.

The title compound was prepared according to the general procedure for the synthesis of Example 5, except that the mixture of products obtained in the previous step was used as the starting material. Additionally, the crude product was triturated with a 20:1 mixture of dichloromethane and methanol, to provide the title compound as a beige solid. Yield: 8 mg, 0.045 mmol, 35%. LCMS *m/z* 175.1 (M-1). ^{1}H NMR (400 MHz, CD_3OD) δ 2.46 (s, 3H), 7.64 (dd, *J*=8.1, 5.6 Hz, 1H), 8.47 (dd, *J*=5.8, 1.4 Hz, 1H), 8.63 (dd, *J*=8.0, 1.5 Hz, 1 H).

Example 18

6-hydroxyfuro[3,2-b]pyridin-5(4*H*)-one



Step 1. Preparation of *tert*-butyl (2-formyl-3-furyl)carbamate.

tert-Butyl carbamate (1.51 g, 12.9 mmol), cesium carbonate (4.89 g, 15.0 mmol), tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (99.4 mg, 0.096 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos, 180 mg, 0.311 mmol) and 3-bromo-2-furaldehyde (1.87 g, 10.7 mmol) were combined in toluene (50 mL), and degassed by carrying out three cycles of a vacuum/ nitrogen introduction procedure. The reaction mixture was then heated to 100°C for about 18 hours, after which it was cooled, diluted with dichloromethane and filtered through Celite. The yellow filtrate was washed with saturated aqueous ammonium chloride solution, dried over sodium sulfate, filtered and concentrated *in vacuo*. The resulting dark oil was purified via silica gel chromatography (Gradient: 100% heptane to 100% ethyl acetate) to provide *tert*-butyl (2-formyl-3-furyl)carbamate as a light yellow solid. Yield: 1.88 g, 8.90 mmol, 83%. LCMS *m/z* 210.1 (M-1). ^{1}H NMR (400 MHz, CD_3OD) δ 1.54 (s, 9H), 7.17 (br s, 1H), 7.72 (d, *J*=1.9 Hz, 1H), 9.68 (s, 1H).

Step 2. Preparation of ethyl 3-{3-[(*tert*-butoxycarbonyl)amino]-2-furyl}-3-hydroxy-2-methoxypropanoate.

Ethyl methoxyacetate (97%, 2.80 mL, 23.1 mmol) in tetrahydrofuran (25 mL) was added to a -78°C solution of lithium bis(trimethylsilyl)amide (1.0M solution in tetrahydrofuran, 23.1 mL, 23.1 mmol). After 30 minutes, a solution of the product from Step 1 (1.88 g, 8.90 mmol) in tetrahydrofuran (15 mL) was added drop-wise. After 1 hour at -78°C, the reaction was quenched with water, and extracted with dichloromethane. The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting yellow oil was subjected to silica gel chromatography (Gradient: 100% heptane to 100% ethyl acetate) to provide ethyl 3-{3-[(*tert*-butoxycarbonyl)amino]-2-furyl}-3-hydroxy-2-methoxypropanoate as a colorless oil, which by ^{1}H NMR was a roughly 3:1 mixture of diastereomers. Yield: 2.77 g, 8.41 mmol, 94%. LCMS *m/z* 328.1 (M-1). ^{1}H NMR (400 MHz, CD_3OD) δ 1.19 and 1.25 (two triplets, *J*=7.1 Hz, 3H), 1.50 (s, 9H), 3.37 and 3.41 (2 singlets, 3H), 4.08 and 4.14 (2 doublets, *J*=5.8, 6.6 Hz, 1H), 4.12 and 4.20 (2 multiplets, apparent broad quartets, *J*=7 Hz, 2H), 4.96 and 5.01 (2 br doublets, *J*=6.6, 5.8 Hz, 1H), 6.72 (br s, 1H), 7.33 and 7.34 (2 doublets, *J*=1.9, 2.1 Hz, 1H).

Step 3. Preparation of ethyl (2Z)-3-(3-amino-2-furyl)-2-methoxyacrylate.

The product from Step 2 (2.3 g, 7.0 mmol) was mixed with dichloromethane (15 mL) and cooled to -10°C. After addition of boron tribromide (1.0M solution in dichloromethane, 6.28 mL, 6.28 mmol), the reaction was stirred at -10°C for 1 hour, then carefully quenched with methanol (5 mL), and partitioned between water and dichloromethane (50 mL). The aqueous layer was extracted five times with dichloromethane, and the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification via silica gel chromatography (Gradient: 100% heptane to 100% ethyl acetate, followed by flushing with a gradient of 100% ethyl acetate to 10% methanol in ethyl acetate) provided ethyl (2Z)-3-(3-amino-2-furyl)-2-methoxyacrylate as an orange oil. Yield: 310 mg, 1.4 mmol, 20%. ^{1}H NMR (400 MHz, CD_3OD) δ 1.33 (t, *J*=7.1 Hz, 3H), 3.66 (s, 3H), 4.24 (q, *J*=7 Hz, 2H), 6.17 (s, 1H), 7.10 (s, 1H), 7.37 (br s, 1H).

Step 4. Preparation of 6-methoxyfuro[3,2-b]pyridin-5(4*H*)-one.

The product from Step 3 (0.31 g, 1.4 mmol) was dissolved in 5 mL of THF and added drop-wise to a -78°C solution of lithium bis(trimethylsilyl)amide (1.0M solution in tetrahydrofuran, 4.4 mL, 4.4 mmol). The reaction was allowed to warm to about 25°C. After 3 hours, it was again cooled to -78°C and treated with additional lithium bis(trimethylsilyl)amide (1.0M solution in tetrahydrofuran, 1.5 mL, 1.5 mmol). After 1 h the reaction was quenched with saturated aqueous ammonium chloride solution (2 mL), and solvents were removed *in vacuo*. The resulting material was mixed with dichloromethane and filtered; the solid was washed with 10% methanol in dichloromethane and filtered to obtain 6-methoxyfuro[3,2-b]pyridin-5(4*H*)-one as a beige solid. Yield: 74 mg, 0.45 mmol, 32%. LCMS *m/z* 166.0 (M+1). ^{1}H NMR (400 MHz, CD_3OD) δ 3.87 (s, 3H), 6.60 (br s, 1H), 7.43 (s, 1H), 7.70 (d, *J*=2.1 Hz, 1H).

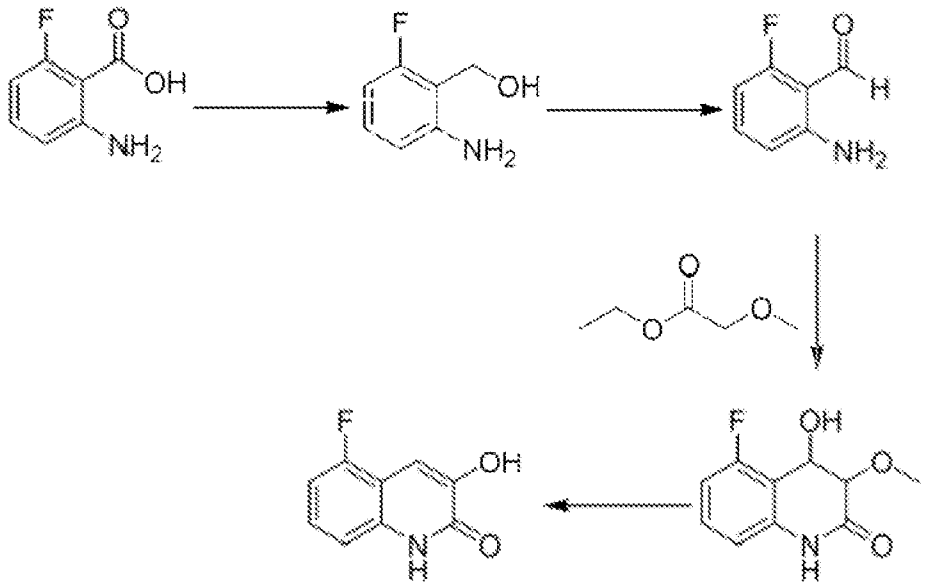
Step 5. Preparation of compound 6-hydroxyfuro[3,2-b]pyridin-5(4*H*)-one.

The product from Step 4 (29 mg, 0.18 mmol) was combined with dichloromethane (2 mL), and the heterogeneous mixture was cooled to -10°C and treated drop-wise with boron tribromide (1.0M solution in dichloromethane, 0.54 mL, 0.54 mmol). After 10 minutes, the reaction was warmed to about 25°C, at which point the reaction had proceeded to less than 50% completion, by LCMS analysis. Additional dichloromethane (12 mL) was added, and the flask was recooled to -10°C and again treated with boron tribromide (1.0M solution in dichloromethane, 1.4 mL, 1.4 mmol). After warming to about 25°C and stirring for an hour, the reaction was quenched with methanol (1 mL) and filtered. The filtrate was allowed to stand for several hours while a precipitate formed; the supernatant was then removed and concentrated *in vacuo*. The resulting residue was triturated with 10% methanol in dichloromethane, to provide the title compound as a beige solid. Yield: 4 mg, 0.026 mmol, 14%. MS (APCI) *m/z* 152.0 (M+1). ^{1}H NMR (400

MHz, CD_3OD) δ 6.73 (dd, *J*=2.2, 0.9 Hz, 1H), 7.50 (d, *J*=1.0 Hz, 1H), 7.83 (d, *J*=2.3 Hz, 1H).

Example 19

5-fluoro-3-hydroxyquinolin-2(1*H*)-one



Step 1. Preparation of (2-amino-6-fluorophenyl)methanol.

A solution of lithium aluminum hydride (1.0M solution in tetrahydrofuran, 18 mL, 18 mmol) was cooled in an ice bath, and treated drop-wise with a solution of 2-amino-6-fluorobenzoic acid (2.00 g, 12.9 mmol) in tetrahydrofuran (30 mL). The ice bath was allowed to melt over the following 18 hours and the reaction mixture warmed to about 25°C. The reaction was then quenched by the addition of sodium sulfate decahydrate (2 g) and saturated aqueous sodium chloride solution (6 mL). The resulting mixture was stirred for 1.5 hours, and then filtered through Celite. The filter pad was rinsed with diethyl ether (2 x 10 mL), and the filtrates were concentrated *in vacuo*. The resulting material was loaded onto silica gel by dissolution in tetrahydrofuran, treatment with silica gel and removal of solvent under reduced pressure. Purification by dry column vacuum chromatography (Eluant: 100% heptane to 2:1 ethyl acetate:heptane) provided (2-amino-6-fluorophenyl)methanol as a light yellow solid. Yield: 549 mg, 3.89 mmol, 30%. MS (APCI) *m/z* 139.8 (M-1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (br s,

1H), 4.33 (br s, 2H), 4.79 (s, 2H), 6.46 (m, 2H), 7.05 (ddd, *J*=8.2, 8.2, 6.4 Hz, 1H).

Step 2. Preparation of 2-amino-6-fluorobenzaldehyde.

The product from the previous step (250 mg, 1.77 mmol) was mixed with dichloromethane (1 mL) and treated with manganese(IV) oxide (770 mg, 8.9 mmol). Additional dichloromethane (1 mL) was used to rinse the sides of the reaction vessel. The heterogeneous reaction mixture was vigorously stirred for about 18 hours, then filtered through a 1.5 cm plug of silica gel, which was rinsed with additional dichloromethane (3 x 8 mL). The filtrates were concentrated *in vacuo* to afford 2-amino-6-fluorobenzaldehyde as a waxy yellow solid. Yield: 187 mg, 1.34 mmol, 76%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (ddd, *J*=11.0, 8.0, 0.9 Hz, 1H), 6.40 (dd, *J*=8.5, 0.7 Hz, 1H), 7.24 (ddd, *J*=8.3, 8.3, 6.2 Hz, 1H), 10.31 (s, 1H).

Step 3. Preparation of 5-fluoro-4-hydroxy-3-methoxy-3,4-dihydroquinolin-2(1*H*)-one.

