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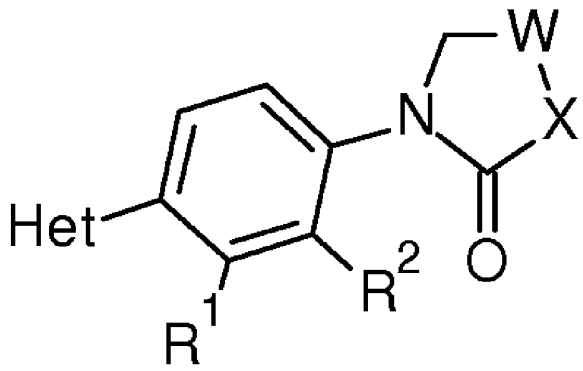
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(54) Title: N-PHENYL-LACTAM DERIVATIVES CAPABLE OF STIMULATING NEUROGENESIS AND THEIR USE IN THE TREATMENT OF NEUROLOGICAL DISORDERS



I

(57) Abstract: The present invention relates to compounds of the general formula I wherein Het is oxazole-5-yl, pyridin-4-yl, or pyrazol-4-yl; R^1/ R^2 are, independently from each other, hydrogen, lower alkyl, lower alkoxy, or halogen; W is $-CH_2-$ or $-CH_2CH_2-$; X is CR^3R^4 or NR^5; R^3 is hydrogen or lower alkyl; R^4 is $-(CH_2)_n$-phenyl, optionally substituted by halogen, lower alkoxy, lower alkyl substituted by halogen, lower alkoxy substituted by halogen or lower alkyl; R^5 is CHR-phenyl or CH2CHR-phenyl, optionally substituted by halogen, lower alkoxy, lower alkyl substituted by halogen, lower alkoxy substituted by halogen or lower alkyl, or is CHR-pyridin-2, 3 or 4 -yl; R is hydrogen or lower alkyl; n is 0 or 1; or to a pharmaceutically acceptable acid addition salt, to a racemic mixture or to its corresponding enantiomer and/or optical isomer thereof. The compounds may be used for the treatment of schizophrenia, obsessive-compulsive personality disorder, depression, bipolar disorders, anxiety disorders, normal aging, epilepsy, retinal degeneration, traumatic brain injury, spinal cord injury, post-traumatic stress disorder, panic disorder, Parkinson's disease, dementia, Alzheimer's disease, cognitive impairment, chemotherapy-induced cognitive dysfunction, Down syndrome, autism spectrum disorders, hearing loss, tinnitus, spinocerebellar ataxia, amyotrophic lateral sclerosis, multiple sclerosis, Huntington's disease, stroke, radiation therapy, chronic stress, abuse of neuro-active drugs, selected from alcohol, opiates, methamphetamine, phencyclidine and cocaine.

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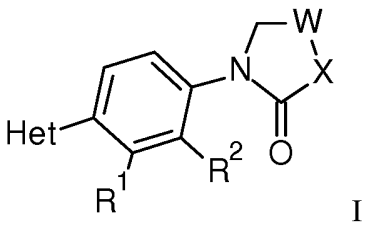
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N-PHENYL-LACTAM DERIVATIVES CAPABLE OF STIMULATING NEUROGENESIS AND THEIR USE IN THE TREATMENT OF NEUROLOGICAL DISORDERS

The present invention relates to compounds of the general formula



I

wherein

Het	is oxazole-5-yl, pyridin-4-yl, or pyrazol-4-yl;
R^1/ R^2	are, independently from each other, hydrogen, lower alkyl, lower alkoxy, or halogen;
W	is $-CH_2-$ or $-CH_2CH_2-$;
X	is CR^3R^4 or NR^5;
R^3	is hydrogen or lower alkyl;
R^4	is $-(CH_2)_n$-phenyl, optionally substituted by halogen, lower alkoxy, lower alkyl substituted by halogen, lower alkoxy substituted by halogen or lower alkyl;
R^5	is CHR-phenyl or CH_2CHR-phenyl, optionally substituted by halogen, lower alkoxy, lower alkyl substituted by halogen, lower alkoxy substituted by halogen or lower alkyl, or is CHR-pyridin-2, 3 or 4 –yl; R is hydrogen or lower alkyl;
n	is 0 or 1;

or to a pharmaceutically acceptable acid addition salt, to a racemic mixture or to its corresponding enantiomer and/or optical isomer thereof.

Now it has been shown that the present compounds stimulate neurogenesis from neural stem cells (NSCs). Neurogenesis occurs in the developing and adult brain. Conceptually, this process of neurogenesis can be divided into four steps: (i) proliferation of NSCs; (ii) neuronal fate determination of NSC; (iii) survival and maturation of new neurons;

and (iv) functional integration of new neurons into the neuronal network.

Adult neurogenesis is a developmental process that occurs throughout live in the adult brain whereby new functional neurons are generated from adult neural stem cells. Constitutive adult neurogenesis under physiological conditions occurs mainly in two "neurogenic" brain regions, 1) the sub-granular zone (SGZ) in the dentate gyrus of the hippocampus, where new dentate granule cells are generated, 2) the sub-ventricular zone (SVZ) of the lateral ventricles, where new neurons are generated and then migrate through the rostral migratory stream (RMS) to the olfactory bulb to become interneurons.

Extensive evidence suggests that hippocampal adult neurogenesis plays an important role in cognitive and emotional states albeit the precise function remains elusive. It has been argued that the relatively small number of newborn granule neurons can affect global brain function because they innervate many interneurons within the dentate gyrus, each of which inhibits hundreds of mature granule cells leading to a neurogenesis-dependent feedback inhibition. In combination with a low threshold for firing the newborn neurons trigger responses to very subtle changes in context. Disturbances in this process may manifest behaviorally in deficits in pattern separation related to psychiatric diseases. For example, adult hippocampal neurogenesis correlates with cognitive and emotional capacity, e.g. physical exercise, exposure to an enriched environment and typical antidepressants concomitantly promote adult hippocampal neurogenesis and cognition and/or emotional states, while chronic stress, depression, sleep deprivation and aging decrease adult neurogenesis and associate with negative cognitive and/or emotional states (Neuron 70, May 26, 2011, pp 582 -588 and pp 687 – 702; WO 2008/046072). Interestingly, antidepressants promote hippocampal adult neurogenesis and their effects on certain behaviors require the stimulation of neurogenesis. Neurogenesis in other adult CNS regions is generally believed to be very limited under normal physiological conditions, but could be induced after injury such as stroke, and central and peripheral brain damage.

It is therefore believed that stimulation of adult neurogenesis represents a neuro-regenerative therapeutic target for normal aging and in particular for a variety of neurodegenerative and neuropsychiatric diseases, including schizophrenia, obsessive-compulsive personality disorder, major depression, bipolar disorders, anxiety disorders, epilepsy, retinal degeneration, traumatic brain injury, spinal cord injury, post-traumatic stress disorder, panic disorder, Parkinson's disease, dementia, Alzheimer's disease, mild cognitive impairment, chemotherapy-induced cognitive dysfunction ("chemobrain"), Down

syndrome, autism spectrum disorders, hearing loss (Neuroscience, 167 (2010) 1216-1226; Nature Medicine, Vol. 11, number 3, (2005), 271-276) tinnitus, spinocerebellar ataxia, amyotrophic lateral sclerosis, multiple sclerosis, Huntington's disease, stroke, and disturbances due to radiation therapy, chronic stress, or abuse of neuro-active drugs, such as alcohol, opiates, methamphetamine, phencyclidine and cocaine (US 2012/0022096). The stimulation of adult neurogenesis represents also a therapeutic target for optic neuropathy (S. Isenmann, A. Kretz, A. Cellerino, Progress in Retinal and Eye Research, 22, (2003) 483) and macular degeneration (G. Landa, O. Butovsky, J. Shoshani, M. Schwartz, A. Pollack, Current Eye Research 33, (2008) 1011).

Hence, chemical stimulation of adult neurogenesis offers new regenerative avenues and opportunities to develop novel drugs for treating neurological diseases and neuropsychiatric disorders.

Therefore, the object of the present invention was to identify compounds that modulate neurogenesis. It has been found that the compounds of formula I are active in this area and they may therefore be used for the treatment of schizophrenia, obsessive-compulsive personality disorder, depression, bipolar disorders, anxiety disorders, normal aging, epilepsy, retinal degeneration, traumatic brain injury, spinal cord injury, post-traumatic stress disorder, panic disorder, Parkinson's disease, dementia, Alzheimer's disease, mild cognitive impairment, chemotherapy-induced cognitive dysfunction ("chemobrain"), Down syndrome, autism spectrum disorders, hearing loss, tinnitus, spinocerebellar ataxia, amyotrophic lateral sclerosis, multiple sclerosis, Huntington's disease, stroke, and disturbances due to radiation therapy, chronic stress, optic neuropathy or macular degeneration, or abuse of neuro-active drugs, such as alcohol, opiates, methamphetamine, phencyclidine or cocaine.

The most preferred indications for compounds of formula I are Alzheimer's disease, depression, anxiety disorders and stroke.

The present invention relates to compounds of formula I and to their pharmaceutically acceptable salts, in cases where this applies to mixtures of enantiomers or diastereomers or their enantiomerically or diastereomerically pure forms, to these compounds as pharmaceutically active substances, to the processes for their production, as well as to the use in the treatment or prevention of disorders, relating to neurogenesis, schizophrenia, obsessive-compulsive personality disorder, depression, bipolar disorders, anxiety disorders, normal aging, epilepsy, retinal degeneration, traumatic brain injury, spinal cord injury,

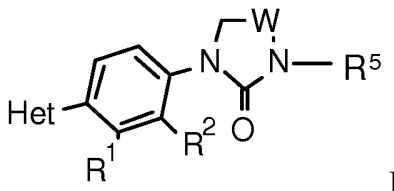
post-traumatic stress disorder, panic disorder, Parkinson's disease, dementia, Alzheimer's disease, mild cognitive impairment, chemotherapy-induced cognitive dysfunction ("chemobrain"), Down syndrome, autism spectrum disorders, hearing loss, tinnitus, spinocerebellar ataxia, amyotrophic lateral sclerosis, multiple sclerosis, Huntington's disease, stroke, and disturbances due to radiation therapy, chronic stress, optic neuropathy or macular degeneration, or abuse of neuro-active drugs, such as alcohol, opiates, methamphetamine, phencyclidine or cocaine.

One further object of the invention are pharmaceutical compositions, containing a compound of formula I.

One further object of the present invention is the use of a compound of formula I for the preparation of medicaments for the therapeutic and/or prophylactic treatment of the above-mentioned diseases.

A further object of the invention is a method for the treatment of schizophrenia, obsessive-compulsive personality disorder, major depression, bipolar disorders, anxiety disorders, normal aging, epilepsy, retinal degeneration, traumatic brain injury, spinal cord injury, post-traumatic stress disorder, panic disorder, Parkinson's disease, dementia, Alzheimer's disease, cognitive impairment, chemotherapy-induced cognitive dysfunction, Down syndrome, autism spectrum disorders, hearing loss, tinnitus, spinocerebellar ataxia, amyotrophic lateral sclerosis, multiple sclerosis, Huntington's disease, stroke, radiation therapy, chronic stress, abuse of neuro-active drugs, such as alcohol, opiates, methamphetamine, phencyclidine and cocaine, which method comprises administering an effective amount of a compound of formula I.

One embodiment of the invention are compounds of formula **Ia**



Ia

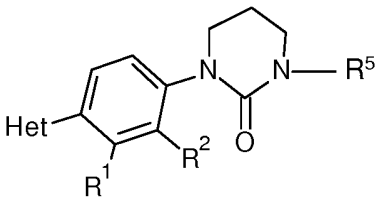
wherein

Het	is oxazole-5-yl, pyridin-4-yl, or pyrazol-4-yl;
R^1/ R^2	are, independently from each other, hydrogen, lower alkyl, lower alkoxy, or halogen;
W	is $-CH_2-$ or $-CH_2CH_2-$;

R^5 is CHR-phenyl or CH_2CHR-phenyl, optionally substituted by halogen, lower alkoxy, lower alkyl substituted by halogen, lower alkoxy substituted by halogen or lower alkyl, or is
CHR-pyridin-2, 3 or 4 –yl;
R is hydrogen or lower alkyl;

or a pharmaceutically acceptable acid addition salt, a racemic mixture or its corresponding enantiomer and/or optical isomer thereof

One embodiment of the invention are further compounds of formula **Ia-1**,



Ia-1

wherein

Het is oxazole-5-yl, pyridin-4-yl, or pyrazol-4-yl;

R^1/ R^2 are, independently from each other, hydrogen, lower alkyl, lower alkoxy, or halogen;

R^5 is CHR-phenyl or CH_2CHR-phenyl, optionally substituted by halogen, lower alkoxy, lower alkyl substituted by halogen, lower alkoxy substituted by halogen or lower alkyl, or is
CHR-pyridin-2, 3 or 4 –yl;
R is hydrogen or lower alkyl;

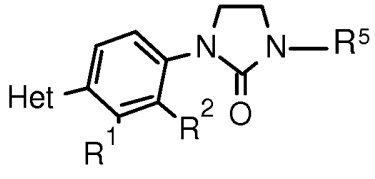
or a pharmaceutically acceptable acid addition salt, a racemic mixture or its corresponding enantiomer and/or optical isomer thereof, for example the following compounds

1-benzyl-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]hexahydropyrimidin-2-one

1-[(2-chlorophenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]hexahydropyrimidin-2-one or

1-[(3-methoxyphenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]hexahydropyrimidin-2-one.

One object of the invention are further compounds of formula **Ia-2**,



Ia-2

wherein

Het is oxazole-5-yl, pyridin-4-yl, or pyrazol-4-yl;

R^1/ R^2 are, independently from each other, hydrogen, lower alkyl, lower alkoxy, or halogen;

R^5 is CHR-phenyl or CH_2CHR-phenyl, optionally substituted by halogen, lower alkoxy, lower alkyl substituted by halogen, lower alkoxy substituted by halogen or lower alkyl, or is

CHR-pyridin-2, 3 or 4 –yl;

R is hydrogen or lower alkyl;

or a pharmaceutically acceptable acid addition salt, a racemic mixture or its corresponding enantiomer and/or optical isomer thereof, for example the following compounds

1-benzyl-3-(4-(pyridin-4-yl)phenyl)imidazolidin-2-one

1-benzyl-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one

1-[(2-chlorophenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one

1-[(3-methoxyphenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one

1-[(3-chlorophenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one

1-[(3-fluorophenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one

1-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-[[3-(trifluoromethyl)phenyl]methyl]imidazolidin-2-one

1-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-[[3-(trifluoromethoxy)phenyl]methyl]imidazolidin-2-one

1-[(3-ethoxyphenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one

1-[(3-methoxyphenyl)methyl]-3-[4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one

1-[(3-methoxyphenyl)methyl]-3-[3-methyl-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one

1-[3-chloro-4-(1H-pyrazol-4-yl)phenyl]-3-[(3-methoxyphenyl)methyl]imidazolidin-2-one

1-[2-fluoro-4-(1H-pyrazol-4-yl)phenyl]-3-[(3-methoxyphenyl)methyl]imidazolidin-2-one

1-[3-fluoro-4-(1H-pyrazol-4-yl)phenyl]-3-[(3-methoxyphenyl)methyl]imidazolidin-2-one

1-[3-ethoxy-4-(1H-pyrazol-4-yl)phenyl]-3-[(3-methoxyphenyl)methyl]imidazolidin-2-one

1-[(2-fluorophenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one

1-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-(o-tolylmethyl)imidazolidin-2-one

1-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-(m-tolylmethyl)imidazolidin-2-one

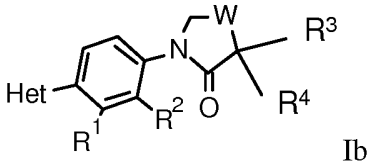
1-[(3-methoxyphenyl)methyl]-3-[2-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one

1-[(2-methoxyphenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one

1-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-(2-phenylethyl)imidazolidin-2-one

1-[2-(2-methoxyphenyl)ethyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one
1-[2-(2-chlorophenyl)ethyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one
1-[2-chloro-4-(1H-pyrazol-4-yl)phenyl]-3-[(3-methoxyphenyl)methyl]imidazolidin-2-one
1-[(4-fluorophenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one
1-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-(3-pyridylmethyl)imidazolidin-2-one
1-[2-(3-chlorophenyl)ethyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one
1-[2-(4-chlorophenyl)ethyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one
1-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-(1-phenylpropyl)imidazolidin-2-one
1-[3-methoxy-4-(4-pyridyl)phenyl]-3-[[2-(trifluoromethyl)phenyl]methyl]imidazolidin-2-one
1-[3-methoxy-4-(4-pyridyl)phenyl]-3-(4-pyridylmethyl)imidazolidin-2-one
1-[(3-methoxyphenyl)methyl]-3-[4-(1,3-oxazol-5-yl)phenyl]imidazolidin-2-one
1-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-(4-pyridylmethyl)imidazolidin-2-one
1-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-(2-pyridylmethyl)imidazolidin-2-one
1-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-(2-phenylpropyl)imidazolidin-2-one
1-[3-methoxy-4-(4-pyridyl)phenyl]-3-(m-tolylmethyl)imidazolidin-2-one
1-[3-methoxy-4-(4-pyridyl)phenyl]-3-(3-pyridylmethyl)imidazolidin-2-one
1-[3-methoxy-4-(1,3-oxazol-5-yl)phenyl]-3-[(2-methoxyphenyl)methyl]imidazolidin-2-one
1-[3-methoxy-4-(1,3-oxazol-5-yl)phenyl]-3-[(3-methoxyphenyl)methyl]imidazolidin-2-one
1-[(2-chlorophenyl)methyl]-3-[3-methoxy-4-(1,3-oxazol-5-yl)phenyl]imidazolidin-2-one
1-[(3-fluorophenyl)methyl]-3-[4-(1,3-oxazol-5-yl)phenyl]imidazolidin-2-one
1-[(2-fluorophenyl)methyl]-3-[4-(1,3-oxazol-5-yl)phenyl]imidazolidin-2-one
1-[(2-fluorophenyl)methyl]-3-[3-methoxy-4-(1,3-oxazol-5-yl)phenyl]imidazolidin-2-one or
1-[(3-fluorophenyl)methyl]-3-[3-methoxy-4-(1,3-oxazol-5-yl)phenyl]imidazolidin-2-one.

A further object of the invention are compounds of formula **Ib**.



Ib

wherein

Het is oxazole-5-yl, pyridin-4-yl, or pyrazol-4-yl;

R^1/ R^2 are, independently from each other, hydrogen, lower alkyl, lower alkoxy, or halogen;

W is $-CH_2-$ or $-CH_2CH_2-$;

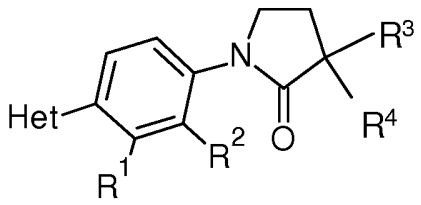
R^3 is hydrogen or lower alkyl;

R^4 is $-(CH_2)_n$-phenyl, optionally substituted by halogen, lower alkoxy, lower alkyl substituted by halogen, lower alkoxy substituted by halogen or lower alkyl;

n is 0 or 1;

or a pharmaceutically acceptable acid addition salt, a racemic mixture or its corresponding enantiomer and/or optical isomer thereof.

A further object of the invention are compounds of formula **Ib-1**



Ib-1

wherein

Het is oxazole-5-yl, pyridin-4-yl, or pyrazol-4-yl;

R^1/ R^2 are, independently from each other, hydrogen, lower alkyl, lower alkoxy, or halogen;

R^3 is hydrogen or lower alkyl;

R^4 is $-(CH_2)_n$-phenyl, optionally substituted by halogen, lower alkoxy, lower alkyl substituted by halogen, lower alkoxy substituted by halogen or lower alkyl;

n is 0 or 1;

or a pharmaceutically acceptable acid addition salt, a racemic mixture or its corresponding enantiomer and/or optical isomer thereof, for example the following compounds

3-ethyl-1-(3-methoxy-4-(oxazol-5-yl)phenyl)-3-phenylpyrrolidin-2-one

1-(3-methoxy-4-oxazol-5-yl-phenyl)-3-(3-methoxyphenyl)pyrrolidin-2-one

3-(2-chlorophenyl)-1-(3-methoxy-4-oxazol-5-yl-phenyl)pyrrolidin-2-one

1-(3-methoxy-4-oxazol-5-yl-phenyl)-3-phenyl-pyrrolidin-2-one

1-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-phenyl-pyrrolidin-2-one

3-phenyl-1-[4-(1H-pyrazol-4-yl)phenyl]pyrrolidin-2-one

3-(3-methoxyphenyl)-1-[4-(1H-pyrazol-4-yl)phenyl]pyrrolidin-2-one

3-(4-chlorophenyl)-1-[4-(1H-pyrazol-4-yl)phenyl]pyrrolidin-2-one

3-(4-fluorophenyl)-1-[4-(1H-pyrazol-4-yl)phenyl]pyrrolidin-2-one

3-(3-chlorophenyl)-1-[4-(1H-pyrazol-4-yl)phenyl]pyrrolidin-2-one

3-benzyl-1-(3-methoxy-4-(1H-pyrazol-4-yl)phenyl)pyrrolidin-2-one

1-(3-methoxy-4-(1H-pyrazol-4-yl)phenyl)-3-(3-methoxyphenyl)pyrrolidin-2-one

3-(3-chlorophenyl)-1-(3-methoxy-4-(1H-pyrazol-4-yl)phenyl)pyrrolidin-2-one

3-(3-fluorophenyl)-1-(3-methoxy-4-(1H-pyrazol-4-yl)phenyl)pyrrolidin-2-one

3-[(3-chlorophenyl)methyl]-1-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]pyrrolidin-2-one

3-[(2-chlorophenyl)methyl]-1-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]pyrrolidin-2-one

3-(3-chlorophenyl)-1-[3-methoxy-4-(1,3-oxazol-5-yl)phenyl]pyrrolidin-2-one

3-[(3-methoxyphenyl)methyl]-1-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]pyrrolidin-2-one

1-[3-methoxy-4-(1,3-oxazol-5-yl)phenyl]-3-(2-methoxyphenyl)pyrrolidin-2-one

3-(3-methoxyphenyl)-1-[4-(1,3-oxazol-5-yl)phenyl]pyrrolidin-2-one

1-[4-(1,3-oxazol-5-yl)phenyl]-3-phenylpyrrolidin-2-one

1-[3-methoxy-4-(1,3-oxazol-5-yl)phenyl]-3-[3-(trifluoromethyl)phenyl]pyrrolidin-2-one

3-(2-fluorophenyl)-1-[4-(1,3-oxazol-5-yl)phenyl]pyrrolidin-2-one

3-(2-fluorophenyl)-1-[3-methoxy-4-(1,3-oxazol-5-yl)phenyl]pyrrolidin-2-one

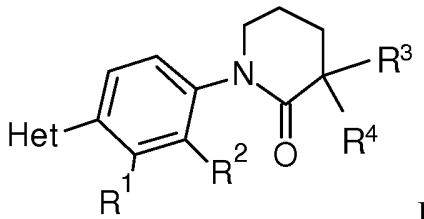
3-(3-fluorophenyl)-1-[4-(1,3-oxazol-5-yl)phenyl]pyrrolidin-2-one

3-(3-fluorophenyl)-1-[3-methoxy-4-(1,3-oxazol-5-yl)phenyl]pyrrolidin-2-one

3-(3-methoxyphenyl)-1-(3-methoxy-4-pyridin-4-ylphenyl)pyrrolidin-2-one or

3-(3-methoxyphenyl)-1-(4-pyridin-4-ylphenyl)pyrrolidin-2-one.

One further object of the present invention are compounds of formula Ib-2



Ib-2

wherein

Het	is oxazole-5-yl, pyridin-4-yl, or pyrazol-4-yl;
R^1/ R^2	are, independently from each other, hydrogen, lower alkyl, lower alkoxy, or halogen;
R^3	is hydrogen or lower alkyl;

R^4 is -$(CH_2)_n$-phenyl, optionally substituted by halogen, lower alkoxy, lower alkyl substituted by halogen, lower alkoxy substituted by halogen or lower alkyl;

n is 0 or 1;

or a pharmaceutically acceptable acid addition salt, a racemic mixture or its corresponding enantiomer and/or optical isomer thereof.

The following definitions of the general terms used in the present description apply irrespective of whether the terms in question appear alone or in combination.

As used herein, the term "lower alkyl" denotes a saturated, i.e. aliphatic hydrocarbon group including a straight or branched carbon chain with 1 – 7 carbon atoms. Examples for "alkyl" are methyl, ethyl, n-propyl, and isopropyl.

The term "alkoxy" denotes a group -O-R' wherein R' is lower alkyl as defined above.

The term "lower alkyl substituted by halogen" denotes a lower alkyl group as defined above, wherein at least one hydrogen atom is replaced by a halogen atom. The preferred group is CF_3.

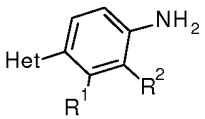
The term "lower alkoxy substituted by halogen" denotes a lower alkoxy group as defined above, wherein at least one hydrogen atom is replaced by a halogen atom. The preferred group is OCF_3.

The term "halogen" denotes chlorine, bromine, fluorine or iodine.

Compounds of formula **I** can be prepared according to the below process steps and in accordance with Schemes 1 – 7.

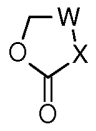
The present new compounds of formula I and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example, by processes described below, which process comprises

a) reacting a compound of formula



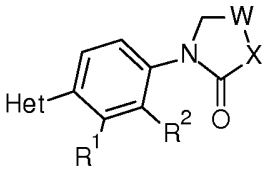
1

with a compound of formula



2

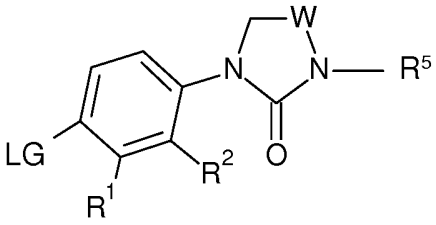
to a compound of formula



I

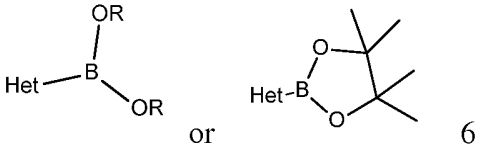
and, if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts, or

b) reacting a compound of formula



5

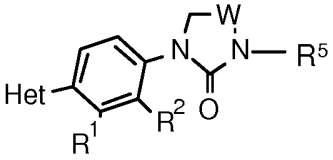
with a compound of formula



6

for R being hydrogen or lower alkyl,

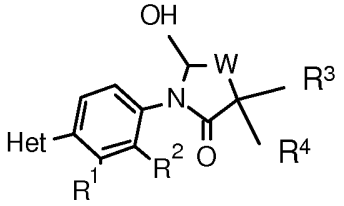
to a compound of formula



Ia

and, if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts, or

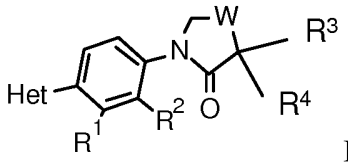
c) reacting a compound of formula



14

with a reducing agent, selected from Et_3SiH

to a compound of formula



Ib

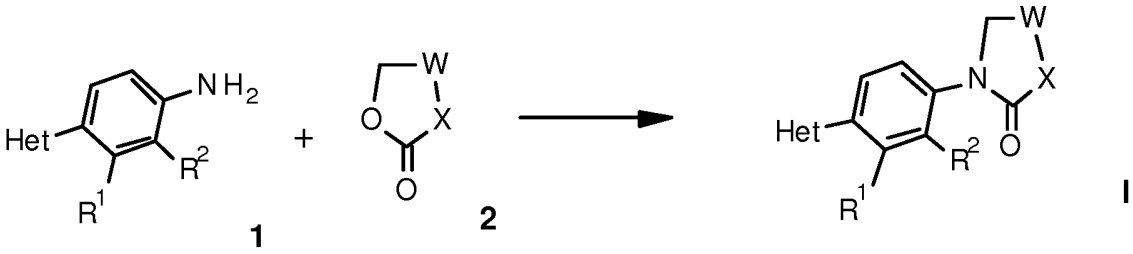
and, if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

The definitions of substituents is as described above.

The preparation of compounds of formula **I** of the present invention may be carried out in sequential or convergent synthetic routes. Syntheses of the compounds of the invention are shown in the following scheme 1. The skills required for carrying out the reaction and purification of the resulting products are known to those skilled in the art. The substituents and indices used in the following description of the processes have the significance given herein before unless indicated to the contrary.

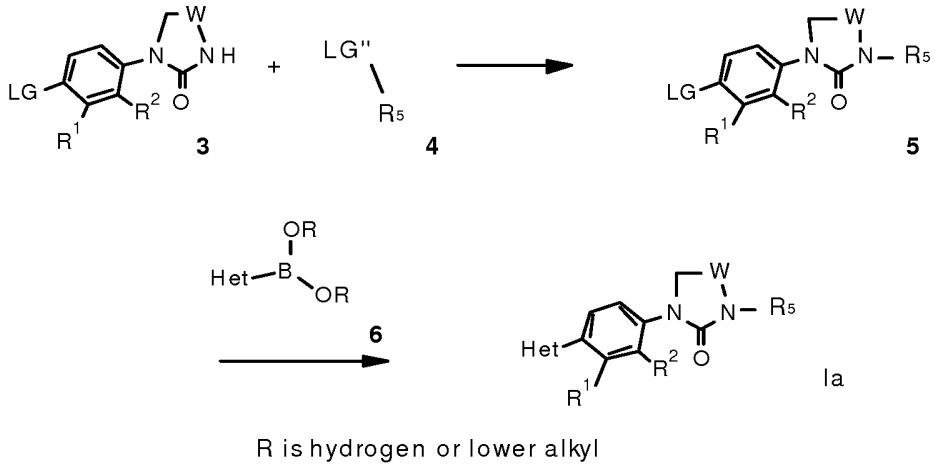
In more detail, the compounds of formula **I** can be manufactured by the methods given below, by the methods given in the examples or by analogous methods. Appropriate reaction conditions for the individual reaction steps are known to a person skilled in the art. The reaction sequence is not limited to the one displayed in scheme 1, however, depending on the starting materials and their respective reactivity the sequence of reaction steps can be freely altered. Starting materials are either commercially available or can be prepared by methods analogous to the methods given below, by methods described in references cited in the description or in the examples, or by methods known in the art.

Scheme 1



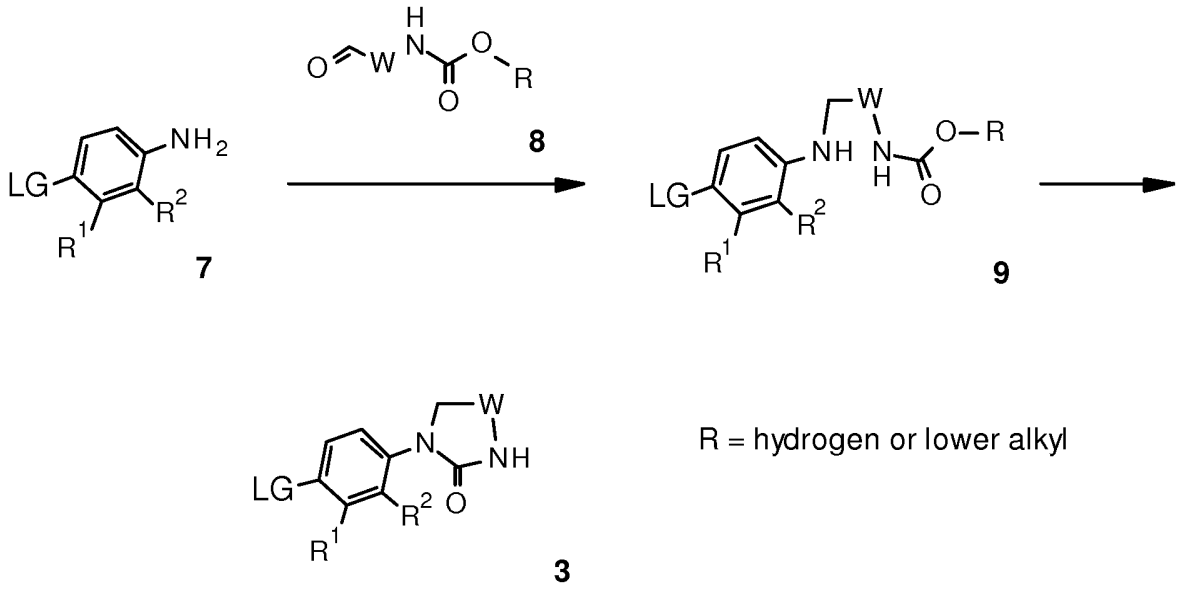
Compounds of formula **I** can be prepared according to Scheme 1, by reaction of an aromatic amine **1** with a lactone **2**. Amine **1** may be treated with a suitable base, such as trimethylaluminum, for increased reactivity. Suitable starting materials **1** and **2** are commercially available or can be prepared by methods known in the art.