Ethyl methoxyacetate (253 uL, 2.15 mmol) was added to a -78°C solution of lithium bis(trimethylsilyl)amide (1.0M solution in tetrahydrofuran, 2.2 mL, 2.2 mmol) in tetrahydrofuran (2 mL). After 20 minutes, a solution of the product from the previous step (100 mg, 0.719 mmol) in tetrahydrofuran (2 mL) was added drop-wise from a syringe. The resulting yellow solution was kept at -78°C for 15 minutes, then the cooling bath was removed and the reaction mixture allowed to warm to about 25°C. The reaction was quenched with 6N hydrochloric acid (360 uL, 2.2 mmol), providing a precipitate, which was collected by filtration. Purification via silica gel chromatography (Gradient: dichloromethane to 10:2 dichloromethane:methanol) provided compound 5-fluoro-4-hydroxy-3-methoxy-3,4-dihydroquinolin-2(1*H*)-one as a white solid, characterized by ^{1}H NMR as one major product containing a small amount of its diastereomer. Yield: 100 mg, 0.47 mmol, 65%. MS (APCI) *m/z* 209.8 (M-1). ^{1}H NMR (400 MHz, CD_3OD) δ 3.64 (s, 3H), 4.11 (d, *J*=3.7 Hz, 1H), 5.24 (d, *J*=3.7 Hz, 1H), 6.73 (d, *J*=8.0 Hz, 1H), 6.80 (br dd, apparent t, *J*=9, 9 Hz, 1H), 7.29 (ddd, apparent td, *J*=8.2, 8.2, 6.0 Hz, 1H). Partial ^{1}H

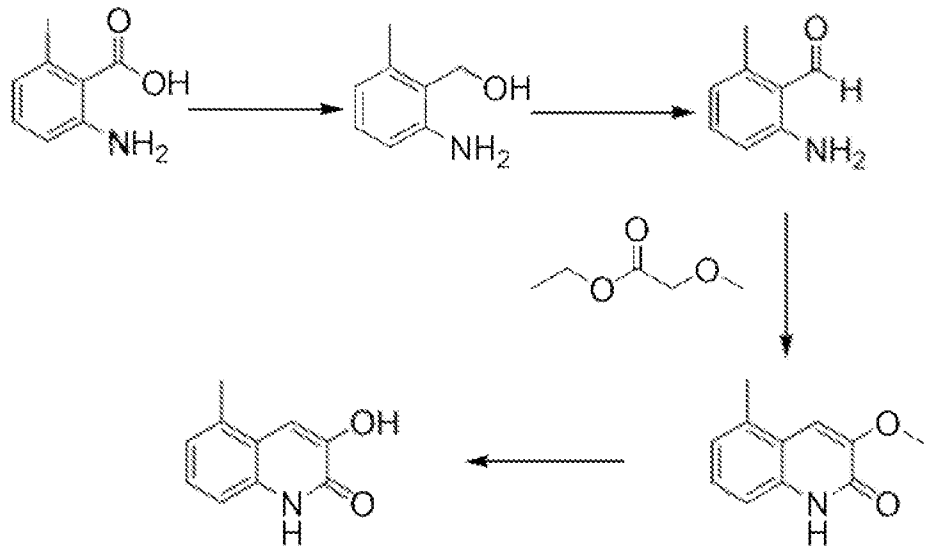
NMR of minor diastereomer: δ 3.45 (s, 3H), 3.77 (d, *J*=3.1 Hz, 1H), 5.02 (d, *J*=2.9 Hz, 1H).

Step 4. Preparation of compound 5-fluoro-3-hydroxyquinolin-2(1*H*)-one.

The title compound was prepared according to the general procedure for the synthesis of Example 10, except that 5-fluoro-4-hydroxy-3-methoxy-3,4-dihydroquinolin-2(1*H*)-one was used as the starting material. The title compound was obtained as a tan solid. Yield: 23 mg, 0.13 mmol, 91%. LCMS *m/z* 180.1 (M+1). ^{1}H NMR (400 MHz, CD_3OD) δ 6.95 (dd, *J*=10.1, 8.0 Hz, 1H), 7.12 (d, *J*=8.4 Hz, 1H), 7.27 (s, 1H), 7.32 (ddd, apparent td, *J*=8.2, 8.2, 5.8 Hz, 1H).

Example 20

3-hydroxy-5-methylquinolin-2(1*H*)-one



Step 1. Preparation of (2-amino-6-methylphenyl)methanol.

A solution of lithium aluminum hydride (94%, 1.07 g, 26.5 mmol) was cooled in an ice bath, and treated drop-wise with a solution of 2-amino-6-methylbenzoic acid (2.00 g, 13.2 mmol) in tetrahydrofuran (30 mL). The ice bath was allowed to melt and the reaction mixture warmed to about 25°C. It was allowed to stir for 1 hour, then heated at reflux for 2.5 hours. The reaction was then cooled in an ice bath and carefully quenched by the addition of sodium sulfate decahydrate (3 g) and saturated aqueous sodium

chloride solution (10 mL). The resulting mixture was stirred for 30 minutes at 0°C, 15 minutes at 25°C, and was then filtered through Celite. The filter pad was rinsed with tetrahydrofuran (2 x 10 mL), and the filtrates were concentrated *in vacuo*; the resulting material was loaded onto silica gel and purified via dry column vacuum chromatography (Eluant: 100% heptane to 100% ethyl acetate), to afford (2-amino-6-methylphenyl)methanol as a tan solid. Yield: 1.33 g, 9.69 mmol, 73%. MS (APCI) *m/z* 135.8 (M-1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 4.75 (s, 2H), 6.59 (m, 2H), 7.02 (dd, apparent t, *J*=7.7, 7.7 Hz, 1H).

Step 2. Preparation of 2-amino-6-methylbenzaldehyde.

2-Amino-6-methylbenzaldehyde was prepared according to the general procedure for the synthesis of Example 19, except that 2-amino-6-methylbenzaldehyde was used as the starting material. The solid obtained in this way was recrystallized from heptane, to afford 2-amino-6-methylbenzaldehyde as bright yellow crystals. Yield: 256 mg, 1.89 mmol, 52%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.58 (s, 3H), 6.39 (br s, 2H), 6.48 (m, 2H), 7.17 (dd, *J*=8, 8 Hz, 1H), 10.38 (s, 1H).

Step 3. Preparation of 3-methoxy-5-methylquinolin-2(1*H*)-one.

Ethyl methoxyacetate (0.35 mL, 3.0 mmol) was added to a -78°C solution of lithium bis(trimethylsilyl)amide (1.0M solution in tetrahydrofuran, 3.0 mL, 3.0 mmol) in tetrahydrofuran (3 mL). After 20 minutes, a solution of the product from the previous step (135 mg, 1.00 mmol) in tetrahydrofuran (3 mL) was added drop-wise from a syringe. The resulting yellow solution was allowed to come slowly to about 25°C as the dry ice/acetone bath warmed up. After 18 hours, the reaction was quenched with 6N hydrochloric acid (0.36 mL, 2.2 mmol), and the resulting precipitate was removed by filtration. The filtrate was concentrated *in vacuo* and purified by silica gel chromatography (Gradient: dichloromethane to 10:2 dichloromethane:methanol). The product crystallized out of one of the fractions, and was collected by filtration, to afford 3-methoxy-5-methylquinolin-2(1*H*)-one as a white crystalline solid. Yield: 33 mg, 0.17 mmol, 17%. MS (APCI) *m/z* 187.8 (M-1). ^{1}H NMR (400 MHz,

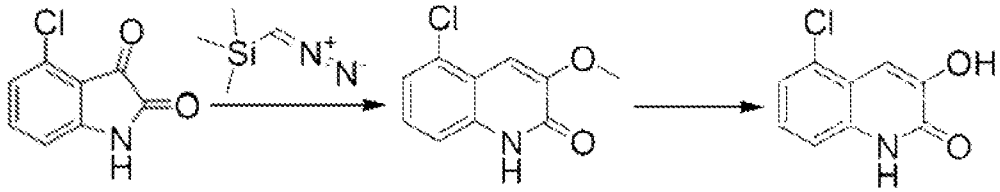
CD_3OD) δ 2.56 (s, 3H), 3.95 (s, 3H), 7.09 (d, *J*=7.2 Hz, 1H), 7.16 (d, *J*=8.2 Hz, 1H), 7.27 (m, 1H), 7.29 (s, 1H).

Step 4. Preparation of compound 3-hydroxy-5-methylquinolin-2(1*H*)-one.

The title compound was prepared according to the general procedure for the synthesis of Example 10, except that 3-methoxy-5-methylquinolin-2(1*H*)-one was used as the starting material. The title compound was obtained as a tan solid. Yield: 34 mg, 0.19 mmol, quantitative. LCMS *m/z* 176.1 (M+1). ^{1}H NMR (400 MHz, CD_3OD) δ 2.55 (s, 3H), 7.20 (d, *J*=7.0 Hz, 1H), 7.30 (d, *J*=7.8 Hz, 1H), 7.36 (dd, *J*=7.2, 7.2 Hz, 1H), 7.57 (s, 1H).

Example 21

5-chloro-3-hydroxyquinolin-2(1*H*)-one



Step 1. Preparation of 5-chloro-3-methoxyquinolin-2(1*H*)-one.

4-Chloro-1*H*-indole-2,3-dione (182 mg, 1.00 mmol), diethylamine (0.207 mL, 2.0 mmol), and (trimethylsilyl)diazomethane (2M solution in hexanes, 1.0 mL, 2.0 mmol) were dissolved in ethanol (5 mL) and stirred at about 25°C for about 18 hours. Filtration of the heterogeneous reaction provided a solid, which was rinsed with ethanol (2 x 1 mL) to provide 5-chloro-3-methoxyquinolin-2(1*H*)-one as a gray solid. Yield: 125 mg, 0.60 mmol, 60%. LCMS *m/z* 210.1 (M+1).

Step 2. Preparation of 5-chloro-3-hydroxyquinolin-2(1*H*)-one.

The title compound was prepared according to the general procedure for the synthesis of Example 11, except that 5-chloro-3-hydroxyquinolin-2(1*H*)-one was used as the starting material, and that the crude product was slurried with hot methanol rather than triturated with dichloromethane. The slurry was cooled to about 25°C and filtered to provide the title compound as a gray solid. Yield: 67 mg, 0.34 mmol, 70%. LCMS *m/z* 194.0 (M-1). ^{1}H

NMR (400 MHz, DMSO-d_6) δ 7.22 (s, 1H), 7.27 (m, 3H), 10.03 (br s, 1H), 12.24 (br s, 1H).

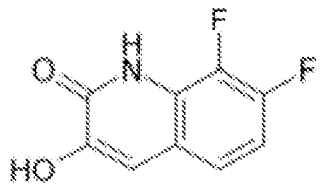
Example 22

6-bromo-3-hydroxy-1,8-naphthyridin-2(1*H*)-one hydrobromide

The title compound was prepared from 2-amino-5-bromo-3-pyridinecarboxaldehyde using the procedure described in Example 8. APCI *m/z* 239 (M-1). ^{1}H NMR (400 MHz, DMSO) δ 12.57 (s, 1H), 10.11 (s, 1H), 8.37 (s, 1H), 8.20 (s, 1H), 7.01 (s, 1H).

Example 23

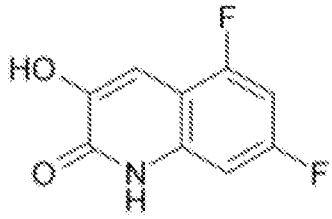
7,8-difluoro-3-hydroxyquinolin-2(1H)-one



The title compound was prepared from 6,7-difluoro-1H-indole-2,3-dione using the procedure described in Example 21. APCI *m/z* 196.1 (M-1). ^{1}H NMR (400 MHz, CD3OD) δ 7.30-7.26 (m, 1H), 7.11-7.04 (m, 2H).

Example 24

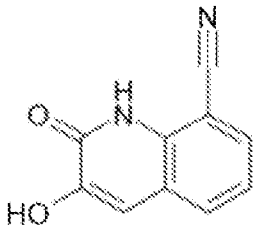
5,7-difluoro-3-hydroxyquinolin-2(1H)-one



The title compound was prepared from 4,6-difluoro-1H-indole-2,3-dione using the procedure described in Example 21. APCI *m/z* 196.1 (M-1). ^{1}H NMR (400 MHz, DMSO) δ 12.28 (s, 1H), 9.93 (s, 1H), 7.08-7.02 (m, 1H), 6.99 (s, 1H), 6.84 (m, 1H).

Example 25

3-hydroxy-2-oxo-1,2-dihydroquinoline-8-carbonitrile



Step 1. Preparation of 8-iodo-3-methoxyquinolin-2(1*H*)-one.

8-Iodo-3-methoxyquinolin-2(1*H*)-one was prepared from 7-iodo-1*H*-indole-2,3-dione using the same procedure as described in step 1 of Example 21. APCI *m/z* 301.9 (M+1). ^{1}H NMR (400 MHz, CD3OD) δ 7.87 (m, 1H), 7.62 (m, 1H), 7.21 (m, 1H), 6.99 (m, 1H), 3.92 (s, 3H).

Step 2. Preparation of 3-methoxyquinolin-2(1*H*)-one-8-carbonitrile.

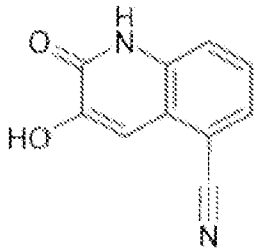
8-Iodo-3-methoxyquinolin-2(1*H*)-one (90mg, 0.30 mmol), zinc cyanide (41.8 mg, 0.356 mmol), xanthphos (3.50 mg, 0.0060 mmol), Pd2(dba)3 (2.80 mg, 0.0180 mmol) and TMEDA (14.5 mg, 0.125 mmol) were loaded into a 10 mL microwave tube (under nitrogen) with a stirring bar. DMF (2 mL) was added to the reaction mixture to produce a pale purple/pink homogeneous reaction mixture, and the tube was heated to 180°C for 20 minutes using microwave irradiation. The reaction mixture was partitioned between water and ethyl acetate, and the brown-yellow ethyl acetate layer was collected. The aqueous layer was washed 3 times with ethyl acetate, and the combined organics were dried over sodium sulfate, filtered and concentrated to afford 20 mg of a brown solid. APCI *m/z* 201 (M+1). ^{1}H NMR (400 MHz, CD3OD) δ 7.87 (m, 1H), 7.73 (m, 1H), 7.32-7.28 (m, 2H), 3.93 (s, 3H).

Step 3. Preparation of 3-hydroxy-2-oxo-1,2-dihydroquinoline-8-carbonitrile.

The title compound was prepared from 3-methoxyquinolin-2(1*H*)-one-8-carbonitrile using the procedure described in Example 10, step 3. APCI *m/z* 185.1 (M-1). ^{1}H NMR (400 MHz, CD3OD) δ 7.81 (d, 1H), 7.72 (d, 1H), 7.31 (dd, 1H), 7.19 (s, 1H).

Example 26

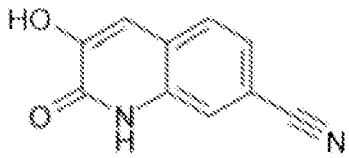
3-hydroxy-2-oxo-1,2-dihydroquinoline-5-carbonitrile



The title compound was prepared from 4-bromo-1H-indole-2,3-dione using the procedure described in Example 25. APCI *m/z* 185.1 (M-1). ^{1}H NMR (400 MHz, CD3OD) δ 7.60 (d, 1H), 7.54 (d, 1H), 7.46-7.42 (dd, 1H), 7.32 (s, 1H).

Example 27

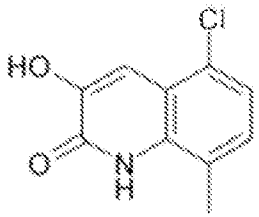
3-hydroxy-2-oxo-1,2-dihydroquinoline-7-carbonitrile



The title compound was prepared from 6-bromo-1H-indole-2,3-dione using the procedure described in Example 25. APCI *m/z* 185.0 (M-1). ^{1}H NMR (400 MHz, CD3OD) δ 7.64 (m, 1H), 7.58 (m, 1H), 7.44 (m, 1H), 7.18 (s, 1H).

Example 28

5-chloro-3-hydroxy-8-methylquinolin-2(1H)-one



The title compound was prepared from 4-chloro-7-methyl-1H-indole-2,3-dione using the procedure described in Example 21. APCI *m/z* 208.1 (M-1). ^{1}H NMR (400 MHz, DMSO) δ 11.32 (s, 1H), 9.99 (s, 1H),, 7.21 (s, 1H), 7.15-7.09 (m, 2H), 2.36 (s, 3H).

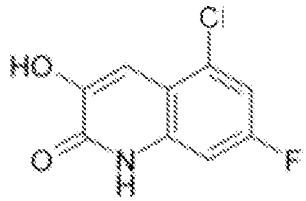
Example 29

5-chloro-3-hydroxy-6-methylquinolin-2(1H)-one

The title compound was prepared from 4-chloro-5-methyl-1H-indole-2,3-dione using the procedure described in Example 21. APCI *m/z* 208.1 (M-1). ^{1}H NMR (400 MHz, DMSO) δ 12.11 (s, 1H), 9.90 (s, 1H), 7.24-7.22 (m, 2H), 7.12 (m, 1H), 2.33 (s, 3H).

Example 30

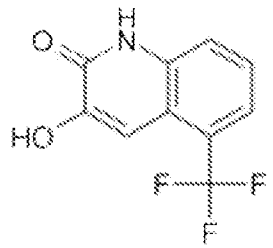
5-chloro-7-fluoro-3-hydroxyquinolin-2(1H)-one



The title compound was prepared from 4-chloro-6-fluoro-1H-indole-2,3-dione using the procedure described in Example 21, step 1, except that only 0.8 equivalents of the TMS diazomethane reagent was added to the reaction mixture. The product was taken up into alcohol and treated with 1N HCl in dioxane and then concentrated to give the title compound as a hydrochloride salt. APCI *m/z* 212.1 (M-1). ^{1}H NMR (400 MHz, DMSO) δ 12.27 (s, 1H), 10.03 (s, 1H), 7.27 (m, 1H), 7.16 (s, 1H), 6.99 (m, 1H).

Example 31

3-hydroxy-5-(trifluoromethyl)quinolin-2(1H)-one



The title compound was prepared from 4-(trifluoromethyl)-1H-indole-2,3-dione using the procedure described in Example 21. APCI *m/z* 228.1 (M-1). ^{1}H NMR (400 MHz, DMSO) δ 12.34 (s, 1H), 10.20 (s, 1H), 7.49 (m, 2H), 7.40 (m, 1H), 7.10 (s, 1H).

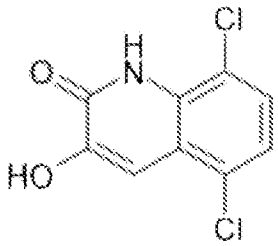
Example 32

5-bromo-3-hydroxyquinolin-2(1H)-one

The title compound was prepared from 4-bromo-1H-indole-2,3-dione using the procedure described in Example 21. APCI *m/z* 240, 242 (M+1). ^{1}H NMR (400 MHz, DMSO) δ 12.18 (s, 1H), 7.39 (m, 1H), 7.24 (m, 1H), 7.19-7.15 (m, 2H).

Example 33

5,8-dichloro-3-hydroxyquinolin-2(1H)-one



The title compound was prepared from 4,7-dichloro-1H-indole-2,3-dione using the procedure described in Example 21. APCI *m/z* 228, 230, 232 (M-1). ^{1}H NMR (400 MHz, DMSO) δ 11.52 (s, 1H), 10.39 (s, 1H), 7.41 (d, 1H), 7.28 (d, 1H), 7.21 (s, 1H).

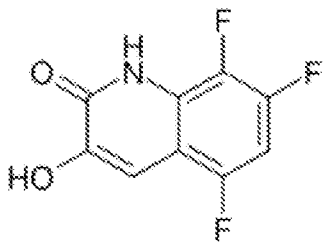
Example 34

5,6-dichloro-3-hydroxyquinolin-2(1H)-one

The title compound was prepared from 4,5-dichloro-1H-indole-2,3-dione using the procedure described in Example 21. APCI *m/z* 228, 230, 232 (M-1). ^{1}H NMR (400 MHz, DMSO) δ 12.30 (s, 1H), 10.25 (broad s, 1H), 7.47 (m, 1H), 7.21 (m, 2H).

Example 35

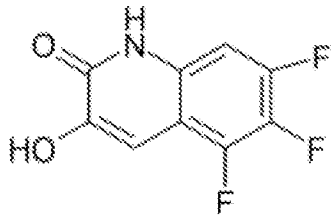
5,7,8-trifluoro-3-hydroxyquinolin-2(1H)-one



The title compound was prepared from 4,6,7-trifluoro-1H-indole-2,3-dione using the procedure described in Example 21. APCI *m/z* 216.2 (M+1). ^{1}H NMR (400 MHz, DMSO) δ 6.99 (s, 1 H) 7.29 (td, J=10.55, 6.06 Hz, 1 H) 10.13 (s, 1 H) 12.49 (br. s.,1 H).

Example 36

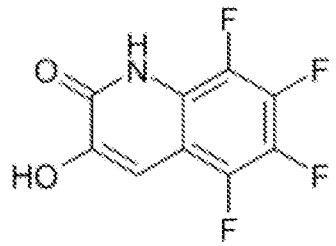
5,6,7-trifluoro-3-hydroxyquinolin-2(1H)-one



The title compound was prepared from 4,5,6-trifluoro-1H-indole-2,3-dione using the procedure described in Example 21. APCI *m/z* 216.2 (M+1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.98 (s, 1 H) 7.01 (dd, J=6.55, 1.66 Hz, 1 H) 10.13 (s, 1 H) 12.24 (s, 1 H).

Example 37

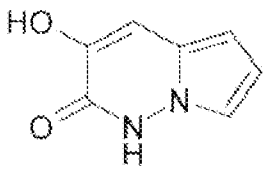
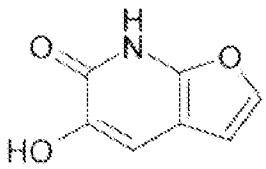
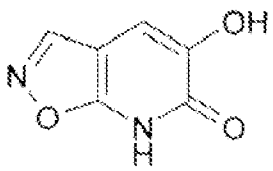
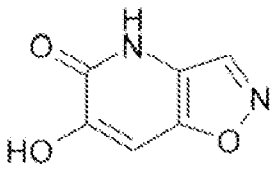
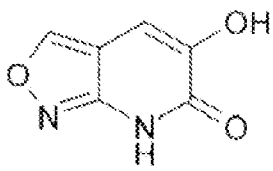
5,6,7,8-tetrafluoro-3-hydroxyquinolin-2(1H)-one

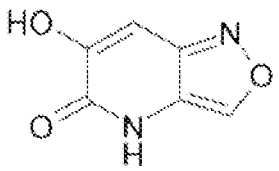
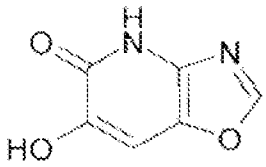
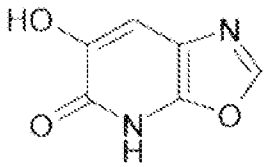
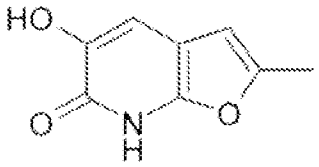
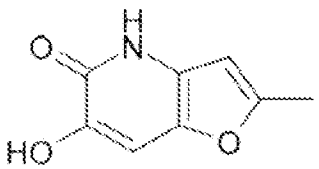
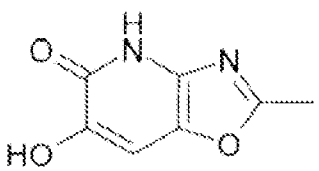


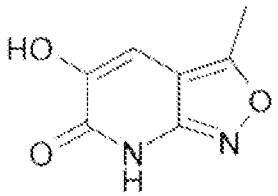
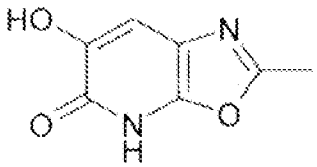
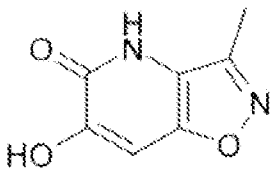
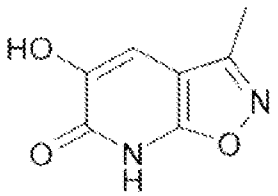
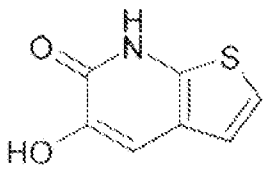
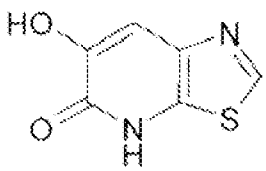
The title compound was prepared from 4,5,6,7-tetrafluoro-1H-indole-2,3-dione using the procedure described in Example 21. APCI *m/z* 234.1 (M+1). ^{1}H NMR (400 MHz, METHANOL-d_4) δ 7.12 (d, J=1.37 Hz, 1 H).