Scheme 2



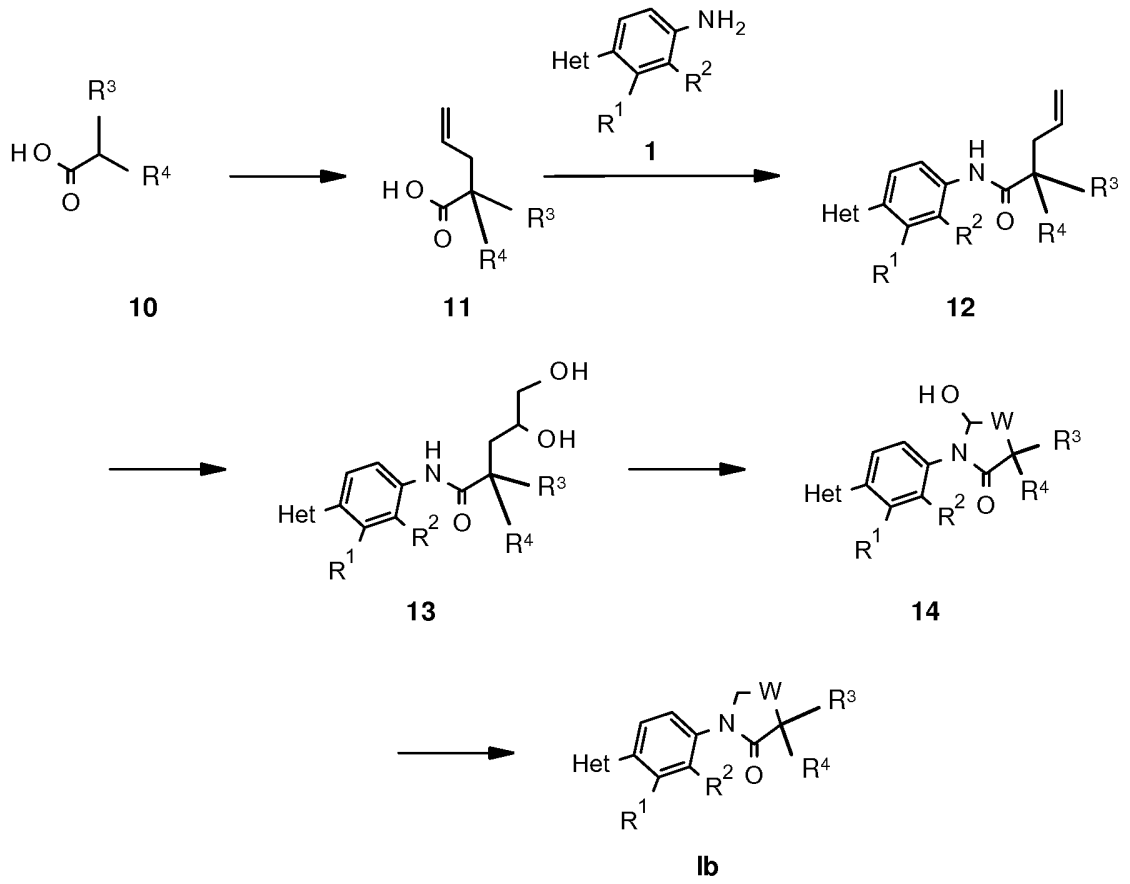
Compounds of formula **Ia** can be prepared according to Scheme 2. An arylimidazole **3**, in which LG is a suitable leaving group, such as Br, is first reacted with a suitable base, such as sodium hydride, and then with compound 4, in which LG'' is a suitable leaving group, such as Br. The resulting compound **5** is then reacted with a boronic acid, or a boronic acid ester, **6**, in the presence of a suitable catalyst, such as tetrakis(triphenylphosphine)palladium, and a suitable base, such as sodium carbonate, to give compound **Ia**. Arylimidazoles **3** are commercially available, can be prepared by methods known in the art, or can be prepared according to scheme 3.

Scheme 3



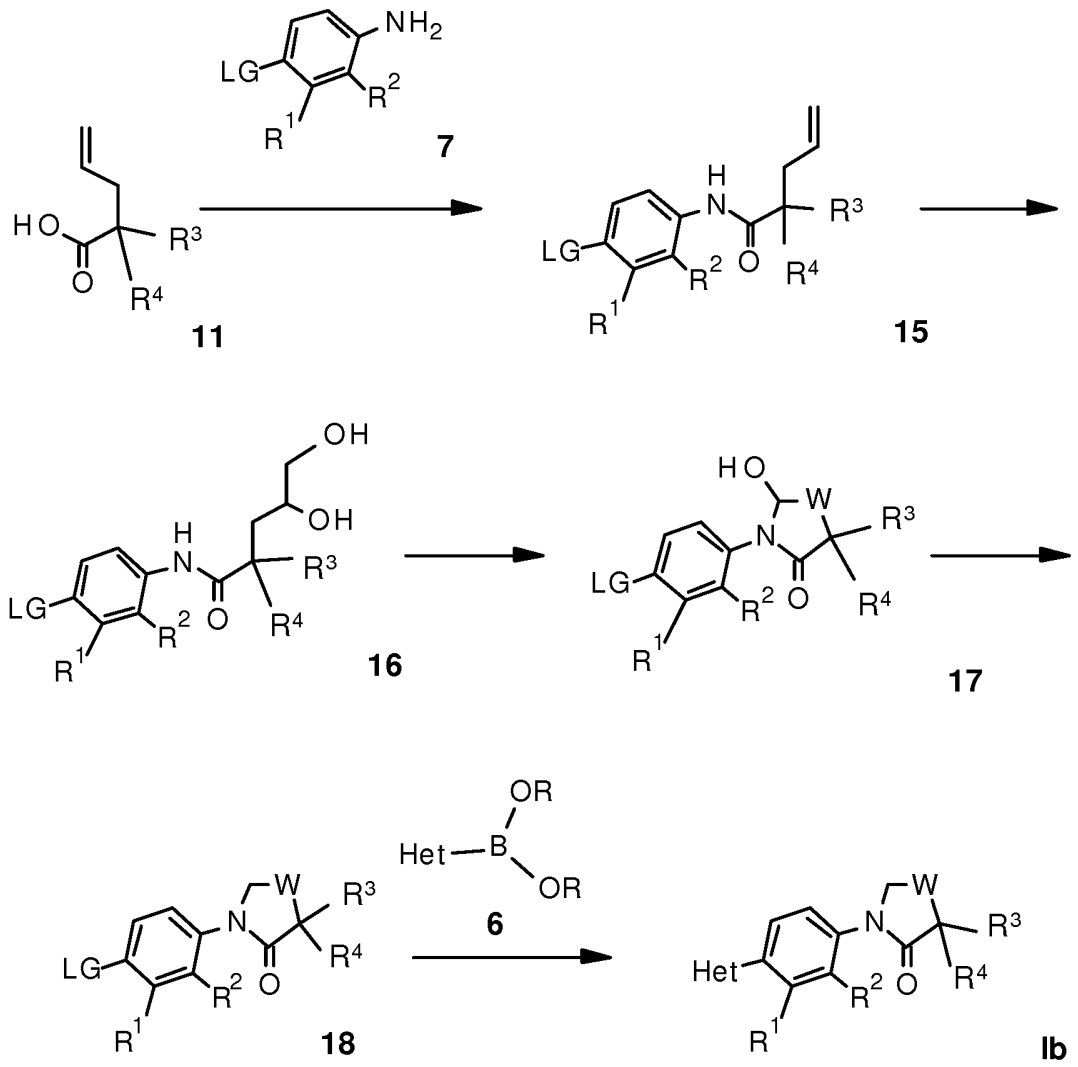
Compounds of formula **3** can be prepared according to Scheme 3: An arylamine **7**, in which LG is a suitable leaving group such as Br, is reacted with an alkoxycarbonylaminoaldehyde **8** and a reducing agent, such as $NaBH(OAc)_3$ / AcOH to give **9** in a process known as reductive amination. Compound **9** can be transformed into **3** by treatment with a suitable base such as KOtBu.

Scheme 4



Compounds of formula **Ib** can be prepared according to scheme 4. An arylacetic acid **10** is treated with a suitable base, such as LiHMDS, and subsequently with allyl iodide to give **11**. Acid **11** is treated with an activating agent, such as PyBOP, and converted with an aromatic amine **1** into **12**. Compound **12** is then oxidized by suitable oxidizing agents, such as NMO, OsO_4, and $NaIO_4$ to give **14**, possibly via a diol intermediate **13**. Compound **14** is then reduced to compound **Ib** with a suitable reducing agent, such as Et_3SiH.

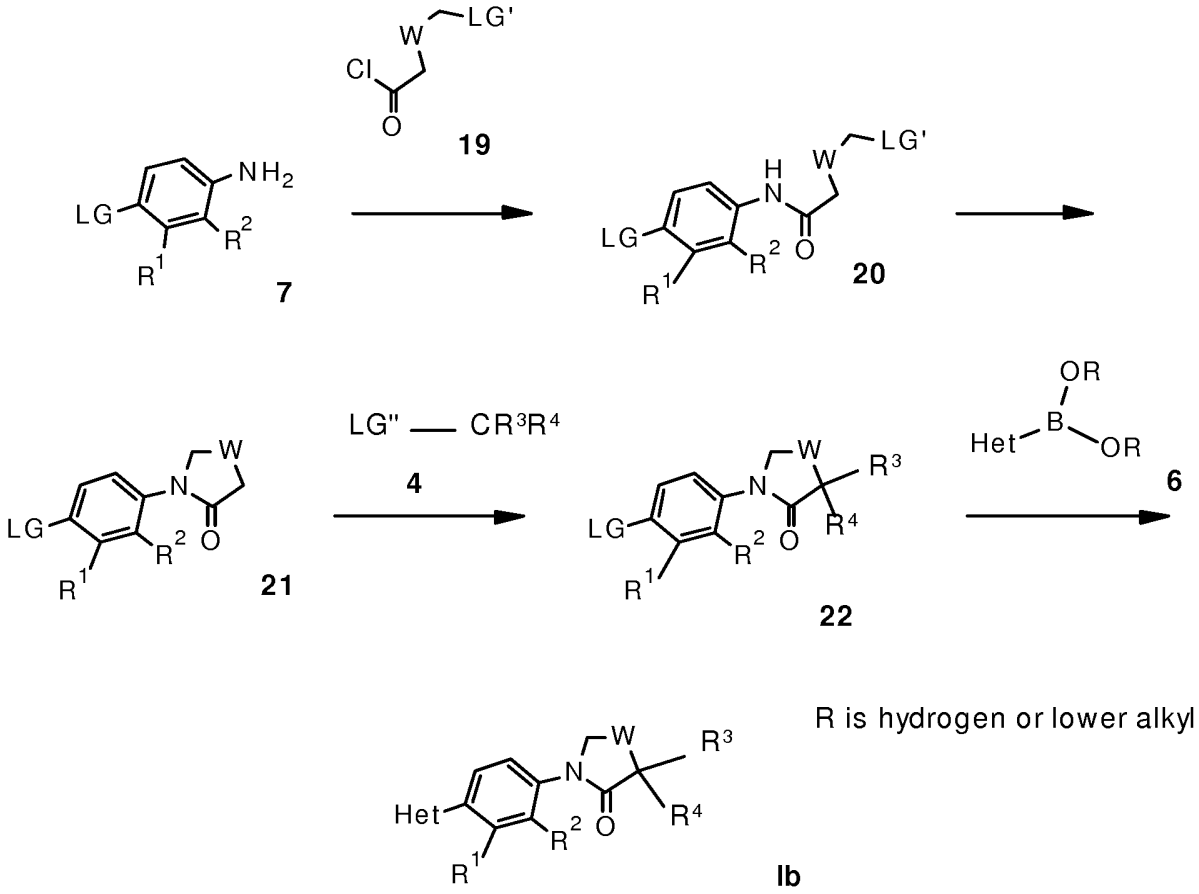
Scheme 5



R is hydrogen or lower alkyl

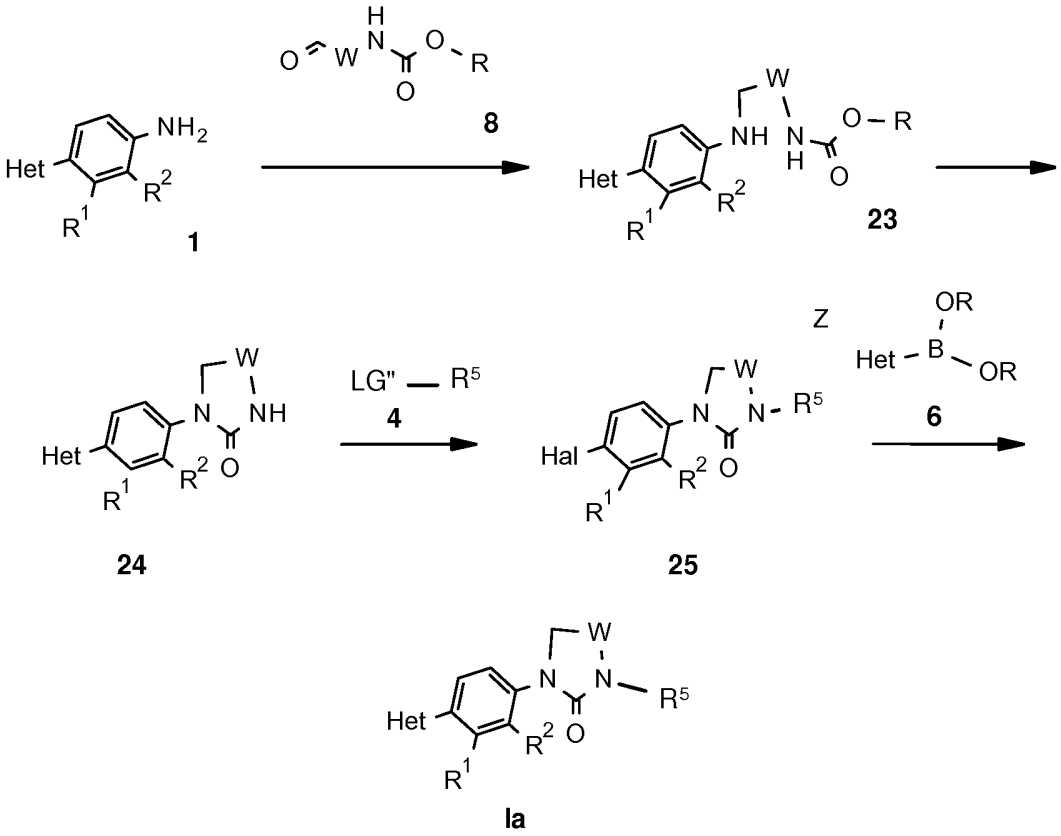
Alternatively, compounds of formula **Ib** can be prepared according to scheme 5. Allylarylacetic acid **11** is treated with an activating agent, such as PyBOP, and converted with an aromatic amine **7**, in which LG is a suitable leaving group, such as Br, into **15**. In analogy to scheme 4, compound **15** is then oxidized by suitable oxidizing agents, such as NMO, OsO_4, and $NaIO_4$ to give **17**, possibly via a diol intermediate **16**. Compound **17** is then reduced to compound **18** with a suitable reducing agent, such as Et_3SiH. Compound **18** is then reacted with a boronic acid, or a boronic acid ester, **6**, in the presence of a suitable catalyst, such as tetrakis(triphenylphosphine)palladium, and a suitable base, such as sodium carbonate, to give compound **Ib**.

Scheme 6

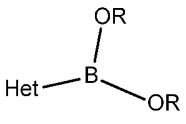


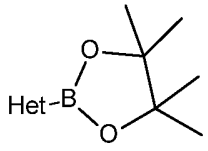
Compounds of formula **Ib** can be prepared according to scheme 6. An arylamine **7**, in which LG is a suitable leaving group such as Br, is reacted with an acid chloride **19**, or a similarly activated acid, in which LG' is a suitable leaving group such as Br, to give **20**. Treatment with a suitable base, such as KOH, furnishes **21**. Treatment with another suitable base, such as a lithium amide, and compound **4**, in which LG'' is a suitable leaving group such as bromine, gives **22**. Compound **22** is then reacted with a boronic acid, or a boronic acid ester, **6**, in the presence of a suitable catalyst, such as tetrakis(triphenylphosphine)palladium, and a suitable base, such as sodium carbonate, to give compound **Ib.**

Scheme 7



Compounds of formula **Ia** can also be prepared according to Scheme 7. An arylamine **1** is reacted with an alkoxycarbonylaminoaldehyde **8** and a reducing agent, such as $NaBH(OAc)_3$ / AcOH to give **23** in a process known as reductive amination. Compound **23** can be transformed into **24** by treatment with a suitable base such as KOtBu. **23** is first reacted with a suitable base, such as sodium hydride, and then with compound **4**, in which LG is a suitable leaving group, such as Br. The resulting compound **25** is then reacted with a boronic acid, or a boronic acid ester, **6**, in the presence of a suitable catalyst, such as tetrakis(triphenylphosphine)palladium, and a suitable base, such as sodium carbonate, to give compound **I-a**.

Structure 6 in the schemes  includes also the following structure:



.

Isolation and purification of the compounds

Isolation and purification of the compounds and intermediates described herein can be effected, if desired, by any suitable separation or purification procedure such as, for example, filtration, extraction, crystallization, column chromatography, thin-layer chromatography, thick-layer chromatography, preparative low or high-pressure liquid chromatography or a combination of these procedures. Specific illustrations of suitable separation and isolation procedures can be had by reference to the preparations and examples herein below. However, other equivalent separation or isolation procedures could, of course, also be used. Racemic mixtures of chiral compounds of formula I can be separated using chiral HPLC.

Salts of compounds of formula I

The compounds of formula I are basic and may be converted to a corresponding acid addition salt. The conversion is accomplished by treatment with at least a stoichiometric amount of an appropriate acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. Typically, the free base is dissolved in an inert organic solvent such as diethyl ether, ethyl acetate, chloroform, ethanol or methanol and the like, and the acid added in a similar solvent. The temperature is maintained between 0 °C and 50 °C. The resulting salt precipitates spontaneously or may be brought out of solution with a less polar solvent.

The acid addition salts of the basic compounds of formula I may be converted to the corresponding free bases by treatment with at least a stoichiometric equivalent of a suitable base such as sodium or potassium hydroxide, potassium carbonate, sodium bicarbonate, ammonia, and the like.

The compounds of formula I and their pharmaceutically usable addition salts possess valuable pharmacological properties. Specifically, it has been found that the compounds of the present invention have an activity as neurogenic agents.
The compounds were investigated in accordance with the test given hereinafter.

Neurogenesis assay

Neural Stem Cell Proliferation Assay

Neurogenic properties of small molecules are determined based on the proliferation of human embryonic stem cell derived neural stem cells (NSCs) which were derived via a dual smad

inhibition as previously described (Chambers, S.M., et al., *Highly efficient neural conversion of human ES and iPS cells by dual inhibition of SMAD signaling,* Nature biotechnology, 2009. **27**(3): p. 275-80.)

Compounds respond is measured by the increase in cells based on ATP levels (Promega:CellTiterGlo®) after an incubation period of 4 days.

NSCs are thawed and expanded over 3 passages. On the 14th day, NSCs are seeded in Polyornithin/ Laminin coated 384 well plates at a cell density of 21'000 cells/cm^2 in a media volume of 38 µl.

4 hours after cell seeding, compound solutions are added at a volume of 2 µl. Stock solutions of the compounds (water, 5% DMSO) are diluted to obtain a dose response (11 points, dilution factor is 2), ranging from 8 µM to 8 nM. Controls are run to consistently determine the neurogenic properties of the cells:

Negative (neutral) control is cell culture Media (final DMSO concentration: 0.25 %).

Positive controls are:

1. cell culture Media + 100 ng/ml FGF2 (final DMSO concentration: 0.1 %)
2. cell culture Media + 20 ng/ml EGF (final DMSO concentration: 0.1 %)
3. cell culture Media + 100 ng/ml Wnt3a (final DMSO concentration: 0.1 %)

After 4 days incubation at 37° C, 5 % CO_2, the amount of ATP per well is quantified. The ATP concentration is proportional to the cell number. ATP is quantified by using the Promega CellTiterGlo® kit. The CellTiterGlo® reagents contain a cell lysis buffer, a thermo stable luciferase (UltraGlo™ recombinant luciferase), magnesium and luciferin. Luciferin reacts with ATP producing oxyluciferin, AMP and light. The luminescence signal is proportional to the ATP content.

The value of negative (neutral) control is determined for each assay plate by taking the average of 16 negative control wells. The neurogenic compound response is calculated for each compound as (compound/Negative Control)*100.

The values of EC_{150} from the dose response curve are determined for each test compound. The EC150 is the compound concentration at which 150 % activity of control (100 %) is reached.

The preferred compounds show a EC_{150} (µM) in the range of < 3.0 µM as shown in Table 1.

Table 1

List of examples and EC_{150} data

Expl. No	Compound name	EC_{150}(uM)
1	3-Ethyl-1-(3-methoxy-4-(oxazol-5-yl)phenyl)-3-phenylpyrrolidin-2-one	3.2257
2	1-Benzyl-3-(4-(pyridin-4-yl)phenyl)imidazolidin-2-one	1.0425
3	1-(3-Methoxy-4-oxazol-5-yl-phenyl)-3-(3-methoxyphenyl)pyrrolidin-2-one	0.0814
4	3-(2-Chlorophenyl)-1-(3-methoxy-4-oxazol-5-yl-phenyl)pyrrolidin-2-one	0.6783
5	1-Benzyl-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]hexahydropyrimidin-2-one	1.3254
6	1-[(2-Chlorophenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]hexahydropyrimidin-2-one	1.9918
7	1-[(3-Methoxyphenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]hexahydropyrimidin-2-one	0.1144
8	1-(3-Methoxy-4-oxazol-5-yl-phenyl)-3-phenyl-pyrrolidin-2-one	0.4712
9	1-Benzyl-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one	0.1612
10	1-[(2-Chlorophenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one	0.2695
11	1-[(3-Methoxyphenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one	0.0239
12	1-[3-Methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-phenyl-pyrrolidin-2-one	0.0414
13	3-Phenyl-1-[4-(1H-pyrazol-4-yl)phenyl]pyrrolidin-2-one	0.2048
14	3-(3-Methoxyphenyl)-1-[4-(1H-pyrazol-4-yl)phenyl]pyrrolidin-2-one	0.0405
15	3-(4-Chlorophenyl)-1-[4-(1H-pyrazol-4-yl)phenyl]pyrrolidin-2-one	0.384
16	3-(4-Fluorophenyl)-1-[4-(1H-pyrazol-4-yl)phenyl]pyrrolidin-2-one	0.0417
17	3-(3-Chlorophenyl)-1-[4-(1H-pyrazol-4-yl)phenyl]pyrrolidin-2-one	0.2304
18	1-[(3-chlorophenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one	0.3946

19	1-[(3-Fluorophenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one	0.047
20	1-[3-Methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-[[3-(trifluoromethyl)phenyl]methyl]imidazolidin-2-one	0.0086
21	1-[3-Methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-[[3-(trifluoromethoxy)phenyl]methyl]imidazolidin-2-one	0.0092
22	1-[(3-Ethoxyphenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one	0.0739
23	3-Benzyl-1-(3-methoxy-4-(1H-pyrazol-4-yl)phenyl)pyrrolidin-2-one	0.6122
24	1-(3-Methoxy-4-(1H-pyrazol-4-yl)phenyl)-3-(3-methoxyphenyl)pyrrolidin-2-one	0.0299
25	3-(3-Chlorophenyl)-1-(3-methoxy-4-(1H-pyrazol-4-yl)phenyl)pyrrolidin-2-one	0.0659
26	3-(3-Fluorophenyl)-1-(3-methoxy-4-(1H-pyrazol-4-yl)phenyl)pyrrolidin-2-one	0.0776
27	1-[(3-Methoxyphenyl)methyl]-3-[4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one	0.2944
28	1-[(3-Methoxyphenyl)methyl]-3-[3-methyl-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one	1.2174
29	1-[3-Chloro-4-(1H-pyrazol-4-yl)phenyl]-3-[(3-methoxyphenyl)methyl]imidazolidin-2-one	0.3664
30	1-[2-Fluoro-4-(1H-pyrazol-4-yl)phenyl]-3-[(3-methoxyphenyl)methyl]imidazolidin-2-one	0.0416
31	1-[3-Fluoro-4-(1H-pyrazol-4-yl)phenyl]-3-[(3-methoxyphenyl)methyl]imidazolidin-2-one	0.0157
32	1-[3-Ethoxy-4-(1H-pyrazol-4-yl)phenyl]-3-[(3-methoxyphenyl)methyl]imidazolidin-2-one	0.8349
33	1-[(2-Fluorophenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one	0.2246
34	1-[3-Methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-(o-tolylmethyl)imidazolidin-2-one	0.2004
35	1-[3-Methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-(m-tolylmethyl)imidazolidin-2-one	2.6464

36	3-[(3-Chlorophenyl)methyl]-1-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]pyrrolidin-2-one	1.6485
37	3-[(2-Chlorophenyl)methyl]-1-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]pyrrolidin-2-one	1.1254
38	3-(3-Chlorophenyl)-1-[3-methoxy-4-(1,3-oxazol-5-yl)phenyl]pyrrolidin-2-one	1.3515
39	1-[(3-Methoxyphenyl)methyl]-3-[2-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one	0.393
40	3-[(3-Methoxyphenyl)methyl]-1-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]pyrrolidin-2-one	0.334
41	1-[3-Methoxy-4-(1,3-oxazol-5-yl)phenyl]-3-(2-methoxyphenyl)pyrrolidin-2-one	2.9106
42	1-[(2-Methoxyphenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one	0.3085
43	1-[3-Methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-(2-phenylethyl)imidazolidin-2-one	0.3093
44	1-[2-(2-Methoxyphenyl)ethyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one	1.9784
45	1-[2-(2-Chlorophenyl)ethyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one	0.1358
46	1-[2-Chloro-4-(1H-pyrazol-4-yl)phenyl]-3-[(3-methoxyphenyl)methyl]imidazolidin-2-one	1.8344
47	1-[(4-Fluorophenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one	0.7685
48	1-[3-Methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-(3-pyridylmethyl)imidazolidin-2-one	0.1195
49	1-[2-(3-Chlorophenyl)ethyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one	1.7318
50	1-[2-(4-Chlorophenyl)ethyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one	2.0118
51	1-[3-Methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-(1-phenylpropyl)imidazolidin-2-one	0.5942

52	3-(3-Methoxyphenyl)-1-[4-(1,3-oxazol-5-yl)phenyl]pyrrolidin-2-one	0.5169
53	1-[4-(1,3-Oxazol-5-yl)phenyl]-3-phenylpyrrolidin-2-one	2.2077
54	1-[3-Methoxy-4-(4-pyridyl)phenyl]-3-[[2-(trifluoromethyl)phenyl]methyl]imidazolidin-2-one	0.0351
55	1-[3-Methoxy-4-(4-pyridyl)phenyl]-3-(4-pyridylmethyl)imidazolidin-2-one	0.3765
56	1-[3-Methoxy-4-(1,3-oxazol-5-yl)phenyl]-3-[3-(trifluoromethyl)phenyl]pyrrolidin-2-one	1.8592
57	3-(2-Fluorophenyl)-1-[4-(1,3-oxazol-5-yl)phenyl]pyrrolidin-2-one	0.525
58	3-(2-Fluorophenyl)-1-[3-methoxy-4-(1,3-oxazol-5-yl)phenyl]pyrrolidin-2-one	0.2297
59	1-[(3-Methoxyphenyl)methyl]-3-[4-(1,3-oxazol-5-yl)phenyl]imidazolidin-2-one	0.1225
60	3-(3-Fluorophenyl)-1-[4-(1,3-oxazol-5-yl)phenyl]pyrrolidin-2-one	0.6045
61	3-(3-Fluorophenyl)-1-[3-methoxy-4-(1,3-oxazol-5-yl)phenyl]pyrrolidin-2-one	0.2623
62	1-[3-Methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-(4-pyridylmethyl)imidazolidin-2-one	0.042
63	1-[3-Methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-(2-pyridylmethyl)imidazolidin-2-one	0.2551
64	1-[3-Methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-(2-phenylpropyl)imidazolidin-2-one	0.3873
65	1-[3-Methoxy-4-(4-pyridyl)phenyl]-3-(m-tolylmethyl)imidazolidin-2-one	0.0298
66	1-[3-Methoxy-4-(4-pyridyl)phenyl]-3-(3-pyridylmethyl)imidazolidin-2-one	0.4002
67	1-[3-Methoxy-4-(1,3-oxazol-5-yl)phenyl]-3-[(2-methoxyphenyl)methyl]imidazolidin-2-one	0.7015
68	1-[3-Methoxy-4-(1,3-oxazol-5-yl)phenyl]-3-[(3-methoxyphenyl)methyl]imidazolidin-2-one	0.3158
69	1-[(2-Chlorophenyl)methyl]-3-[3-methoxy-4-(1,3-oxazol-5-yl)phenyl]imidazolidin-2-one	2.2373

70	3-(3-Methoxyphenyl)-1-(3-methoxy-4-pyridin-4-ylphenyl)pyrrolidin-2-one	0.0613
71	3-(3-Methoxyphenyl)-1-(4-pyridin-4-ylphenyl)pyrrolidin-2-one	0.0155
72	1-[(3-Fluorophenyl)methyl]-3-[4-(1,3-oxazol-5-yl)phenyl]imidazolidin-2-one	1.0717
73	1-[(2-Fluorophenyl)methyl]-3-[4-(1,3-oxazol-5-yl)phenyl]imidazolidin-2-one	1.492
74	1-[(2-Fluorophenyl)methyl]-3-[3-methoxy-4-(1,3-oxazol-5-yl)phenyl]imidazolidin-2-one	2.6998
75	1-[(3-Fluorophenyl)methyl]-3-[3-methoxy-4-(1,3-oxazol-5-yl)phenyl]imidazolidin-2-one	0.5973

The compounds of formula I and the pharmaceutically acceptable salts of the compounds of formula I can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The compounds of formula I can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acids or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Depending on the nature of the active substance no carriers are however usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, glycerol, vegetable oil and the like. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

The pharmaceutical preparations can, moreover, contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

Medicaments containing a compound of formula I or a pharmaceutically acceptable salt thereof and a therapeutically inert carrier are also an object of the present invention, as is

a process for their production, which comprises bringing one or more compounds of formula I and/or pharmaceutically acceptable acid addition salts and, if desired, one or more other therapeutically valuable substances into a galenical administration form together with one or more therapeutically inert carriers.

The most preferred indications in accordance with the present invention are those which include disorders of the central nervous system, for example the treatment or prevention of depression, psychosis, Parkinson's disease, anxiety, attention deficit hyperactivity disorder (ADHD) and diabetes.