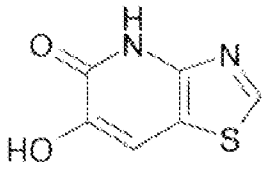
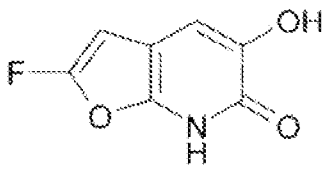
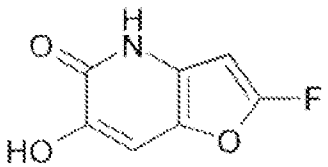
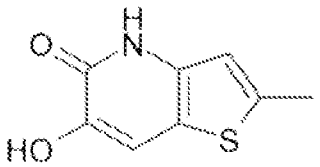
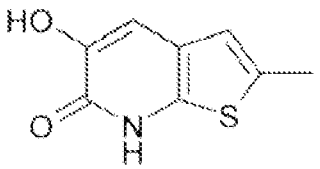
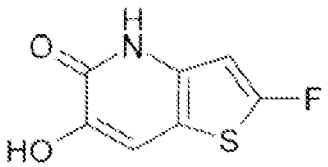
The compounds of Table 1 may be prepared according to methods analogous to those described above for Examples 1-37.

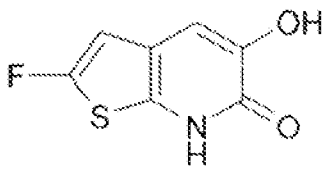
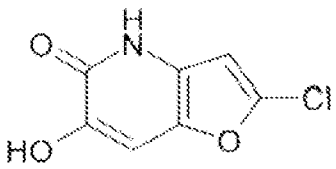
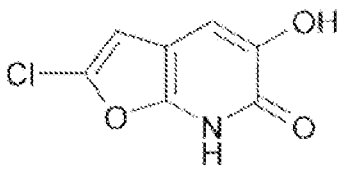
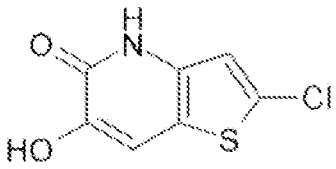
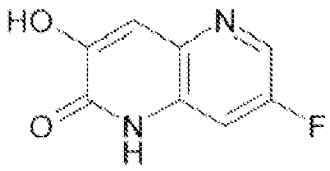
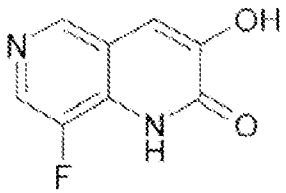
Table 1

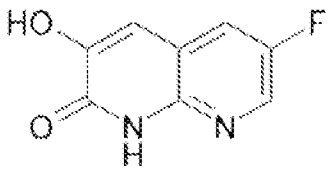
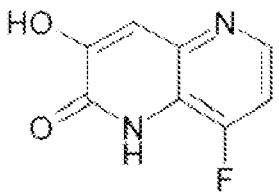
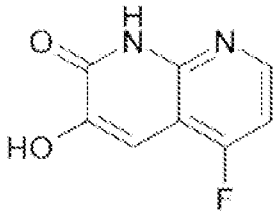
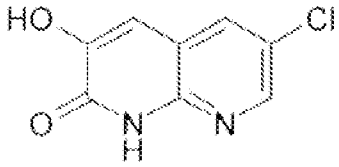
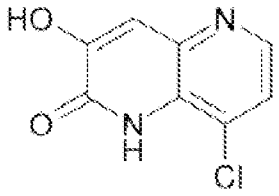
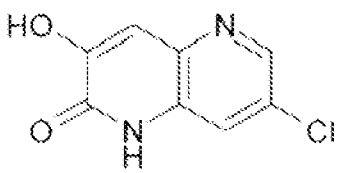
Structure	MW	IUPACNAME
	150	3-hydroxypyrrolo[1,2-b]pyridazin-2(1H)-one
	151	5-hydroxyfuro[2,3-b]pyridin-6(7H)-one
	152	5-hydroxyisoxazolo[5,4-b]pyridin-6(7H)-one
	152	6-hydroxyisoxazolo[4,5-b]pyridin-5(4H)-one
	152	5-hydroxyisoxazolo[3,4-b]pyridin-6(7H)-one

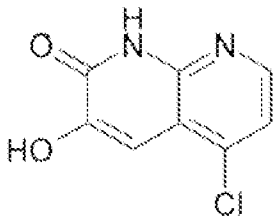
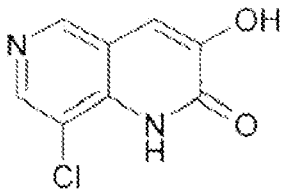
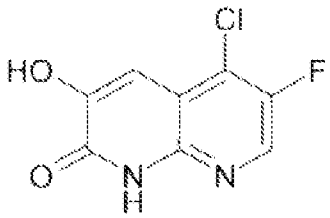
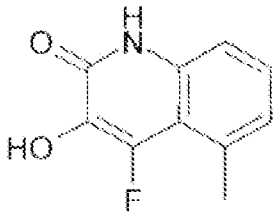
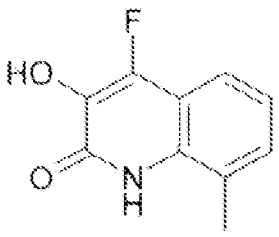
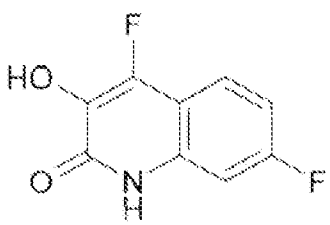
Structure	MW	IUPACNAME
	152	6-hydroxyisoxazolo[4,3-b]pyridin-5(4H)-one
	152	6-hydroxy[1,3]oxazolo[4,5-b]pyridin-5(4H)-one
	152	6-hydroxy[1,3]oxazolo[5,4-b]pyridin-5(4H)-one
	165	5-hydroxy-2-methylfuro[2,3-b]pyridin-6(7H)-one
	165	6-hydroxy-2-methylfuro[3,2-b]pyridin-5(4H)-one
	166	6-hydroxy-2-methyl[1,3]oxazolo[4,5-b]pyridin-5(4H)-one

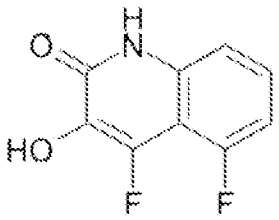
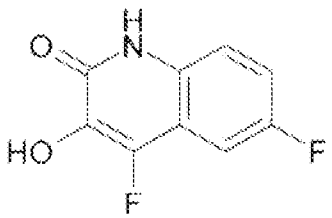
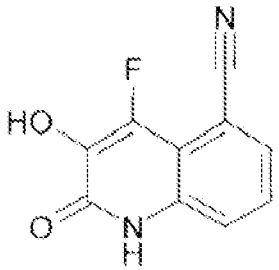
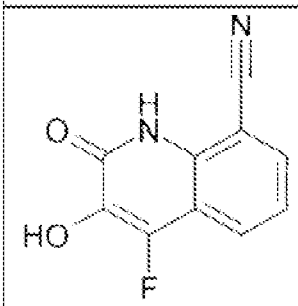
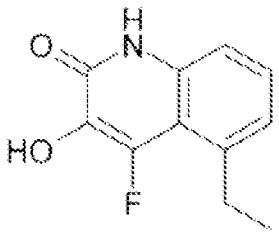
Structure	MW	IUPACNAME
	166	5-hydroxy-3-methylisoxazolo[3,4-b]pyridin-6(7H)-one
	166	6-hydroxy-2-methyl[1,3]oxazolo[5,4-b]pyridin-5(4H)-one
	166	6-hydroxy-3-methylisoxazolo[4,5-b]pyridin-5(4H)-one
	166	5-hydroxy-3-methylisoxazolo[5,4-b]pyridin-6(7H)-one
	167	5-hydroxythieno[2,3-b]pyridin-6(7H)-one
	168	6-hydroxy[1,3]thiazolo[5,4-b]pyridin-5(4H)-one

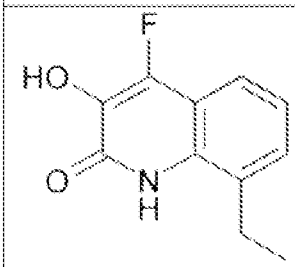
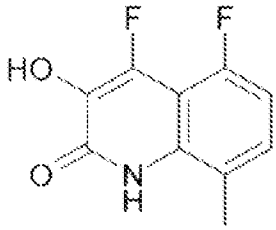
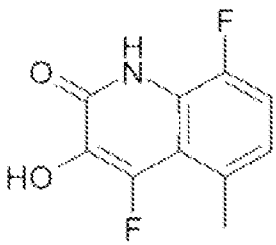
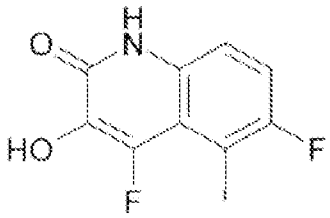
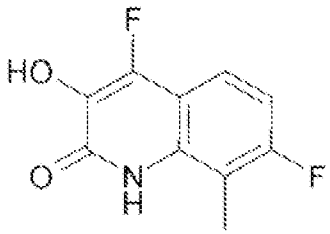
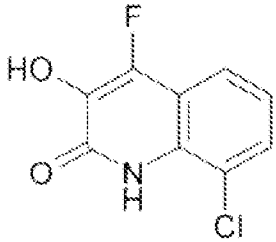
Structure	MW	IUPACNAME
	168	6-hydroxy[1,3]thiazolo[4,5-b]pyridin-5(4H)-one
	169	2-fluoro-5-hydroxyfuro[2,3-b]pyridin-6(7H)-one
	169	2-fluoro-6-hydroxyfuro[3,2-b]pyridin-5(4H)-one
	181	6-hydroxy-2-methylthieno[3,2-b]pyridin-5(4H)-one
	181	5-hydroxy-2-methylthieno[2,3-b]pyridin-6(7H)-one
	185	2-fluoro-6-hydroxythieno[3,2-b]pyridin-5(4H)-one

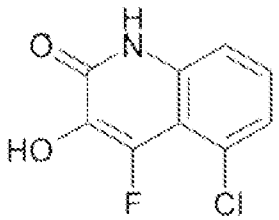
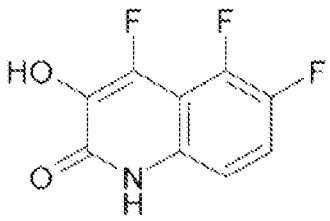
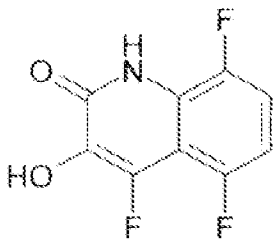
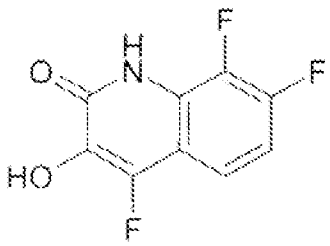
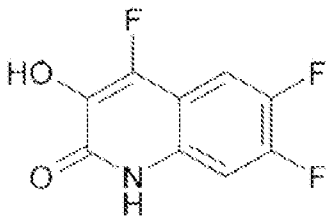
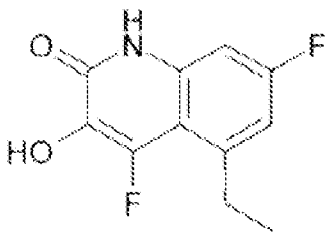
Structure	MW	IUPACNAME
	185	2-fluoro-5-hydroxythieno[2,3-b]pyridin-6(7H)-one
	186	2-chloro-6-hydroxyfuro[3,2-b]pyridin-5(4H)-one
	186	2-chloro-5-hydroxyfuro[2,3-b]pyridin-6(7H)-one
	202	2-chloro-6-hydroxythieno[3,2-b]pyridin-5(4H)-one
	180	7-fluoro-3-hydroxy-1,5-naphthyridin-2(1H)-one
	180	8-fluoro-3-hydroxy-1,6-naphthyridin-2(1H)-one