The dosage can vary within wide limits and will, of course, have to be adjusted to the individual requirements in each particular case. In the case of oral administration the dosage for adults can vary from about 0.01 mg to about 1000 mg per day of a compound of general formula I or of the corresponding amount of a pharmaceutically acceptable salt thereof. The daily dosage may be administered as single dose or in divided doses and, in addition, the upper limit can also be exceeded when this is found to be indicated.

Tablet Formulation (Wet Granulation)

Item	Ingredients	mg/tablet			
		5 mg	25 mg	100 mg	500 mg
1.	Compound of formula I	5	25	100	500
2.	Lactose Anhydrous DTG	125	105	30	150
3.	Sta-Rx 1500	6	6	6	30
4.	Microcrystalline Cellulose	30	30	30	150
5.	Magnesium Stearate	1	1	1	1
	Total	167	167	167	831

Manufacturing Procedure

1. Mix items 1, 2, 3 and 4 and granulate with purified water.
2. Dry the granules at 50°C.
3. Pass the granules through suitable milling equipment.
4. Add item 5 and mix for three minutes; compress on a suitable press.

Capsule Formulation

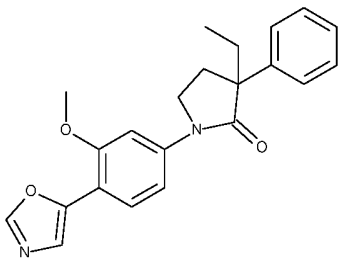
Item	Ingredients	mg/capsule			
		5 mg	25 mg	100 mg	500 mg
1.	Compound of formula I	5	25	100	500
2.	Hydrous Lactose	159	123	148	---
3.	Corn Starch	25	35	40	70
4.	Talc	10	15	10	25
5.	Magnesium Stearate	1	2	2	5
	Total	200	200	300	600

Manufacturing Procedure

1. Mix items 1, 2 and 3 in a suitable mixer for 30 minutes.
2. Add items 4 and 5 and mix for 3 minutes.
3. Fill into a suitable capsule.

Example 1

3-Ethyl-1-(3-methoxy-4-(oxazol-5-yl)phenyl)-3-phenylpyrrolidin-2-one

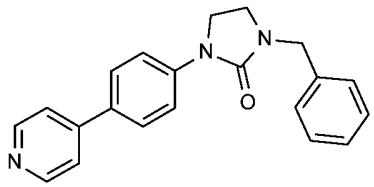


In a 10 ml round-bottomed flask, 3-methoxy-4-(oxazol-5-yl)aniline (commercially available, CAS: 198821-79-3; 200 mg, 1.05 mmol) was combined with dioxane (4 ml) to give a light brown solution. Trimethylaluminum (2M in heptane, 1.05 ml, 2.1 mmol) was added. The reaction mixture was heated to 50 °C and stirred for 30 min. 3-Ethyl-3-phenyldihydrofuran-2(3H)-one (commercially available, CAS: 4064-16-8; 400 mg, 2.1 mmol) was added. The reaction mixture was heated to 100 °C and stirred for 2 d. The reaction mixture was poured into water / Na_2CO_3 and extracted with EtOAc (2 x 25 ml). The organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by flash

chromatography (silica gel, 20 g , 0 % to 50 % EtOAc in heptane) to yield the title compound as a light yellow waxy solid (221 mg, 58.0 %). MS (m/e) = 363.17 $[M+H]^+$.

Example 2

1-Benzyl-3-(4-(pyridin-4-yl)phenyl)imidazolidin-2-one



Step 1: 1-Benzyl-3-(4-bromophenyl)imidazolidin-2-one

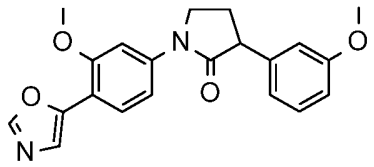
In a 25 ml round-bottomed flask, 1-(4-bromophenyl)imidazolidin-2-one (commercially available, CAS: 530081-14-2; 480 mg, 1.99 mmol) was combined with DMF (10 ml) to give a light yellow solution. The reaction mixture was cooled to 0 °C. Sodium hydride (159 mg, 3.98 mmol) was added. The reaction mixture was stirred 20 min at 0 °C. The reaction mixture was allowed to warm to rt. (Bromomethyl)benzene (521 mg, 362 µl, 2.99 mmol) was added. The reaction mixture was stirred over night at rt. The reaction mixture was poured into water (40 ml) and extracted with EtOAc (3 x 40 ml). The organic layers were combined, washed with satd. NaCl (1 x 40 ml), dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel, 20 g, 0 % to 50 % EtOAc in heptane) to yield the title compound as a white solid (629 mg, 95.4 %). MS (m/e) = 333.4 $[M+H]^+$.

Step 2: 1-Benzyl-3-(4-(pyridin-4-yl)phenyl)imidazolidin-2-one

In a 50 ml round-bottomed flask, a mixture of DMF/water (7:2) (22.5 ml) was deoxygenated with argon. 1-Benzyl-3-(4-bromophenyl)imidazolidin-2-one (200 mg, 604 µmol), pyridin-4-ylboronic acid (148 mg, 1.21 mmol), sodium carbonate (224 mg, 2.11 mmol) and tetrakis(triphenylphosphine)palladium (907 µg, 0.785 µmol) were added. The reaction mixture was heated to reflux and stirred over night. The reaction mixture was poured into water (50 ml) and extracted with EtOAc (3 x 50 ml). The organic layers were dried over Na_2SO_4 and concentrated in vacuo. The yellow solid residue was combined with MeOH (2 ml) and treated 5 min in the ultrasonic bath. The suspension was filtered. The white solid was dried in vacuo to yield the title compound as an off-white solid (89 mg, 44.6 %). MS (m/e) = 330.16 $[M+H]^+$.

Example 3

1-(3-Methoxy-4-oxazol-5-yl-phenyl)-3-(3-methoxyphenyl)pyrrolidin-2-one



Step 1: 2-(3-Methoxyphenyl)pent-4-enoic acid

To a solution of 3-methoxyphenyl acetic acid (30.08 mmol) in THF (150 ml) at -78 °C was added LiHMDS (1M solution in THF; 66.19ml, 66.19mmol), and the reaction mixture was stirred at -78 °C for 0.5 h. Allyl iodide (2.75 ml, 30.08 mmol) was added to the reaction mixture at -78 °C, and the mixture was slowly allowed to warm to 25 °C over a period of 3 h, and then continued to stir at 25 °C for 12 h. The reaction mixture was quenched with saturated ammonium chloride solution, acidified using 1N aqueous HCl solution, and extracted with EtOAc (2 x 130 ml). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude material was purified by column chromatography over silica gel (10-20 %EtOAc/hexane) to get 2-(3-methoxyphenyl) pent-4-enoic acid (5.3 g, 85.48 %) as light yellow oil.

Step 2: N-(3-Methoxy-4-oxazol-5-yl-phenyl)-2-(3-methoxyphenyl)pent-4-enamide

To a solution of 2-(3-methoxyphenyl)pent-4-enoic acid (1.5 g, 7.28 mmol) in DCM (80 ml) were added PyBOP (5.68 g, 10.92 mmol) and DIPEA (3.71 ml, 21.84 mmol) under argon atmosphere and the reaction mixture was stirred at 25 °C for 0.5 h. 3-Methoxy-4-oxazol-5-yl-phenylamine (1.66 g, 8.73 mmol) was added to the reaction mixture, and the resulting mixture was allowed to stir at 25 °C for 16 h. The mixture was washed with water, the organic layer was separated and the aqueous layer was extracted with DCM (60 ml). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated off in vacuo. Resulting crude mass was purified by column chromatography over normal silica gel (30-40 % EtOAc/hexane) to get N-[3-methoxy-4-(1, 3-oxazol-5-yl) phenyl]-2-(3-methoxyphenyl) pent-4-enamide (2.3 g, 83.47 %) as a white solid. LC-MS: 379.4 $(M+H)^+$.

Step 3: 4,5-Dihydroxy-N-(3-methoxy-4-oxazol-5-yl-phenyl)-2-(3-methoxyphenyl)pentanamide

To a solution of N-[3-methoxy-4-(1,3-oxazol-5-yl)phenyl]-2-(3-methoxyphenyl)pent-4-enamide (2.3 g, 6.08 mmol) and NMO (1.42 g, 12.16 mmol) in acetone (100 ml) and water (16.6 ml) at 25 °C was added OsO_4 (4 % in water; 0.15 ml), and the resulting mixture was

stirred at 25 °C for 16 h. Saturated aqueous sodium thiosulfate solution (60 ml) was added to the reaction mixture and extracted with EtOAc (2 x 150 ml). The combined organic layer were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The resulting crude mass was purified by column chromatography over normal silica gel (70 – 80 % EtOAc/hexane) to get 4, 5-dihydroxy-N-[3-methoxy-4-(1, 3-oxazol-5-yl) phenyl]-2-(3-methoxyphenyl) pentanamide (1.89 g, 75.31 %) as a yellow solid. LC-MS: 413.1 $(M+H)^+$.

Step 4: 5-Hydroxy-1-(3-methoxy-4-oxazol-5-yl-phenyl)-3-(3-methoxyphenyl)pyrrolidin-2-one

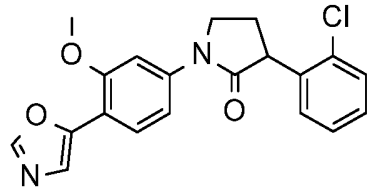
To a solution of 4, 5-dihydroxy-N-[3-methoxy-4-(1, 3-oxazol-5-yl) phenyl]-2-(3-methoxyphenyl) pentanamide (1.89 g, 4.58 mmol) in THF (90 ml) was added a solution of $NaIO_4$ (1.95 g, 9.17 mmol) in water (42 ml), and the resulting mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched using saturated aqueous $Na_2S_2O_3$ solution, and extracted with EtOAc (2 x 100 ml). The combined organic layers were washed with water, dried over anhydrous Na_2SO_4, filtered, and evaporated off in vacuo to get 5-hydroxy-1-[3-methoxy-4-(1, 3-oxazol-5-yl) phenyl]-3-(3-methoxyphenyl) pyrrolidin-2-one (1.63 g) as white solid that was used in the next step without any further purification. LC-MS: 381.2 $(M+H)^+$.

Step 5: 1-(3-Methoxy-4-oxazol-5-yl-phenyl)-3-phenyl-pyrrolidin-2-one

To a solution of 5-hydroxy-1-[3-methoxy-4-(1, 3-oxazol-5-yl) phenyl]-3-(3-methoxyphenyl) pyrrolidin-2-one (1.63 g, 4.28 mmol) in DCM (150 ml) at 0 °C were added Et_3SiH (8ml) and TFA (8 ml), and the reaction mixture was stirred at 25 °C for 2 h. Volatilities were removed in vacuo. The resultant residue was diluted with DCM (120 ml) and washed with saturated aqueous $NaHCO_3$ solution. The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated off under reduced pressure. The resulting crude mass was purified by column chromatography over normal silica gel (50 %EtOAc/hexane) to get 1-[3-methoxy-4-(1, 3-oxazol-5-yl) phenyl]-3-(3-methoxyphenyl) pyrrolidin-2-one (950 mg, 56.92 % from Step 3) as off white solid. LC-MS: 365.3 $(M+H)^+$.

Example 4

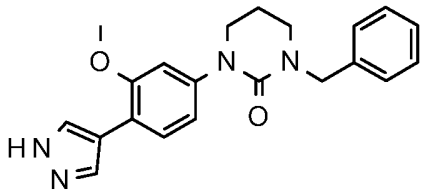
3-(2-Chlorophenyl)-1-(3-methoxy-4-oxazol-5-yl-phenyl)pyrrolidin-2-one



The title compound was prepared in analogy to Example 3, using 2-chlorobenzeneacetic acid in Step 1. LC-MS: 369.0 $(M+H)^+$.

Example 5

1-Benzyl-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]hexahydropyrimidin-2-one



Step 1: Benzyl N-{3-[(4-bromo-3-methoxyphenyl) amino] propyl} carbamate

To a solution of 4-bromo-3-methoxy-phenylamine (2 g, 9.90 mmol) in DCM (100 ml) at 0 °C were added 3-[(benzyloxycarbonyl) amino] propionaldehyde (2.46 g, 11.88 mmol) and AcOH (0.57 ml, 9.90 mmol), and the resulting reaction mixture was stirred at 0 °C for 0.5 h. Then $NaBH(OAc)_3$ (3.14 g, 14.85 mmol) was added to the reaction mixture that was again stirred at 25 °C for 12 h. The mixture was diluted with water (40 ml), the organic layer was separated and the aqueous layer was re-extracted with DCM (2 x 40 ml). The combined organic layers were evaporated off in vacuo. The resulting crude material was purified by column chromatography over normal silica gel (25 – 30 %EtOAc/hexane) to get benzyl N-{3-[(4-bromo-3-methoxyphenyl) amino] propyl} carbamate (1.4 g, 36.21 %) as a yellow sticky solid LC-MS: 395.2 $(M+H)^+$.

Step 2: 1-(4-Bromo-3-methoxyphenyl)-1, 3-diazinan-2-one

To a solution of KOtBu (799 mg, 7.12 mmol) in THF (30 ml) at 0 °C was added a solution of benzyl N-{3-[(4-bromo-3-methoxyphenyl)amino]propyl}carbamate (1.4 g, 3.56 mmol) in THF (30 ml), and the resulting mixture was stirred at 25 °C for 12 h. The mixture was quenched with saturated aqueous ammonium chloride solution and extracted with EtOAc (2 x 80 ml).The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated off in vacuo. The resulting residue was triturated using 30 % EtOAc/hexane to get

1-(4-bromo-3-methoxyphenyl)-1, 3-diazinan-2-one (667 mg, 65.67 %) as a yellow solid. LC-MS: 284.8 $(M+H)^+$.

Step 3: 1-Benzyl-3-(4-bromo-3-methoxyphenyl)-1, 3-diazinan-2-one

To a suspension of NaH (60 % in mineral oil) (31.57 mg, 0.78 mmol) in DMF (2 ml) at 0 °C was added a solution of 1-(4-bromo-3-methoxyphenyl)-1, 3-diazinan-2-one (150 mg, 0.52 mmol) in DMF (5 ml), and the resulting mixture was stirred at 0 °C for 0.5 h. Then benzyl bromide (0.094 ml, 0.78 mmol) was added to the mixture that was allowed to stir at 25 °C for another 12 h. The mixture was diluted with water (15 ml) and extracted with EtOAc (2 x 40 ml). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated off in vacuo to get 1-benzyl-3-(4-bromo-3-methoxyphenyl)-1,3-diazinan-2-one (244 mg, crude) as a light yellow sticky solid that was used in the next step without any further purification.

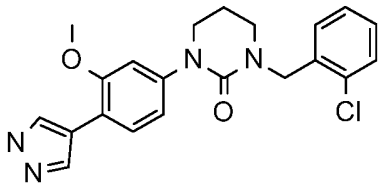
LC-MS: 374.8 $(M+H)^+$.

Step 4: 1-Benzyl-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]hexahydropyrimidin-2-one

To a solution of 1-benzyl-3-(4-bromo-3-methoxyphenyl)-1,3-diazinan-2-one (240 mg, 0.64 mmol) in dioxane (16 ml) and water (4 ml) was added K_2CO_3 (265 mg, 1.92 mmol). The mixture was purged with argon for 10 min. To this mixture were then added [1-(tert-butoxycarbonyl)-1H-pyrazol-4-yl]boronic acid pinacol ester (282 mg, 0.96 mmol) and $Pd(dppf)_2Cl_2$.DCM (20.90 mg, 0.02 mmol), purged again with argon for another 10 min, and then allowed to heat at 80 °C for 16 h. The mixture was diluted with water, and extracted with EtOAc (2 x 30 ml). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated off in vacuo. The resulting crude material was purified by column chromatography over normal silica gel (55 – 65 % EtOAc/hexane) to get 1-benzyl-3-[3-methoxy-4-(1H-pyrazol-4-yl) phenyl]-1, 3-diazinan-2-one (44 mg, 23.09 % from 4) as an off-white solid. LC-MS: 363.0 $(M+H)^+$.