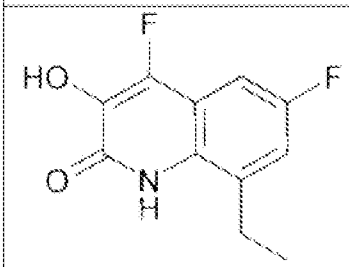
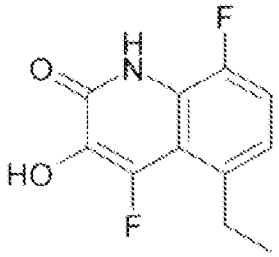
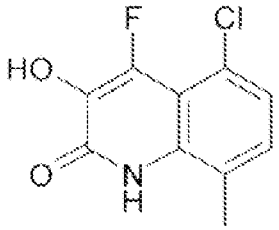
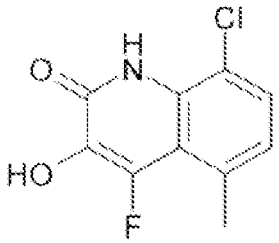
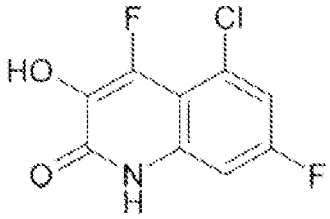
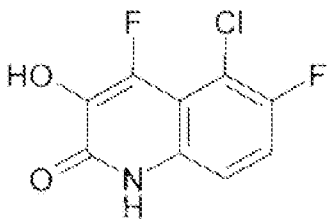
Structure	MW	IUPACNAME
	180	6-fluoro-3-hydroxy-1,8-naphthyridin-2(1H)-one
	180	8-fluoro-3-hydroxy-1,5-naphthyridin-2(1H)-one
	180	5-fluoro-3-hydroxy-1,8-naphthyridin-2(1H)-one
	197	6-chloro-3-hydroxy-1,8-naphthyridin-2(1H)-one
	197	8-chloro-3-hydroxy-1,5-naphthyridin-2(1H)-one
	197	7-chloro-3-hydroxy-1,5-naphthyridin-2(1H)-one

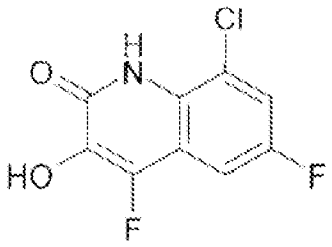
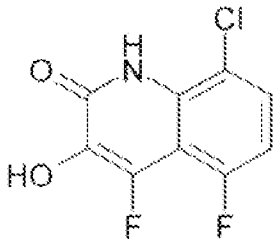
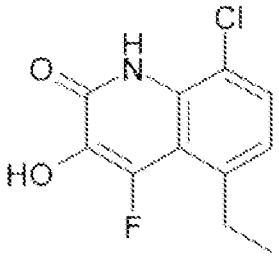
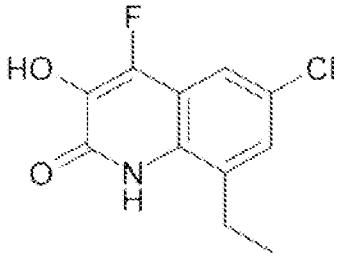
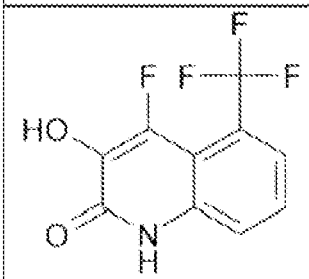
Structure	MW	IUPACNAME
	197	5-chloro-3-hydroxy-1,8-naphthyridin-2(1H)-one
	197	8-chloro-3-hydroxy-1,6-naphthyridin-2(1H)-one
	215	5-chloro-6-fluoro-3-hydroxy-1,8-naphthyridin-2(1H)-one
	193	4-fluoro-3-hydroxy-5-methylquinolin-2(1H)-one
	193	4-fluoro-3-hydroxy-8-methylquinolin-2(1H)-one
	197	4,7-difluoro-3-hydroxyquinolin-2(1H)-one

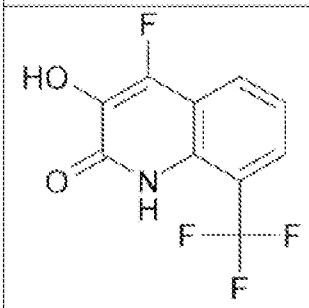
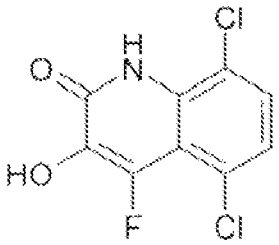
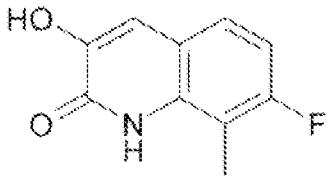
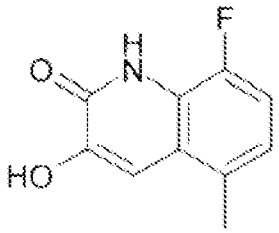
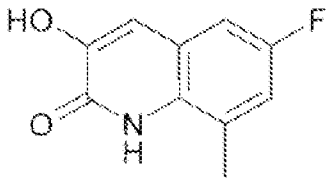
Structure	MW	IUPACNAME
	197	4,5-difluoro-3-hydroxyquinolin-2(1H)-one
	197	4,6-difluoro-3-hydroxyquinolin-2(1H)-one
	204	4-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-5-carbonitrile
	204	4-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-8-carbonitrile
	207	5-ethyl-4-fluoro-3-hydroxyquinolin-2(1H)-one

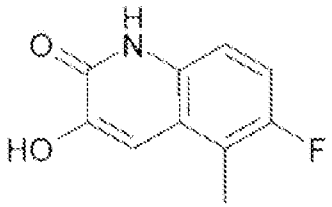
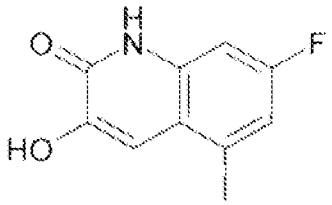
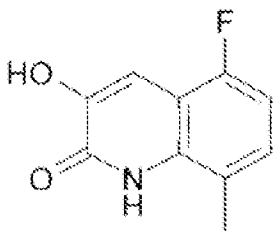
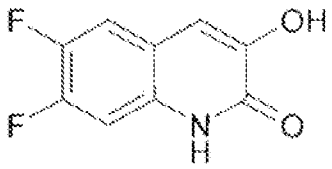
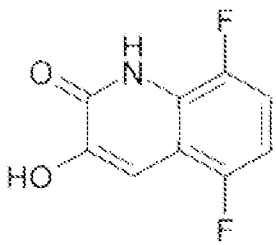
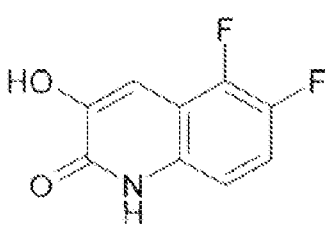
Structure	MW	IUPACNAME
	207	8-ethyl-4-fluoro-3-hydroxyquinolin-2(1H)-one
	211	4,5-difluoro-3-hydroxy-8-methylquinolin-2(1H)-one
	211	4,8-difluoro-3-hydroxy-5-methylquinolin-2(1H)-one
	211	4,6-difluoro-3-hydroxy-5-methylquinolin-2(1H)-one
	211	4,7-difluoro-3-hydroxy-8-methylquinolin-2(1H)-one
	214	8-chloro-4-fluoro-3-hydroxyquinolin-2(1H)-one

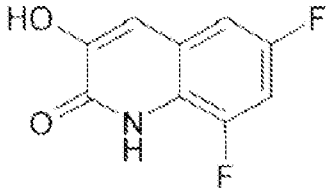
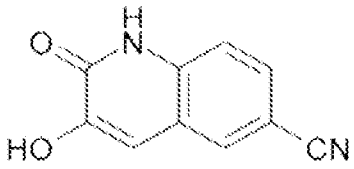
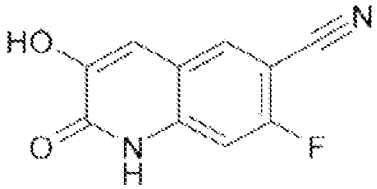
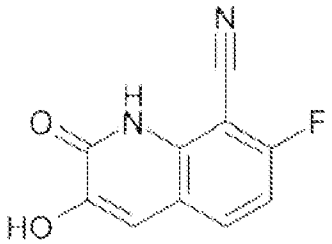
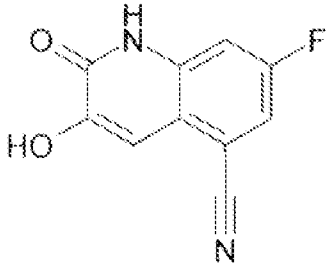
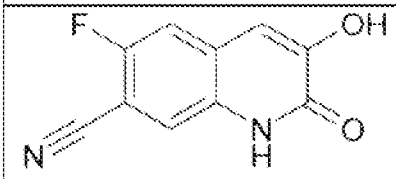
Structure	MW	IUPACNAME
	214	5-chloro-4-fluoro-3-hydroxyquinolin-2(1H)-one
	215	4,5,6-trifluoro-3-hydroxyquinolin-2(1H)-one
	215	4,5,8-trifluoro-3-hydroxyquinolin-2(1H)-one
	215	4,7,8-trifluoro-3-hydroxyquinolin-2(1H)-one
	215	4,6,7-trifluoro-3-hydroxyquinolin-2(1H)-one
	225	5-ethyl-4,7-difluoro-3-hydroxyquinolin-2(1H)-one

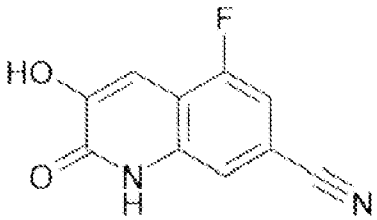
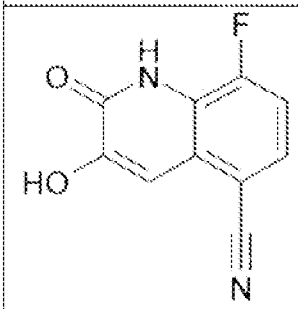
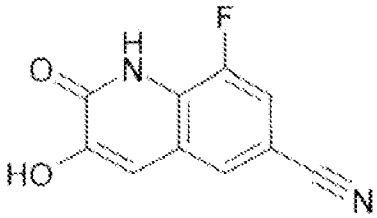
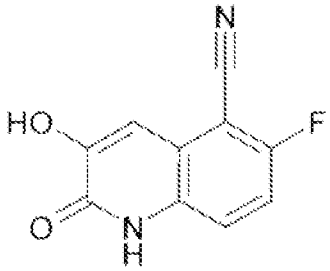
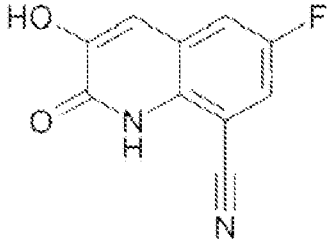
Structure	MW	IUPACNAME
	225	8-ethyl-4,6-difluoro-3-hydroxyquinolin-2(1H)-one
	225	5-ethyl-4,8-difluoro-3-hydroxyquinolin-2(1H)-one
	228	5-chloro-4-fluoro-3-hydroxy-8-methylquinolin-2(1H)-one
	228	8-chloro-4-fluoro-3-hydroxy-5-methylquinolin-2(1H)-one
	232	5-chloro-4,7-difluoro-3-hydroxyquinolin-2(1H)-one
	232	5-chloro-4,6-difluoro-3-hydroxyquinolin-2(1H)-one

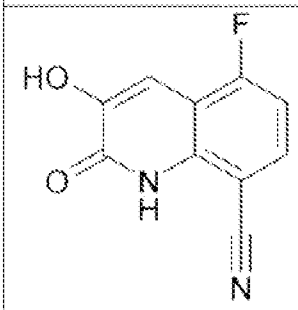
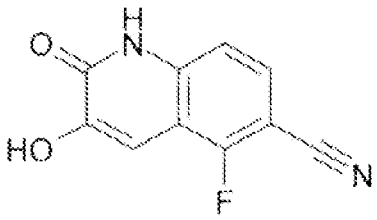
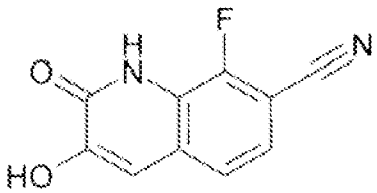
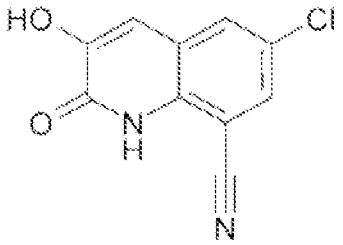
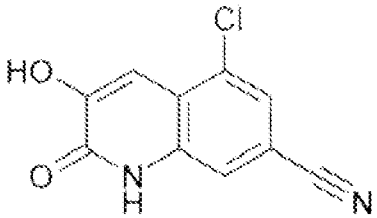
Structure	MW	IUPACNAME
	232	8-chloro-4,6-difluoro-3-hydroxyquinolin-2(1H)-one
	232	8-chloro-4,5-difluoro-3-hydroxyquinolin-2(1H)-one
	242	8-chloro-5-ethyl-4-fluoro-3-hydroxyquinolin-2(1H)-one
	242	6-chloro-8-ethyl-4-fluoro-3-hydroxyquinolin-2(1H)-one
	247	4-fluoro-3-hydroxy-5-(trifluoromethyl)quinolin-2(1H)-one

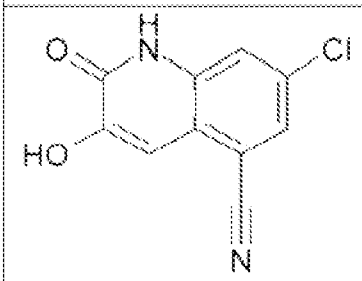
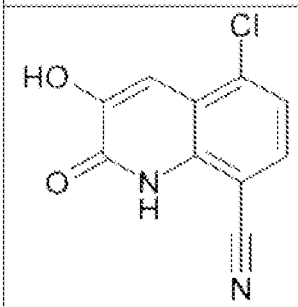
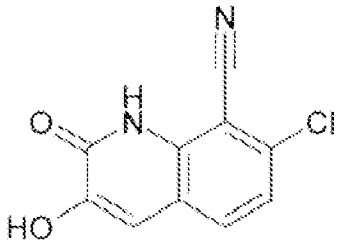
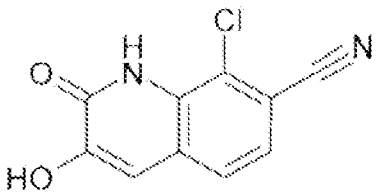
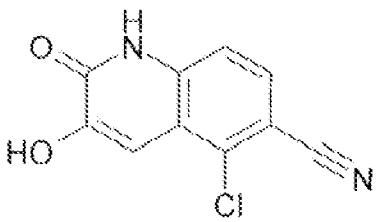
Structure	MW	IUPACNAME
	247	4-fluoro-3-hydroxy-8-(trifluoromethyl)quinolin-2(1H)-one
	248	5,8-dichloro-4-fluoro-3-hydroxyquinolin-2(1H)-one
	193	7-fluoro-3-hydroxy-8-methylquinolin-2(1H)-one
	193	8-fluoro-3-hydroxy-5-methylquinolin-2(1H)-one
	193	6-fluoro-3-hydroxy-8-methylquinolin-2(1H)-one

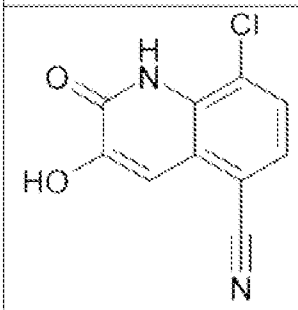
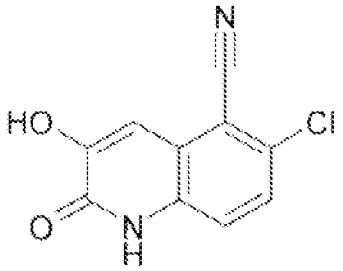
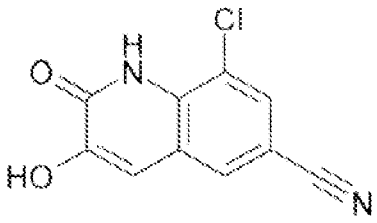
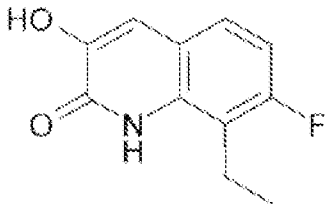
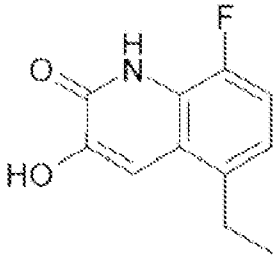
Structure	MW	IUPACNAME
	193	6-fluoro-3-hydroxy-5-methylquinolin-2(1H)-one
	193	7-fluoro-3-hydroxy-5-methylquinolin-2(1H)-one
	193	5-fluoro-3-hydroxy-8-methylquinolin-2(1H)-one
	197	6,7-difluoro-3-hydroxyquinolin-2(1H)-one
	197	5,8-difluoro-3-hydroxyquinolin-2(1H)-one
	197	5,6-difluoro-3-hydroxyquinolin-2(1H)-one

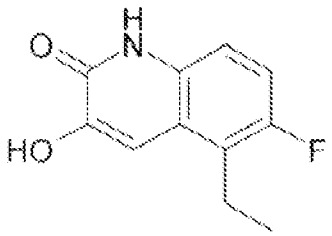
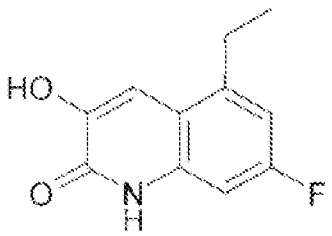
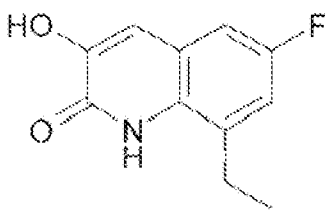
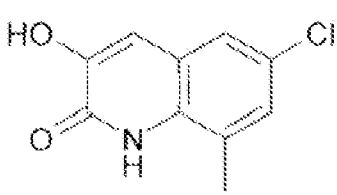
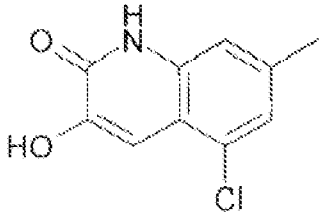
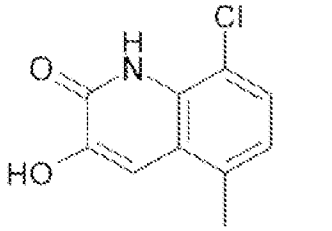
Structure	MW	IUPACNAME
	197	6,8-difluoro-3-hydroxyquinolin-2(1H)-one
	186	3-hydroxy-2-oxo-1,2-dihydroquinoline-6-carbonitrile
	204	7-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-6-carbonitrile
	204	7-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-8-carbonitrile
	204	7-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-5-carbonitrile
	204	6-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-7-carbonitrile

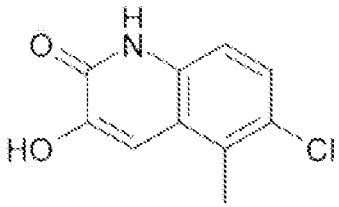
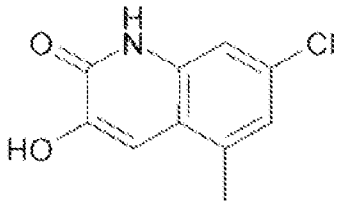
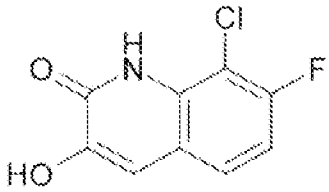
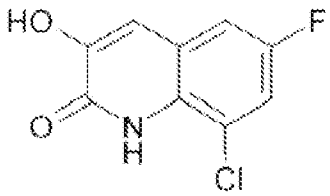
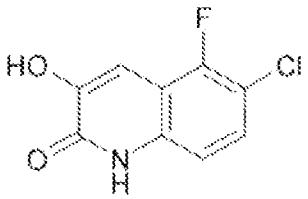
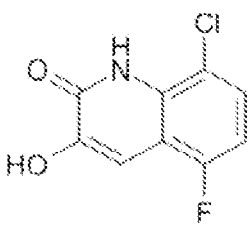
Structure	MW	IUPACNAME
	204	5-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-7-carbonitrile
	204	8-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-5-carbonitrile
	204	8-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-6-carbonitrile
	204	6-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-5-carbonitrile
	204	6-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-8-carbonitrile

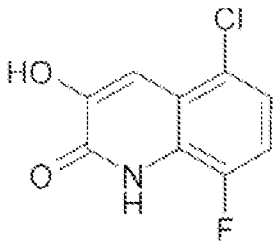
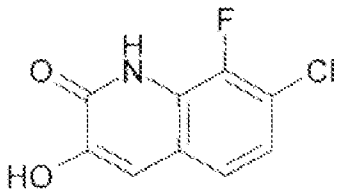
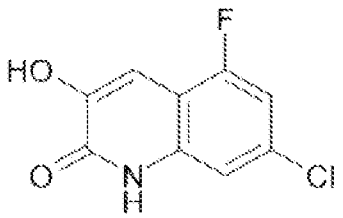
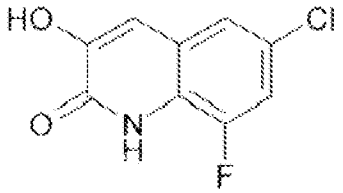
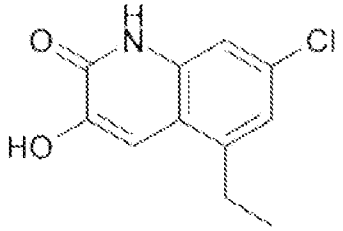
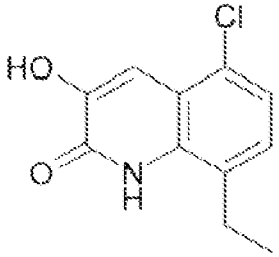
Structure	MW	IUPACNAME
	204	5-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-8-carbonitrile
	204	5-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-6-carbonitrile
	204	8-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-7-carbonitrile
	221	6-chloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-8-carbonitrile
	221	5-chloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-7-carbonitrile

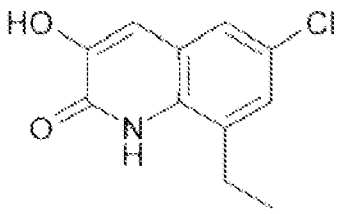
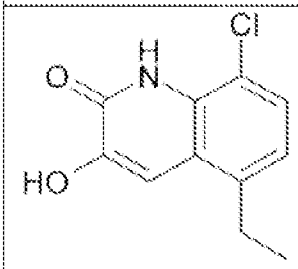
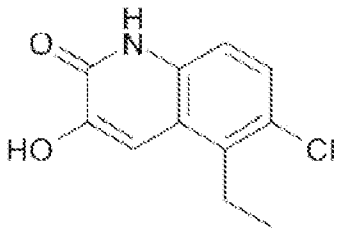
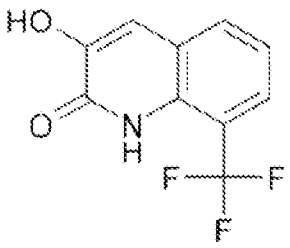
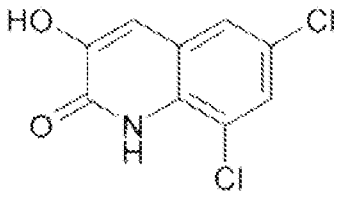
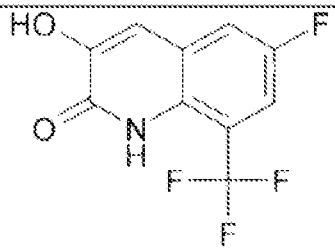
Structure	MW	IUPACNAME
	221	7-chloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-5-carbonitrile
	221	5-chloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-8-carbonitrile
	221	7-chloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-8-carbonitrile
	221	8-chloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-7-carbonitrile
	221	5-chloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-6-carbonitrile