Example 6

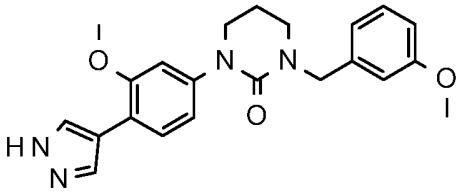
1-[(2-Chlorophenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]hexahydropyrimidin-2-one



The title compound was prepared in analogy to Example 5, using 1-(bromomethyl)-2-chloro-benzene in Step 3. LC-MS: 397.0 $(M+H)^+$.

Example 7

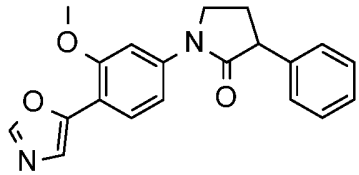
1-[(3-Methoxyphenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]hexahydropyrimidin-2-one



The title compound was prepared in analogy to Example 5, using 1-(bromomethyl)-3-methoxy-benzene in Step 3. LC-MS: 393.0 $(M+H)^+$.

Example 8

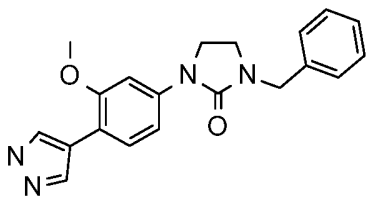
1-(3-Methoxy-4-oxazol-5-yl-phenyl)-3-phenyl-pyrrolidin-2-one



The title compound was prepared in analogy to Example 3, using phenyl acetic acid in Step 1. LC-MS: 335.0 $(M+H)^+$.

Example 9

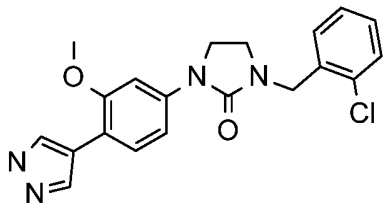
1-Benzyl-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one



The title compound was prepared in analogy to Example 5, using tert-butyl N-(2-oxoethyl)carbamate in Step 1. LC-MS: 349.0 $(M+H)^+$.

Example 10

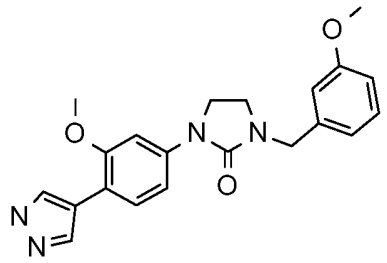
1-[(2-Chlorophenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one



The title compound was prepared in analogy to Example 5, using tert-butyl N-(2-oxoethyl)carbamate in Step 1 and 1-(bromomethyl)-2-chloro-benzene in Step 3. LC-MS: 383.0 $(M+H)^+$.

Example 11

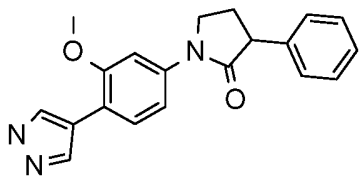
1-[(3-Methoxyphenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one



The title compound was prepared in analogy to Example 5, using tert-butyl N-(2-oxoethyl)carbamate in Step 1 and 1-(bromomethyl)-3-methoxy-benzene in Step 3. LC-MS: 379.0 $(M+H)^+$.

Example 12

1-[3-Methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-phenyl-pyrrolidin-2-one



Step 1: 2-Phenylpent-4-enoic acid

To a solution of phenyl acetic acid (2 g, 14.7 mmol) in THF (60 ml) at -78 °C was added LiHMDS (1M solution in THF) (32.35 ml, 32.35 mmol), and the reaction mixture was stirred at -78 °C for 0.5 h. Allyl iodide (1.34 ml, 14.7 mmol) was added to the reaction mixture at -78 °C, and the mixture was slowly allowed to warm to 25 °C over a period of 3 h. It was

quenched with saturated aqueous ammonium chloride solution, acidified using 1N aqueous HCl solution and extracted with EtOAc (2 x 80 ml). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude material was purified by column chromatography over normal silica gel (10 – 20 % EtOAc/hexane) to get 2-phenylpent-4-enoic acid (2.26 g, 87.21 %) as light yellow oil. LC-MS: 175.2 ($M-H^+$).

Step 2: N-(4-Bromo-3-methoxyphenyl)-2-phenylpent-4-enamide

To a solution of 2-phenylpent-4-enoic acid (1.5 g, 8.52 mmol) in DCM (30 ml) at 0 °C was added oxalyl chloride (1.10 ml, 12.78 mmol), and the mixture was stirred at 25 °C for 3 h. Volatilities were removed in vacuo. Resulting acid chloride was dissolved in DCM (10 ml) and added to a solution of 4-bromo-3-methoxyaniline (1.71 g, 8.50 mmol) and Et_3N (2.37 ml, 8.50 mmol) in DCM (20 ml) at 0 °C. Reaction mixture was stirred at 25 °C for 16 h. Solvent was evaporated off in vacuo, and resulting crude material was purified by column chromatography over normal silica gel (10 – 15 % EtOAc/hexane) to get N-(4-bromo-3-methoxyphenyl)-2-phenylpent-4-enamide (1.9 g, 62.01 %) as yellow sticky solid. LC-MS: 359.8 ($M+H^+$).

Step 3: N-(4-Bromo-3-methoxyphenyl)-4, 5-dihydroxy-2-phenylpentanamide

To a solution of N-(4-bromo-3-methoxyphenyl)-2-phenylpent-4-enamide (1 g, 2.77 mmol) and NMO (976 mg, 8.33 mmol) in acetone (35 ml) and water (4.5 ml) at 25 °C was added OsO_4 (4 % in water) (0.144 ml), and the mixture was stirred at 25 °C for 12 h. It was quenched with 1N aqueous sodium thiosulfate solution (20 ml), and extracted with EtOAc (2 x 80 ml). Combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Resulting crude material was purified by column chromatography over normal silica gel (70 % EtOAc/hexane) to get N-(4-bromo-3-methoxyphenyl)-4,5-dihydroxy-2-phenylpentanamide (538 mg, 49.12 %) as white solid. LC-MS: 394.2 ($M+H^+$).

Step 4: 1-(4-Bromo-3-methoxyphenyl)-5-hydroxy-3-phenylpyrrolidin-2-one

To a solution of N-(4-bromo-3-methoxyphenyl)-4, 5-dihydroxy-2-phenylpentanamide (535 mg, 1.35 mmol) in THF (25 ml) was added a solution of $NaIO_4$ (578 mg, 2.71 mmol) in water (12 ml), and the resulting mixture was stirred at 25 °C for 2 h. It was quenched with saturated aqueous Na_2S2O_4 solution and extracted with EtOAc (2 x 40 ml). Combined organic layers were washed with water, dried over anhydrous Na_2SO_4, filtered, and evaporated off in vacuo

to get 1-(4-bromo-3-methoxyphenyl)-5-hydroxy-3-phenylpyrrolidin-2-one (479 mg, 97.39 %) as off-white solid that was used in the next step with out any further purification. LC-MS: 362.0 ($M+H^+$).

Step 5: 1-(4-Bromo-3-methoxyphenyl)-3-phenylpyrrolidin-2-one

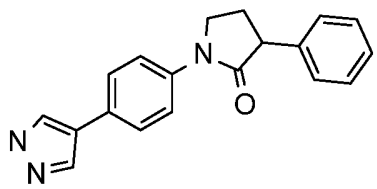
To a solution of 1-(4-bromo-3-methoxyphenyl)-5-hydroxy-3-phenylpyrrolidin-2-one (475 mg, 1.31 mmol) in DCM (15 ml) at 0 °C were added Et_3SiH (2.2 ml) and TFA (2.2 ml), and the resulting mixture was stirred at 25 °C for 2 h. Volatilities were removed in vacuo. The obtained residue was diluted with DCM (50 ml) and washed with saturated aqueous $NaHCO_3$ solution. Organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated off in vacuo. Resulting crude mass was purified by column chromatography over normal silica gel (20 – 25 % EtOAc/hexane) to get 1-(4-bromo-3-methoxyphenyl)-3-phenylpyrrolidin-2-one (345 mg, 75.94 %) as off white solid. LC-MS: 345.8 ($M+H^+$).

Step 6: 1-[3-Methoxy-4-(1H-pyrazol-4-yl) phenyl]-3-phenylpyrrolidin-2-one

To a solution of 1-(4-bromo-3-methoxyphenyl)-3-phenylpyrrolidin-2-one (342 mg, 0.98 mmol) in dioxane (10 ml) and water (4 ml) was added K_2CO_3 (410 mg, 1.48 mmol). The mixture was purged with argon for 10min. Then [1-(tert-butoxycarbonyl)-1H-pyrazol-4-yl]boronic acid pinacol ester (436 mg, 1.48 mmol) and $Pd(dppf)_2Cl_2$*DCM (32.28 mg, 0.04 mmol) were added to the reaction mixture, and purged again with argon for another 10min. Reaction mixture was heated at 80 °C for 16 h. The mixture was diluted with water, and extracted with EtOAc (2 x 40 ml). Combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated off in vacuo. Resulting crude mass was purified by column chromatography over normal silica gel (55 – 65 % EtOAc/hexane) to get 1-[3-methoxy-4-(1H-pyrazol-4-yl) phenyl]-3-phenylpyrrolidin-2-one (80 mg, 24.28 %) as off-white solid. LC-MS: 334.0 ($M+H^+$).

Example 13

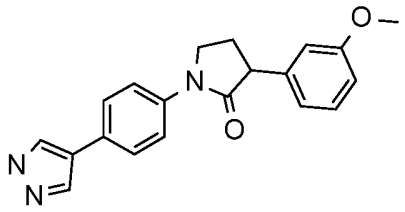
3-Phenyl-1-[4-(1H-pyrazol-4-yl)phenyl]pyrrolidin-2-one



The title compound was prepared in analogy to Example 12, using 4-bromoaniline in Step 2. LC-MS: 304.0 $(M+H)^+$.

Example 14

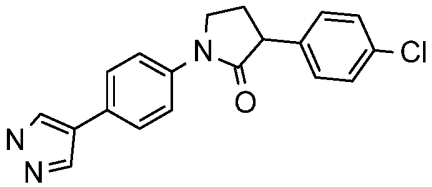
3-(3-Methoxyphenyl)-1-[4-(1H-pyrazol-4-yl)phenyl]pyrrolidin-2-one



The title compound was prepared in analogy to Example 12, using 3-methylphenyl acetic acid in step 1, and 4-bromoaniline in Step 2. LC-MS: 334.2 $(M+H)^+$.

Example 15

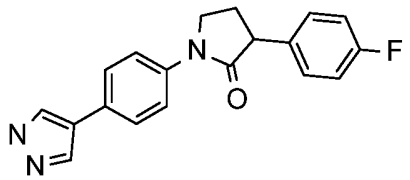
3-(4-Chlorophenyl)-1-[4-(1H-pyrazol-4-yl)phenyl]pyrrolidin-2-one



The title compound was prepared in analogy to Example 12, using 4-chlorophenyl acetic acid in step 1, and 4-bromoaniline in Step 2. LC-MS: 338.2 $(M+H)^+$.

Example 16

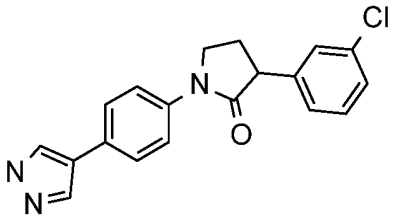
3-(4-Fluorophenyl)-1-[4-(1H-pyrazol-4-yl)phenyl]pyrrolidin-2-one



The title compound was prepared in analogy to Example 12, using 4-fluorophenyl acetic acid in step 1, and 4-bromoaniline in Step 2. LC-MS: 322.0 $(M+H)^+$.

Example 17

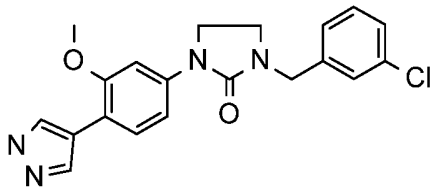
3-(3-Chlorophenyl)-1-[4-(1H-pyrazol-4-yl)phenyl]pyrrolidin-2-one



The title compound was prepared in analogy to Example 12, using 3-chlorophenyl acetic acid in step 1, and 4-bromoaniline in Step 2. LC-MS: 338.2 $(M+H)^+$.

Example 18

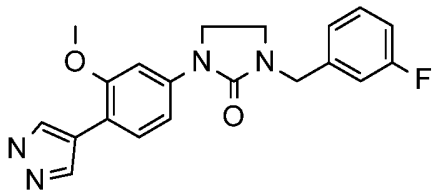
1-[(3-Chlorophenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one



The title compound was prepared in analogy to Example 5, using tert-butyl N-(2-oxoethyl)carbamate in Step 1, and 1-(bromomethyl)-3-chloro-benzene in Step 3. LC-MS: 383.0 $(M+H)^+$.

Example 19

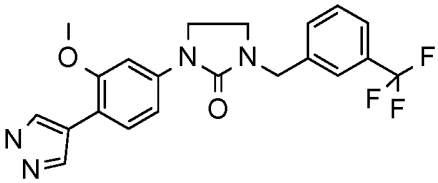
1-[(3-Fluorophenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one



The title compound was prepared in analogy to Example 5, using tert-butyl N-(2-oxoethyl)carbamate in Step 1, and 1-(bromomethyl)-3-fluoro-benzene in Step 3. LC-MS: 366.9 $(M+H)^+$.

Example 20

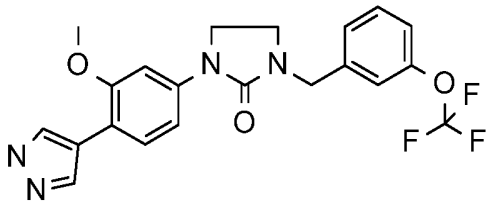
1-[3-Methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-[[3-(trifluoromethyl)phenyl]methyl]imidazolidin-2-one



The title compound was prepared in analogy to Example 5, using tert-butyl N-(2-oxoethyl)carbamate in Step 1, and 1-(bromomethyl)-3-trifluoromethyl-benzene in Step 3. LC-MS: 417.0 $(M+H)^+$.

Example 21

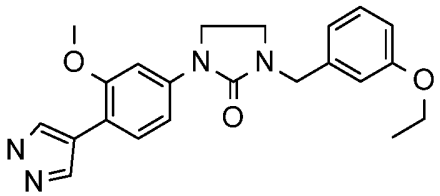
1-[3-Methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-[[3-(trifluoromethoxy)phenyl]methyl]imidazolidin-2-one



The title compound was prepared in analogy to Example 5, using tert-butyl N-(2-oxoethyl)carbamate in Step 1, and 1-(bromomethyl)-3-trifluoromethoxy-benzene in Step 3. LC-MS: 433.1 $(M+H)^+$.

Example 22

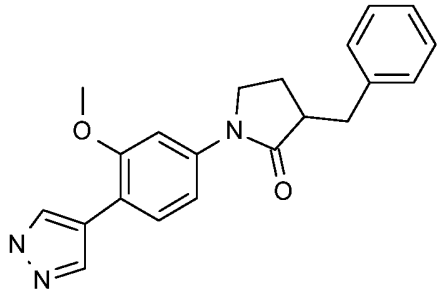
1-[(3-Ethoxyphenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one



The title compound was prepared in analogy to Example 5, using tert-butyl N-(2-oxoethyl)carbamate in Step 1, and 1-(bromomethyl)-3-ethoxy-benzene in Step 3. LC-MS: 393.0 $(M+H)^+$.

Example 23

3-Benzyl-1-(3-methoxy-4-(1H-pyrazol-4-yl)phenyl)pyrrolidin-2-one



Step 1: 1-(4-Bromo-3-methoxyphenyl)pyrrolidin-2-one

Under an atmosphere of nitrogen, in a 100 mL round-bottomed flask at 0 °C, 4-bromo-3-methoxyaniline (2 g, 9.9 mmol) and KOH (6.93 ml, 13.9 mmol) were combined with dichloromethane (30 ml) to give a light brown solution. Then 4-bromobutanoyl chloride (1.84 g, 1.15 ml, 9.9 mmol) was added. The reaction was stirred for 1 h at RT. The reaction mixture

was poured into 50 ml dichloromethane and extracted with water (3 x 20 ml). The organic layer was dried over Na_2SO_4 and concentrated in vacuo.
The residue was dissolved in 30ml dichloromethane. Then tetrabutylammonium bromide (63.8 mg, 198 µmol) and KOH (50 %, 6 ml) were added. The reaction was stirred for 1 h at RT. The reaction mixture was poured into dichloromethane (50 ml) and extracted with water (3 x 20 ml).The organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel, 50 g, 20 % to 50 % EtOAc in heptane). The title compound was obtained as a off-white crystalline (1.92 g, 71.8 %). MS (m/e) = 272.1 $[M+H]^+$.