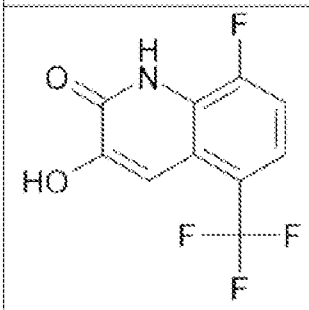
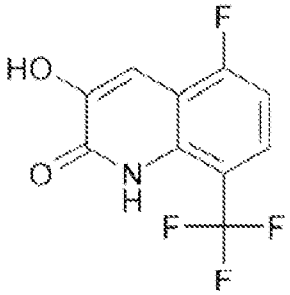
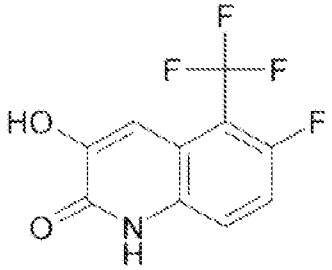
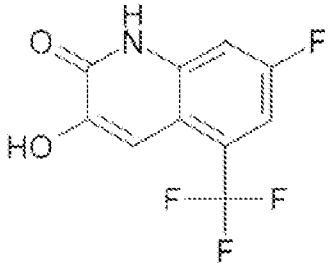
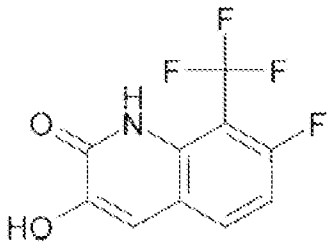
Structure	MW	IUPACNAME
	221	8-chloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-5-carbonitrile
	221	6-chloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-5-carbonitrile
	221	8-chloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-6-carbonitrile
	207	8-ethyl-7-fluoro-3-hydroxyquinolin-2(1H)-one
	207	5-ethyl-8-fluoro-3-hydroxyquinolin-2(1H)-one

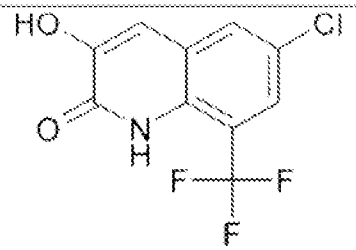
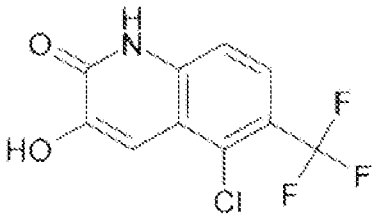
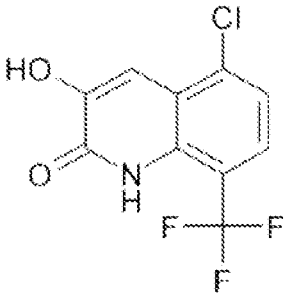
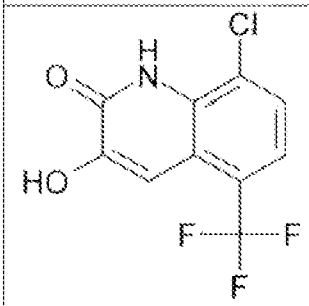
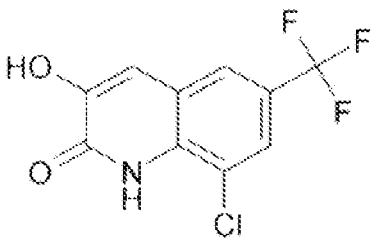
Structure	MW	IUPACNAME
	207	5-ethyl-6-fluoro-3-hydroxyquinolin-2(1H)-one
	207	5-ethyl-7-fluoro-3-hydroxyquinolin-2(1H)-one
	207	8-ethyl-6-fluoro-3-hydroxyquinolin-2(1H)-one
	210	6-chloro-3-hydroxy-8-methylquinolin-2(1H)-one
	210	5-chloro-3-hydroxy-7-methylquinolin-2(1H)-one
	210	8-chloro-3-hydroxy-5-methylquinolin-2(1H)-one

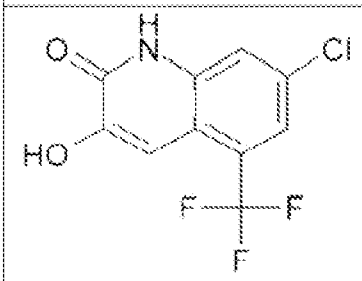
Structure	MW	IUPACNAME
	210	6-chloro-3-hydroxy-5-methylquinolin-2(1H)-one
	210	7-chloro-3-hydroxy-5-methylquinolin-2(1H)-one
	214	8-chloro-7-fluoro-3-hydroxyquinolin-2(1H)-one
	214	8-chloro-6-fluoro-3-hydroxyquinolin-2(1H)-one
	214	6-chloro-5-fluoro-3-hydroxyquinolin-2(1H)-one
	214	8-chloro-5-fluoro-3-hydroxyquinolin-2(1H)-one

Structure	MW	IUPACNAME
	214	5-chloro-8-fluoro-3-hydroxyquinolin-2(1H)-one
	214	7-chloro-8-fluoro-3-hydroxyquinolin-2(1H)-one
	214	7-chloro-5-fluoro-3-hydroxyquinolin-2(1H)-one
	214	6-chloro-8-fluoro-3-hydroxyquinolin-2(1H)-one
	224	7-chloro-5-ethyl-3-hydroxyquinolin-2(1H)-one
	224	5-chloro-8-ethyl-3-hydroxyquinolin-2(1H)-one

Structure	MW	IUPACNAME
	224	6-chloro-8-ethyl-3-hydroxyquinolin-2(1H)-one
	224	8-chloro-5-ethyl-3-hydroxyquinolin-2(1H)-one
	224	6-chloro-5-ethyl-3-hydroxyquinolin-2(1H)-one
	229	3-hydroxy-8-(trifluoromethyl)quinolin-2(1H)-one
	230	6,8-dichloro-3-hydroxyquinolin-2(1H)-one
	247	6-fluoro-3-hydroxy-8-(trifluoromethyl)quinolin-2(1H)-one

Structure	MW	IUPACNAME
	247	8-fluoro-3-hydroxy-5-(trifluoromethyl)quinolin-2(1H)-one
	247	5-fluoro-3-hydroxy-8-(trifluoromethyl)quinolin-2(1H)-one
	247	6-fluoro-3-hydroxy-5-(trifluoromethyl)quinolin-2(1H)-one
	247	7-fluoro-3-hydroxy-5-(trifluoromethyl)quinolin-2(1H)-one
	247	7-fluoro-3-hydroxy-8-(trifluoromethyl)quinolin-2(1H)-one

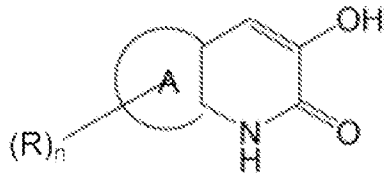
Structure	MW	IUPACNAME
	264	6-chloro-3-hydroxy-8-(trifluoromethyl)quinolin-2(1H)-one
	264	5-chloro-3-hydroxy-6-(trifluoromethyl)quinolin-2(1H)-one
	264	5-chloro-3-hydroxy-8-(trifluoromethyl)quinolin-2(1H)-one
	264	8-chloro-3-hydroxy-5-(trifluoromethyl)quinolin-2(1H)-one
	264	8-chloro-3-hydroxy-6-(trifluoromethyl)quinolin-2(1H)-one

Structure	MW	IUPACNAME
	264	7-chloro-3-hydroxy-5-(trifluoromethyl)quinolin-2(1H)-one

Claims

What is claimed is:

1. A method of treating a disorder or condition that can be treated by inhibiting D-amino acid oxidase (DAAO) acitivity in a mammal, preferably a human, in need of such treatment comprising administering to said mammal an effective amount of a compound of formula:



I

wherein ring "A" is a 6 membered aryl or 5 or 6 membered heteroaryl ring; wherein said 6 membered heteroaryl ring has one nitrogen heteroatom and wherein said 5 membered heteroaryl ring has one or two heteroatoms selected from N, O or S;

each R is independently selected from the group consisting of hydrogen, chloro, fluoro, bromo, methyl, ethyl, methoxy, ethoxy, trifluoromethyl, and cyano;

n is an integer selected from the group consinting of zero, one, two or three; or a pharmaceutically acceptable salt thereof.

2. A method according to claim 1 of enhancing cognition in a mammal, preferably a human, comprising administering to said mammal an effective amount of a compound of formula I.

3. A compound selected from the group consisting of:

7-fluoro-3-hydroxyquinolin-2(1*H*)-one;

5-chloro-6-fluoro-3-hydroxyquinolin-2(1*H*)-one;

7-ethyl-3-hydroxyquinolin-2(1*H*)-one;

4-fluoro-3-hydroxyquinolin-2(1*H*)-one;

4,8-difluoro-3-hydroxyquinolin-2(1*H*)-one;

3-hydroxy-1,5-naphthyridin-2(1*H*)-one;

3-hydroxy-1,7-naphthyridin-2(1*H*)-one;

3-hydroxy-1,6-naphthyridin-2(1*H*)-one;

5-hydroxy-1-methyl-1,7-dihydro-6*H*-pyrazolo[3,4-*b*]pyridin-6-one;
6-hydroxythieno[3,2-*b*]pyridin-5(4*H*)-one;
8-fluoro-3-hydroxyquinolin-2(1*H*)-one;
3-hydroxy-7-methylquinolin-2(1*H*)-one;
4-bromo-7-chloro-3-hydroxyquinolin-2(1*H*)-one;
6,7-dichloro-3-hydroxyquinolin-2(1*H*)-one;
7,8-dichloro-3-hydroxyquinolin-2(1*H*)-one;
7-chloro-3-hydroxy-8-methylquinolin-2(1*H*)-one;
3-hydroxy-4-methyl-1,8-naphthyridin-2(1*H*)-one;
6-hydroxyfuro[3,2-b]pyridin-5(4*H*)-one;
5-fluoro-3-hydroxyquinolin-2(1*H*)-one;
3-hydroxy-5-methylquinolin-2(1*H*)-one;
5-chloro-3-hydroxyquinolin-2(1*H*)-one;
3-hydroxypyrrolo[1,2-b]pyridazin-2(1H)-one;
5-hydroxyfuro[2,3-b]pyridin-6(7H)-one;
5-hydroxyisoxazolo[5,4-b]pyridin-6(7H)-one;
6-hydroxyisoxazolo[4,5-b]pyridin-5(4H)-one;
5-hydroxyisoxazolo[3,4-b]pyridin-6(7H)-one;
6-hydroxyisoxazolo[4,3-b]pyridin-5(4H)-one;
6-hydroxy[1,3]oxazolo[4,5-b]pyridin-5(4H)-one;
6-hydroxy[1,3]oxazolo[5,4-b]pyridin-5(4H)-one;
5-hydroxy-2-methylfuro[2,3-b]pyridin-6(7H)-one;
6-hydroxy-2-methylfuro[3,2-b]pyridin-5(4H)-one;
6-hydroxy-2-methyl[1,3]oxazolo[4,5-b]pyridin-5(4H)-one;
5-hydroxy-3-methylisoxazolo[3,4-b]pyridin-6(7H)-one;
6-hydroxy-2-methyl[1,3]oxazolo[5,4-b]pyridin-5(4H)-one;
6-hydroxy-3-methylisoxazolo[4,5-b]pyridin-5(4H)-one;
5-hydroxy-3-methylisoxazolo[5,4-b]pyridin-6(7H)-one;
5-hydroxythieno[2,3-b]pyridin-6(7H)-one;
6-hydroxy[1,3]thiazolo[5,4-b]pyridin-5(4H)-one;
6-hydroxy[1,3]thiazolo[4,5-b]pyridin-5(4H)-one;

2-fluoro-5-hydroxyfuro[2,3-b]pyridin-6(7H)-one;
2-fluoro-6-hydroxyfuro[3,2-b]pyridin-5(4H)-one;
6-hydroxy-2-methylthieno[3,2-b]pyridin-5(4H)-one;
5-hydroxy-2-methylthieno[2,3-b]pyridin-6(7H)-one;
2-fluoro-6-hydroxythieno[3,2-b]pyridin-5(4H)-one;
2-fluoro-5-hydroxythieno[2,3-b]pyridin-6(7H)-one;
2-chloro-6-hydroxyfuro[3,2-b]pyridin-5(4H)-one;
2-chloro-5-hydroxyfuro[2,3-b]pyridin-6(7H)-one;
2-chloro-6-hydroxythieno[3,2-b]pyridin-5(4H)-one;
7-fluoro-3-hydroxy-1,5-naphthyridin-2(1H)-one;
8-fluoro-3-hydroxy-1,6-naphthyridin-2(1H)-one;
6-fluoro-3-hydroxy-1,8-naphthyridin-2(1H)-one;
8-fluoro-3-hydroxy-1,5-naphthyridin-2(1H)-one;
5-fluoro-3-hydroxy-1,8-naphthyridin-2(1H)-one;
6-chloro-3-hydroxy-1,8-naphthyridin-2(1H)-one;
8-chloro-3-hydroxy-1,5-naphthyridin-2(1H)-one;
7-chloro-3-hydroxy-1,5-naphthyridin-2(1H)-one;
5-chloro-3-hydroxy-1,8-naphthyridin-2(1H)-one;
8-chloro-3-hydroxy-1,6-naphthyridin-2(1H)-one;
5-chloro-6-fluoro-3-hydroxy-1,8-naphthyridin-2(1H)-one;
4-fluoro-3-hydroxy-1,8-naphthyridin-2(1H)-one;
4-fluoro-3-hydroxy-1,5-naphthyridin-2(1H)-one;
4-fluoro-3-hydroxy-1,6-naphthyridin-2(1H)-one;
4-fluoro-3-hydroxy-5-methylquinolin-2(1H)-one;
4-fluoro-3-hydroxy-8-methylquinolin-2(1H)-one;
4,7-difluoro-3-hydroxyquinolin-2(1H)-one;
4,5-difluoro-3-hydroxyquinolin-2(1H)-one;
4,6-difluoro-3-hydroxyquinolin-2(1H)-one;
4,7-difluoro-3-hydroxy-1,5-naphthyridin-2(1H)-one;
4,8-difluoro-3-hydroxy-1,5-naphthyridin-2(1H)-one;
4,5-difluoro-3-hydroxy-1,8-naphthyridin-2(1H)-one;

4,8-difluoro-3-hydroxy-1,6-naphthyridin-2(1H)-one;
4-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-5-carbonitrile;
4-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-8-carbonitrile;
5-ethyl-4-fluoro-3-hydroxyquinolin-2(1H)-one;
8-ethyl-4-fluoro-3-hydroxyquinolin-2(1H)-one;
4,5-difluoro-3-hydroxy-8-methylquinolin-2(1H)-one;
4,8-difluoro-3-hydroxy-5-methylquinolin-2(1H)-one;
4,6-difluoro-3-hydroxy-5-methylquinolin-2(1H)-one;
4,7-difluoro-3-hydroxy-8-methylquinolin-2(1H)-one;
8-chloro-4-fluoro-3-hydroxyquinolin-2(1H)-one;
5-chloro-4-fluoro-3-hydroxyquinolin-2(1H)-one;
8-chloro-4-fluoro-3-hydroxy-1,5-naphthyridin-2(1H)-one;
8-chloro-4-fluoro-3-hydroxy-1,6-naphthyridin-2(1H)-one;
4,5,6-trifluoro-3-hydroxyquinolin-2(1H)-one;
4,5,8-trifluoro-3-hydroxyquinolin-2(1H)-one;
4,7,8-trifluoro-3-hydroxyquinolin-2(1H)-one;
4,6,7-trifluoro-3-hydroxyquinolin-2(1H)-one;
5-ethyl-4,7-difluoro-3-hydroxyquinolin-2(1H)-one;
8-ethyl-4,6-difluoro-3-hydroxyquinolin-2(1H)-one;
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8-chloro-4-fluoro-3-hydroxy-5-methylquinolin-2(1H)-one;
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5-chloro-4,6-difluoro-3-hydroxyquinolin-2(1H)-one;
8-chloro-4,6-difluoro-3-hydroxyquinolin-2(1H)-one;
8-chloro-4,5-difluoro-3-hydroxyquinolin-2(1H)-one;
8-chloro-5-ethyl-4-fluoro-3-hydroxyquinolin-2(1H)-one;
6-chloro-8-ethyl-4-fluoro-3-hydroxyquinolin-2(1H)-one;
4-fluoro-3-hydroxy-5-(trifluoromethyl)quinolin-2(1H)-one;
4-fluoro-3-hydroxy-8-(trifluoromethyl)quinolin-2(1H)-one;
5,8-dichloro-4-fluoro-3-hydroxyquinolin-2(1H)-one;

7-fluoro-3-hydroxy-8-methylquinolin-2(1H)-one;
8-fluoro-3-hydroxy-5-methylquinolin-2(1H)-one;
6-fluoro-3-hydroxy-8-methylquinolin-2(1H)-one;
6-fluoro-3-hydroxy-5-methylquinolin-2(1H)-one;
7-fluoro-3-hydroxy-5-methylquinolin-2(1H)-one;
5-fluoro-3-hydroxy-8-methylquinolin-2(1H)-one;
6,7-difluoro-3-hydroxyquinolin-2(1H)-one;
5,8-difluoro-3-hydroxyquinolin-2(1H)-one;
7,8-difluoro-3-hydroxyquinolin-2(1H)-one;
5,6-difluoro-3-hydroxyquinolin-2(1H)-one;
5,7-difluoro-3-hydroxyquinolin-2(1H)-one;
6,8-difluoro-3-hydroxyquinolin-2(1H)-one;
3-hydroxy-2-oxo-1,2-dihydroquinoline-8-carbonitrile;
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3-hydroxy-2-oxo-1,2-dihydroquinoline-7-carbonitrile;
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8-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-5-carbonitrile;
8-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-6-carbonitrile;
6-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-5-carbonitrile;
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5-fluoro-3-hydroxy-2-oxo-1,2-dihydroquinoline-6-carbonitrile;
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7-chloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-5-carbonitrile;

5-chloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-8-carbonitrile;
7-chloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-8-carbonitrile;
8-chloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-7-carbonitrile;
5-chloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-6-carbonitrile;
8-chloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-5-carbonitrile;
6-chloro-3-hydroxy-2-oxo-1,2-dihydroquinoline-5-carbonitrile;
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6-chloro-5-fluoro-3-hydroxyquinolin-2(1H)-one;
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5-chloro-8-fluoro-3-hydroxyquinolin-2(1H)-one;
7-chloro-8-fluoro-3-hydroxyquinolin-2(1H)-one;
7-chloro-5-fluoro-3-hydroxyquinolin-2(1H)-one;
6-chloro-8-fluoro-3-hydroxyquinolin-2(1H)-one;
5-chloro-7-fluoro-3-hydroxyquinolin-2(1H)-one;
7-chloro-5-ethyl-3-hydroxyquinolin-2(1H)-one;
5-chloro-8-ethyl-3-hydroxyquinolin-2(1H)-one;
6-chloro-8-ethyl-3-hydroxyquinolin-2(1H)-one;
8-chloro-5-ethyl-3-hydroxyquinolin-2(1H)-one;

6-chloro-5-ethyl-3-hydroxyquinolin-2(1H)-one;
3-hydroxy-5-(trifluoromethyl)quinolin-2(1H)-one;
3-hydroxy-8-(trifluoromethyl)quinolin-2(1H)-one;
5,8-dichloro-3-hydroxyquinolin-2(1H)-one;
6,8-dichloro-3-hydroxyquinolin-2(1H)-one;
6-fluoro-3-hydroxy-8-(trifluoromethyl)quinolin-2(1H)-one;
8-fluoro-3-hydroxy-5-(trifluoromethyl)quinolin-2(1H)-one;
5-fluoro-3-hydroxy-8-(trifluoromethyl)quinolin-2(1H)-one;
6-fluoro-3-hydroxy-5-(trifluoromethyl)quinolin-2(1H)-one;
7-fluoro-3-hydroxy-5-(trifluoromethyl)quinolin-2(1H)-one;
7-fluoro-3-hydroxy-8-(trifluoromethyl)quinolin-2(1H)-one;
6-chloro-3-hydroxy-8-(trifluoromethyl)quinolin-2(1H)-one;
5-chloro-3-hydroxy-6-(trifluoromethyl)quinolin-2(1H)-one;
5-chloro-3-hydroxy-8-(trifluoromethyl)quinolin-2(1H)-one;
8-chloro-3-hydroxy-5-(trifluoromethyl)quinolin-2(1H)-one;
8-chloro-3-hydroxy-6-(trifluoromethyl)quinolin-2(1H)-one;
7-chloro-3-hydroxy-5-(trifluoromethyl)quinolin-2(1H)-one;
5,6,7-trifluoro-3-hydroxyquinolin-2(1H)-one;
5,7,8-trifluoro-3-hydroxyquinolin-2(1H)-one; and
5,6,7,8-tetrafluoro-3-hydroxyquinolin-2(1H)-one; or
pharmaceutically acceptable salts thereof.

4. A composition comprising a pharmaceutically effective amount of any one of the compounds of the preceding claims or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

5. A method of treating a cognitive-related disorder comprising administering a pharmaceutically effective amount of the compound of claim 3, or a pharmaceutically acceptable salt thereof, to a patient in need thereof.

6. The method of claim 5, wherein said cognitive-related disorder is selected from the group consisting of psychosis, schizophrenia and related disorders, bipolar disorder, 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 or depression associated with bipolar disorder and mood disorders associated with schizophrenia, cognitive disorders such as dementias (including age related dementia, and senile dementia of the Alzheimer's type), memory disorders and any combination thereof.

7. The method of claims 5 or 6, further comprising administering a second agent to said patient.

8. The method of claims 5 or 6, wherein said second agent is ziprasidone, risperidone, aripiprazole, quetiapine, paliperidone, olanzapine, zyprexa, sertindole, amisulpride, bifeprunox, vabicaserin or ispronicline.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2009/054925

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D201/00 C07D215/06 C07D215/18 C07D261/00 C07D277/60
C07D307/77 C07D333/00 C07D401/04 C07D231/00 A61K31/34
A61K31/381 A61K31/407 A61K31/4162 A61K31/424 A61K31/429

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, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96/04288 A (OREGON STATE [US]; ACEA PHARM INC [US]; UNIV CALIFORNIA [US]) 15 February 1996 (1996-02-15) page 1, lines 7-12 page 10; compounds V-VII page 45; compound 5B page 82, lines 5-19	1,2,4
Y	-----	3,5-8
	-/--	

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

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 February 2010	05/03/2010

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Tullberg, Erik

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2009/054925

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SING-YUEN S ET AL: "3-Hydroxy-quinolin-2-ones: inhibitors of [<3>H]-glycine binding to the site associated with the NMDA receptor" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, ELSEVIER SCIENCE, GB, vol. 6, no. 5, 5 March 1996 (1996-03-05), pages 499-504, XP004135016 ISSN: 0960-894X abstract page 499 page 502; table 1 page 503	3,5-8
A	WO 2007/039773 A (MERCK SHARP & DOHME [GB]; MERCK & CO INC [US]; BRANDISH PHILIP E [US];) 12 April 2007 (2007-04-12) the whole document	1-8
A	WO 2008/089453 A (SEPRACOR INC [US]; HEFFERNAN MICHELE L R [US]; FANG QUN KEVIN [US]; FO) 24 July 2008 (2008-07-24) the whole document	1-8
A	DATABASE WPI Week 198023 Thomson Scientific, London, GB; AN 1980-40463C XP002566117 & JP 55 055194 A (MITSUBISHI PETROCHEMICAL CO LTD) 22 April 1980 (1980-04-22) abstract	1-8
A	WO 2005/049034 A (GLAXO GROUP LTD [GB]; HAGAN JAMES [GB]; ROUTLEDGE CAROL [GB]) 2 June 2005 (2005-06-02) the whole document	1-8
A	SU 368 265 A1 (CHEM-PHOT IND RES AND DES) 26 January 1973 (1973-01-26) the whole document	3

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: -

The expressions "treating a disorder or condition that can be treated by inhibiting D-amino acid oxidase (DAAO) activity in mammal, preferably a human, in need of such treatment" and "cognitive related disorder" according to the subject-matter of claims 1and 5 of the present application do not fulfill the requirements of Article 6 PCT because it is not clear for the skilled person which disorders or conditions fall within or without of the expression. They have therefore been interpreted in light of the disorders and conditions according to claim 6 and page 31 and 32 of the present application.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.2), should the problems which led to the Article 17(2)PCT declaration be overcome.

INTERNATIONAL SEARCH REPORT

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

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

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

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:
see FURTHER INFORMATION sheet PCT/ISA/210

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

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

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

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

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

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search 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 and, where applicable, the payment of a protest fee.

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

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2009/054925

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9604288 A	15-02-1996	AU 3234395 A	04-03-1996
		US 5597922 A	28-01-1997
WO 2007039773 A	12-04-2007	AU 2006298563 A1	12-04-2007
		CA 2624795 A1	12-04-2007
		EP 1942885 A1	16-07-2008
		JP 2009511462 T	19-03-2009
		US 2009306169 A1	10-12-2009
WO 2008089453 A	24-07-2008	AU 2008206039 A1	24-07-2008
		CA 2676432 A1	24-07-2008
		EP 2074092 A2	01-07-2009
		US 2008174768 A1	24-07-2008
		US 2009099248 A1	16-04-2009
JP 55055194 A	22-04-1980	NONE	
WO 2005049034 A	02-06-2005	EP 1687001 A2	09-08-2006
		JP 2007511572 T	10-05-2007
		US 2007142411 A1	21-06-2007
SU 368265 A1	26-01-1973	NONE	