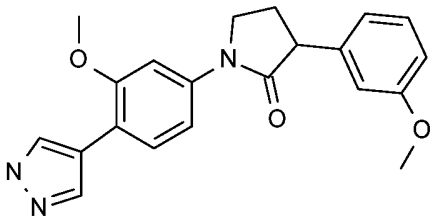
Step 2: 3-Benzyl-1-(4-bromo-3-methoxyphenyl)pyrrolidin-2-one
Under an atmosphere of nitrogen, in a 25 mL three-necked flask, 2,2,6,6-tetramethylpiperidine (188 mg, 1.33 mmol) was combined with THF (4 ml) to give a colorless solution. At 0 °C, n-butyllithium (1.6 M in hexane, 833 µl, 1.33 mmol) was added slowly. The reaction was stirred for 30 min at 0 °C. Then 1-(4-bromo-3-methoxyphenyl)pyrrolidin-2-one (300 mg, 1.11 mmol, Eq: 1.00) diluted in 3 ml THF was added slowly. The reaction was stirred for 1 h at 0 °C. Then (bromomethyl)benzene (228 mg, 159 µl, 1.33 mmol) was added. The reaction was stirred for 30min at 0 °C. The reaction was stirred for 5 d at RT. The reaction mixture was poured into 2 x 20 mL ethyl acetate and extracted with water (2 x 15 ml). The organic layer was washed with 15 ml brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel, 20 g, 0 % to 20 % EtOAc in heptane). The title compound was obtained as a light yellow gum (120 mg, 30.0 %). MS (m/e) = 360.06 $[M+H]^+$.

Step 3: 3-Benzyl-1-(3-methoxy-4-(1H-pyrazol-4-yl)phenyl)pyrrolidin-2-one
3-Benzyl-1-(4-bromo-3-methoxyphenyl)pyrrolidin-2-one (120 mg, 333 µmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate (108 mg, 366 µmol) and sodium carbonate (833 µl, 1.67 mmol) were combined with dioxane (5.00 ml). Under an atmosphere of nitrogen, 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (27.2 mg, 33.3 µmol) was added. The reaction was stirred overnight at 80 °C. The reaction mixture was poured into 25 mL ethyl acetate and extracted with water (2 x 15 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel,

10 g, 30 % to 60 % EtOAc in heptane). The title compound was obtained as a light brown solid (7.3 mg, 6.31 %). MS (m/e) = 348.17 $[M+H]^+$.

Example 24

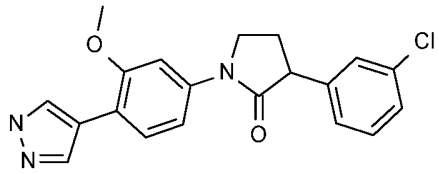
1-(3-Methoxy-4-(1H-pyrazol-4-yl)phenyl)-3-(3-methoxyphenyl)pyrrolidin-2-one



The title compound was prepared in analogy to example 12, using 2-(3-methoxyphenyl)acetic acid in step 1, and 4-bromo-3-methoxyaniline in step 2. MS (m/e) = 364.17 $[M+H]^+$.

Example 25

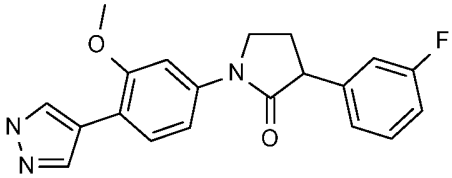
3-(3-Chlorophenyl)-1-(3-methoxy-4-(1H-pyrazol-4-yl)phenyl)pyrrolidin-2-one



The title compound was prepared in analogy to example 12, using 2-(3-chlorophenyl)acetic acid in step 1, and 4-bromo-3-methoxyaniline in step 2. MS (m/e) = 368.11 $[M+H]^+$.

Example 26

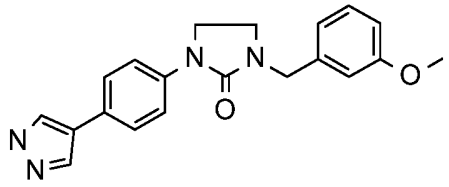
3-(3-Fluorophenyl)-1-(3-methoxy-4-(1H-pyrazol-4-yl)phenyl)pyrrolidin-2-one



The title compound was prepared in analogy to example 12, using 2-(3-fluorophenyl)acetic acid in step 1, and 4-bromo-3-methoxyaniline in step 2. MS (m/e) = 352.14 $[M+H]^+$.

Example 27

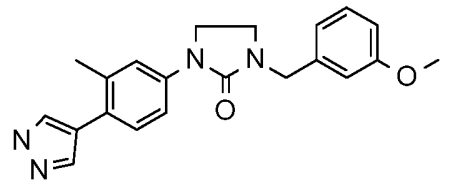
1-[(3-Methoxyphenyl)methyl]-3-[4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one



The title compound was prepared in analogy to Example 5, using tert-butyl N-(2-oxoethyl)carbamate and 4-bromophenylamine in Step 1, and 1-(bromomethyl)-3-methoxy-benzene in Step 3. LC-MS: 349 $(M+H)^+$.

Example 28

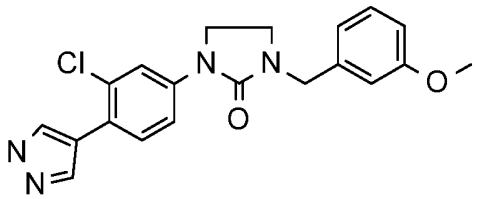
1-[(3-Methoxyphenyl)methyl]-3-[3-methyl-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one



The title compound was prepared in analogy to Example 5, using tert-butyl N-(2-oxoethyl)carbamate and 4-bromo-3-methyl-aniline in Step 1, and 1-(bromomethyl)-3-methoxy-benzene in Step 3. LC-MS: 363 $(M+H)^+$.

Example 29

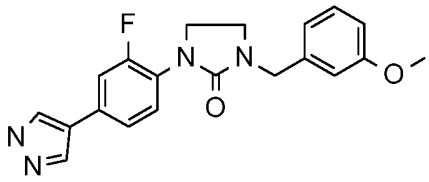
1-[3-Chloro-4-(1H-pyrazol-4-yl)phenyl]-3-[(3-methoxyphenyl)methyl]imidazolidin-2-one



The title compound was prepared in analogy to Example 5, using tert-butyl N-(2-oxoethyl)carbamate and 4-bromo-3-chloro-aniline in Step 1, and 1-(bromomethyl)-3-methoxy-benzene in Step 3. LC-MS: 383 $(M+H)^+$.

Example 30

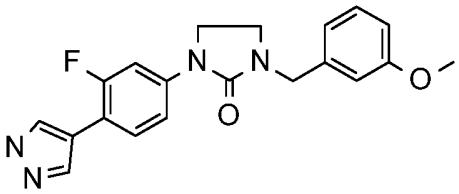
1-[2-Fluoro-4-(1H-pyrazol-4-yl)phenyl]-3-[(3-methoxyphenyl)methyl]imidazolidin-2-one



The title compound was prepared in analogy to Example 5, using tert-butyl N-(2-oxoethyl)carbamate and 4-bromo-2-fluoro-aniline in Step 1, and 1-(bromomethyl)-3-methoxy-benzene in Step 3. LC-MS: 367 $(M+H)^+$.

Example 31

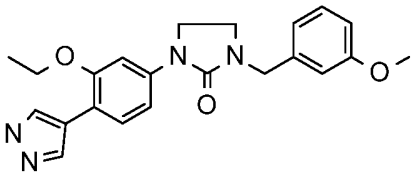
1-[3-Fluoro-4-(1H-pyrazol-4-yl)phenyl]-3-[(3-methoxyphenyl)methyl]imidazolidin-2-one



The title compound was prepared in analogy to Example 5, using tert-butyl N-(2-oxoethyl)carbamate and 4-bromo-3-fluoro-aniline in Step 1, and 1-(bromomethyl)-3-methoxy-benzene in Step 3. LC-MS: 367 $(M+H)^+$.

Example 32

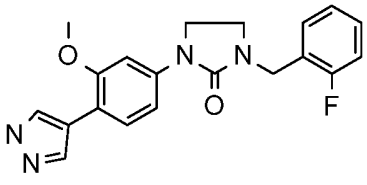
1-[3-Ethoxy-4-(1H-pyrazol-4-yl)phenyl]-3-[(3-methoxyphenyl)methyl]imidazolidin-2-one



The title compound was prepared in analogy to Example 5, using tert-butyl N-(2-oxoethyl)carbamate and 4-bromo-3-ethoxy-aniline in Step 1, and 1-(bromomethyl)-3-methoxy-benzene in Step 3. LC-MS: 393 $(M+H)^+$.

Example 33

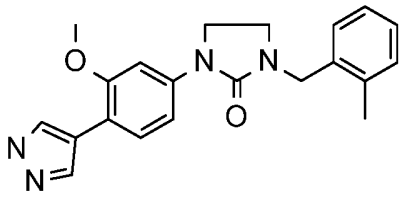
1-[(2-Fluorophenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one



The title compound was prepared in analogy to Example 5, using tert-butyl N-(2-oxoethyl)carbamate in Step 1, and 1-(bromomethyl)-2-fluoro-benzene in Step 3. LC-MS: 367 $(M+H)^+$.

Example 34

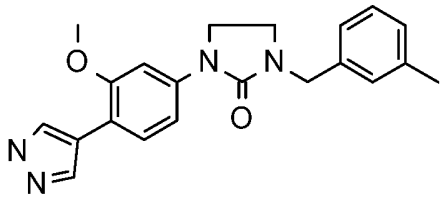
1-[3-Methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-(o-tolylmethyl)imidazolidin-2-one



The title compound was prepared in analogy to Example 5, using tert-butyl N-(2-oxoethyl)carbamate in Step 1, and 1-(bromomethyl)-2-methyl-benzene in Step 3. LC-MS: 363 $(M+H)^+$.

Example 35

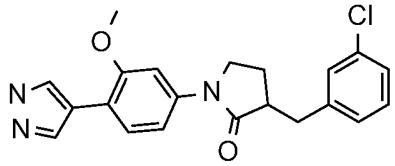
1-[3-Methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-(m-tolylmethyl)imidazolidin-2-one



The title compound was prepared in analogy to Example 5, using tert-butyl N-(2-oxoethyl)carbamate in Step 1, and 1-(bromomethyl)-3-methyl-benzene in Step 3. LC-MS: 363 $(M+H)^+$.

Example 36

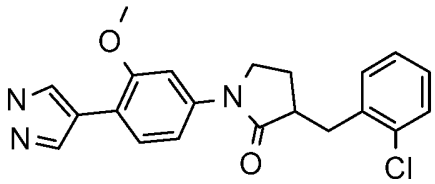
3-[(3-Chlorophenyl)methyl]-1-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]pyrrolidin-2-one



The title compound was obtained in analogy to example 23, using 1-(bromomethyl)-3-chloro-benzene in step 2. MS: 382.0 $(M+H)^+$.

Example 37

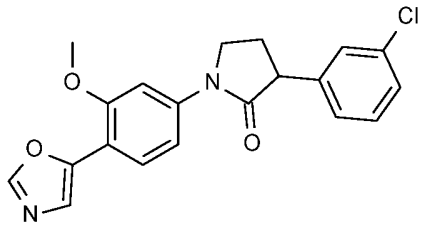
3-[(2-Chlorophenyl)methyl]-1-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]pyrrolidin-2-one



The title compound was obtained in analogy to example 23, using 1-(bromomethyl)-2-chloro-benzene in step 2. MS: 382.0 $(M+H)^+$.

Example 38

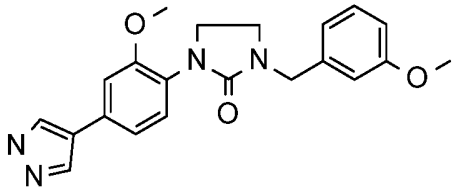
3-(3-Chlorophenyl)-1-[3-methoxy-4-(1,3-oxazol-5-yl)phenyl]pyrrolidin-2-one



The title compound was prepared in analogy to Example 3, using 3-chlorophenylacetic acid in step 1. MS: 367.2 $(M-H)^+$.

Example 39

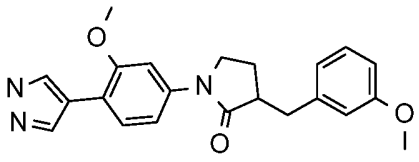
1-[(3-Methoxyphenyl)methyl]-3-[2-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one



The title compound was prepared in analogy to Example 5, using tert-butyl N-(2-oxoethyl)carbamate and 4-bromo-2-methoxy-aniline in Step 1, and 1-(bromomethyl)-3-methoxy-benzene in Step 3. LC-MS: 379 $(M+H)^+$.

Example 40

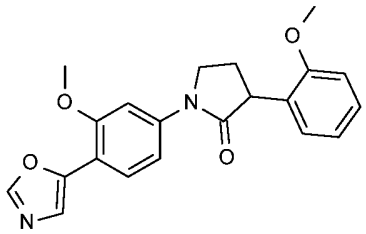
3-[(3-Methoxyphenyl)methyl]-1-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]pyrrolidin-2-one



The title compound was obtained in analogy to example 23, using 1-(bromomethyl)-3-methoxy-benzene in step 2. MS: 378.0 $(M+H)^+$.

Example 41

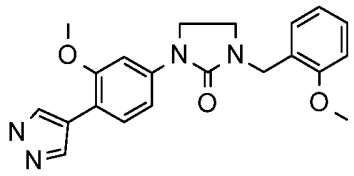
1-[3-Methoxy-4-(1,3-oxazol-5-yl)phenyl]-3-(2-methoxyphenyl)pyrrolidin-2-one



The title compound was prepared in analogy to Example 3, using 2-methoxyphenylacetic acid in step 1. MS: 365.3 $(M+H)^+$.

Example 42

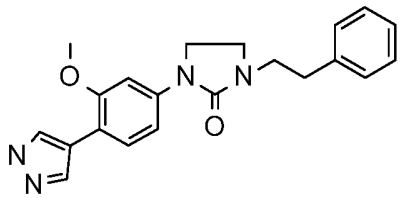
1-[(2-Methoxyphenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one



The title compound was prepared in analogy to Example 5, using tert-butyl N-(2-oxoethyl)carbamate and in Step 1, and 1-(bromomethyl)-2-methoxy-benzene in Step 3. LC-MS: 379 $(M+H)^+$.

Example 43

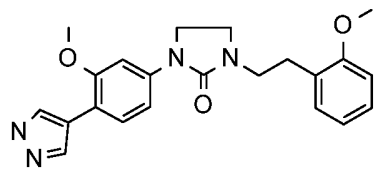
1-[3-Methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-(2-phenylethyl)imidazolidin-2-one



The title compound was prepared in analogy to Example 5, using tert-butyl N-(2-oxoethyl)carbamate and in Step 1, and 2-bromoethylbenzene in Step 3. LC-MS: 363 $(M+H)^+$.

Example 44

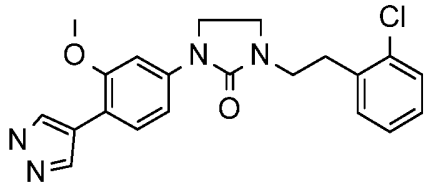
1-[2-(2-Methoxyphenyl)ethyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one



The title compound was prepared in analogy to Example 5, using tert-butyl N-(2-oxoethyl)carbamate and in Step 1, and 1-(2-bromoethyl)-2-methoxy-benzene in Step 3. LC-MS: 393 $(M+H)^+$.

Example 45

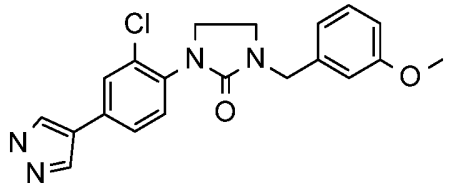
1-[2-(2-Chlorophenyl)ethyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one



The title compound was prepared in analogy to Example 5, using tert-butyl N-(2-oxoethyl)carbamate and in Step 1, and 1-(2-bromoethyl)-2-chloro-benzene in Step 3. LC-MS: 397 $(M+H)^+$.

Example 46

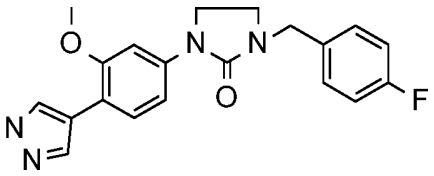
1-[2-Chloro-4-(1H-pyrazol-4-yl)phenyl]-3-[(3-methoxyphenyl)methyl]imidazolidin-2-one



The title compound was prepared in analogy to Example 5, using tert-butyl N-(2-oxoethyl)carbamate and 4-bromo-2-chloro-aniline in Step 1, and 1-(bromomethyl)-3-methoxy-benzene in Step 3. LC-MS: 383 $(M+H)^+$.

Example 47

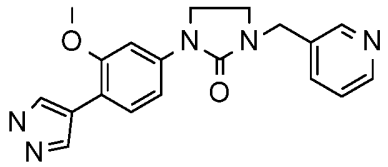
1-[(4-Fluorophenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one



The title compound was prepared in analogy to Example 5, using tert-butyl N-(2-oxoethyl)carbamate in Step 1, and 1-(bromomethyl)-4-fluoro-benzene in Step 3. LC-MS: 367 $(M+H)^+$.

Example 48

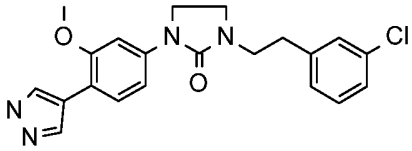
1-[3-Methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-(3-pyridylmethyl)imidazolidin-2-one



The title compound was prepared in analogy to Example 5, using tert-butyl N-(2-oxoethyl)carbamate in Step 1, and 3-(bromomethyl)pyridine in Step 3. LC-MS: 350 $(M+H)^+$.

Example 49

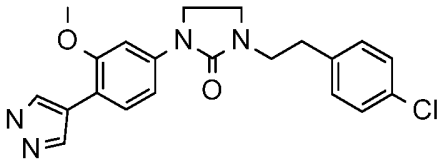
1-[2-(3-Chlorophenyl)ethyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one



The title compound was prepared in analogy to Example 5, using tert-butyl N-(2-oxoethyl)carbamate and in Step 1, and 1-(2-bromoethyl)-3-chloro-benzene in Step 3. LC-MS: 397 $(M+H)^+$.

Example 50

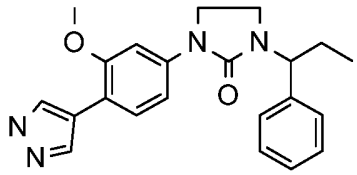
1-[2-(4-Chlorophenyl)ethyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one



The title compound was prepared in analogy to Example 5, using tert-butyl N-(2-oxoethyl)carbamate and in Step 1, and 1-(2-bromoethyl)-4-chloro-benzene in Step 3. LC-MS: 397 $(M+H)^+$.

Example 51

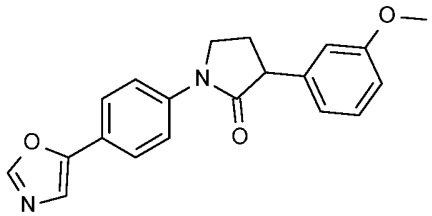
1-[3-Methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-(1-phenylpropyl)imidazolidin-2-one



The title compound was prepared in analogy to example 5, using 1-(4-bromo-3-methoxy-phenyl)-3-(1-phenyl-propyl)-imidazolidin-2-one and 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrazole-1-carboxylic acid tert-butyl ester in Step 4. LC-MS: 377 $(M+H)^+$.

Example 52

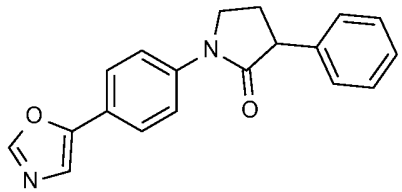
3-(3-Methoxyphenyl)-1-[4-(1,3-oxazol-5-yl)phenyl]pyrrolidin-2-one



The title compound was prepared in analogy to Example 3, using 3-methoxyphenylacetic acid in step 1, and 4-oxazol-5-ylaniline in step 2. MS: 335.3 $(M+H)^+$.

Example 53

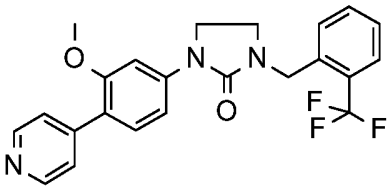
1-[4-(1,3-Oxazol-5-yl)phenyl]-3-phenylpyrrolidin-2-one



The title compound was prepared in analogy to Example 3, using phenylacetic acid in step 1, and 4-oxazol-5-ylaniline in step 2. MS: 305.2 $(M+H)^+$.

Example 54

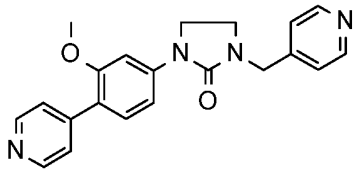
1-[3-Methoxy-4-(4-pyridyl)phenyl]-3-[[2-(trifluoromethyl)phenyl]methyl]imidazolidin-2-one



The title compound was prepared in analogy to Example 5, using tert-butyl N-(2-oxoethyl)carbamate in Step 1, 1-(bromomethyl)-2-trifluoromethyl-benzene in Step 3, and pyridin-4-ylboronic acid in Step 4. LC-MS: 428 $(M+H)^+$.

Example 55

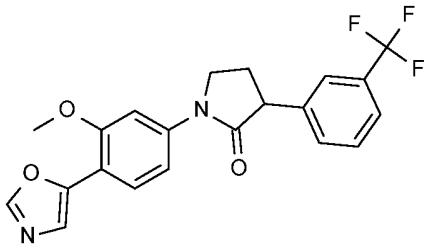
1-[3-Methoxy-4-(4-pyridyl)phenyl]-3-(4-pyridylmethyl)imidazolidin-2-one



The title compound was prepared in analogy to Example 5, using tert-butyl N-(2-oxoethyl)carbamate in Step 1 4-(bromomethyl)pyridine in Step 3, and pyridin-4-ylboronic acid in Step 4. LC-MS: 361 $(M+H)^+$.

Example 56

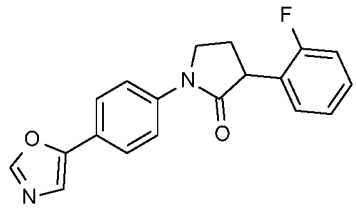
1-[3-Methoxy-4-(1,3-oxazol-5-yl)phenyl]-3-[3-(trifluoromethyl)phenyl]pyrrolidin-2-one



The title compound was prepared in analogy to Example 3, using 3-trifluoromethylphenylacetic acid in step 1. MS: 403.2 $(M+H)^+$.

Example 57

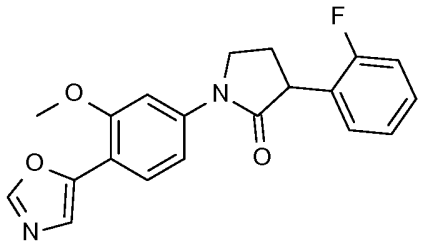
3-(2-Fluorophenyl)-1-[4-(1,3-oxazol-5-yl)phenyl]pyrrolidin-2-one



The title compound was prepared in analogy to Example 3, using 2-fluorophenylacetic acid in step 1, and 4-oxazol-5-ylaniline in step 2. MS: 323.2 $(M+H)^+$.

Example 58

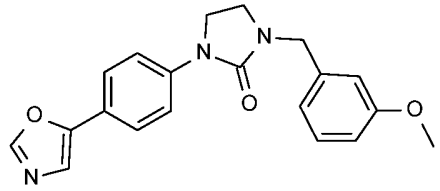
3-(2-Fluorophenyl)-1-[3-methoxy-4-(1,3-oxazol-5-yl)phenyl]pyrrolidin-2-one



The title compound was prepared in analogy to Example 3, using 2-fluorophenylacetic acid in step 1. MS: 353.2 $(M+H)^+$.

Example 59

1-[(3-Methoxyphenyl)methyl]-3-[4-(1,3-oxazol-5-yl)phenyl]imidazolidin-2-one



Step 1: tert-Butyl 2-(4-(oxazol-5-yl)phenylamino)ethylcarbamate

To a solution of 4-(oxazol-5-yl)aniline (0.5 g, 3.12 mmol, Eq: 1.00) in dichloromethane (31.5 ml) at 0 °C were added tert-butyl 2-oxoethylcarbamate (628 mg, 3.75 mmol, Eq: 1.2) and AcOH (187 mg, 179 µl, 3.12 mmol, Eq: 1.00). The solution was stirred at 0 °C for 0.5 h. Then sodium triacetoxyborohydride (992 mg, 4.68 mmol) was added, and the solution was stirred at 23 °C for 6h. The mixture was diluted with water (20 ml), the organic layer was separated and the aqueous layer was extracted with dichloromethane. The organic layers were washed with brine, dried over $MgSO_4$ and evaporated. The crude product (1.25 g) was purified by flash chromatography to give the title compound (0.92 g, 97 %). MS: 304.2 $(M+H)^+$.

Step 2: 1-(4-(Oxazol-5-yl)phenyl)imidazolidin-2-one

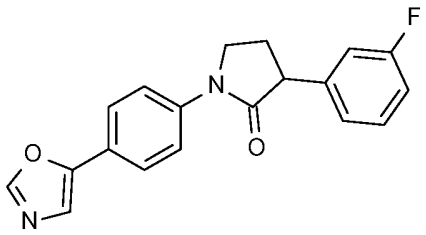
To a solution of potassium tert-butoxide (681 mg, 6.07 mmol) in THF (25.5 ml) at 0 °C was added a solution of tert-butyl 2-(4-(oxazol-5-yl)phenylamino)ethylcarbamate (0.92 g, 3.03 mmol) in THF (25.5 ml), and the resulting solution was stirred at 23 °C for 2 h. The mixture was quenched with 100 ml sat. aqueous NH_4Cl sol. and extracted with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$ and evaporated. The crude product (0.65 g) was triturated with 3 ml AcOEt and 10ml heptane. After ½ h the mixture was filtered, washed with heptane and dried at HV to give the title compound (560 mg, 81 %).

Step 3: 1-[(3-Methoxyphenyl)methyl]-3-[4-(1,3-oxazol-5-yl)phenyl]imidazolidin-2-one

To a suspension of sodium hydride (21.0 mg, 525 µmol) in DMF (1.35 ml) at 0 °C was added a solution of 1-(4-(oxazol-5-yl)phenyl)imidazolidin-2-one (80.2 mg, 0.35 mmol) in DMF (3.37 ml), and the resulting mixture was stirred at 0 °C for 0.5 h. Then 1-(bromomethyl)-3-methoxybenzene (106 mg, 73.5 µl, 525 µmol) was added to the mixture. The solution was stirred for futher 19 h at 23 °C. The mixture was diluted with 20ml water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The crude material (1.31 g) was purified by column chromatography (silica gel, 20 g, heptan/AcOEt 0 – 50 %). The product (0.06 g) was crystallised with 2ml dichloromethane and 15 ml heptan. After ½ h the mixture was filtered, washed with heptane and dried at HV to give 24 mg (20 %) of the title compound. MS: 350.2 $(M+H)^+$.

Example 60

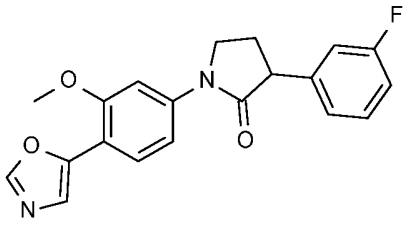
3-(3-Fluorophenyl)-1-[4-(1,3-oxazol-5-yl)phenyl]pyrrolidin-2-one



The title compound was prepared in analogy to Example 3, using 3-fluorophenylacetic acid in step 1, and 4-oxazol-5-ylaniline in step 2. MS: 323.2 $(M+H)^+$.

Example 61

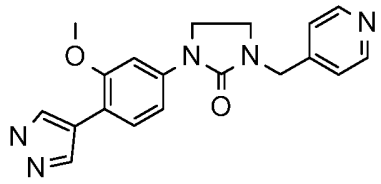
3-(3-Fluorophenyl)-1-[3-methoxy-4-(1,3-oxazol-5-yl)phenyl]pyrrolidin-2-one



The title compound was prepared in analogy to Example 3, using 3-fluorophenylacetic acid in step 1. MS: 353.2 $(M+H)^+$.

Example 62

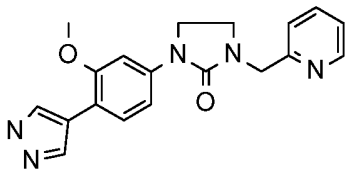
1-[3-Methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-(4-pyridylmethyl)imidazolidin-2-one



The title compound was prepared in analogy to Example 5, using tert-butyl N-(2-oxoethyl)carbamate in Step 1, and 4-(bromomethyl)pyridine in Step 3. LC-MS: 350 $(M+H)^+$.

Example 63

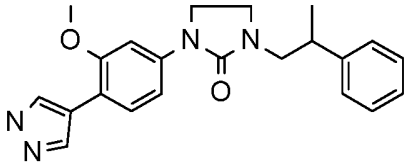
1-[3-Methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-(2-pyridylmethyl)imidazolidin-2-one



The title compound was prepared in analogy to Example 5, using tert-butyl N-(2-oxoethyl)carbamate in Step 1, and 2-(bromomethyl)pyridine in Step 3. LC-MS: 350 $(M+H)^+$.

Example 64

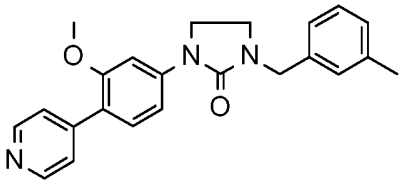
1-[3-Methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-(2-phenylpropyl)imidazolidin-2-one



The title compound was prepared in analogy to Example 5, using tert-butyl N-(2-oxoethyl)carbamate in Step 1, and (2-bromo-1-methyl-ethyl)benzene in Step 3. LC-MS: 377 $(M+H)^+$.

Example 65

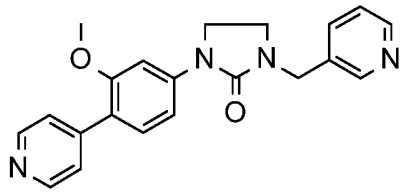
1-[3-Methoxy-4-(4-pyridyl)phenyl]-3-(m-tolylmethyl)imidazolidin-2-one



The title compound was prepared in analogy to Example 5, using tert-butyl N-(2-oxoethyl)carbamate in Step 1, 1-(bromomethyl)-3-methyl-benzene in Step 3, and pyridin-4-ylboronic acid in Step 4. LC-MS: 374 $(M+H)^+$.

Example 66

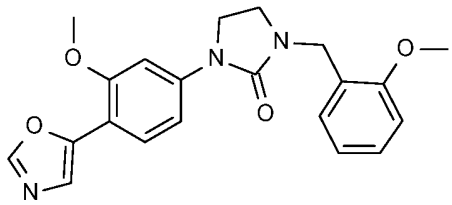
1-[3-Methoxy-4-(4-pyridyl)phenyl]-3-(3-pyridylmethyl)imidazolidin-2-one



The title compound was prepared in analogy to Example 5, using tert-butyl N-(2-oxoethyl)carbamate in Step 1, 3-(bromomethyl)pyridine in Step 3, and pyridin-4-ylboronic acid in Step 4. LC-MS: 361 $(M+H)^+$.

Example 67

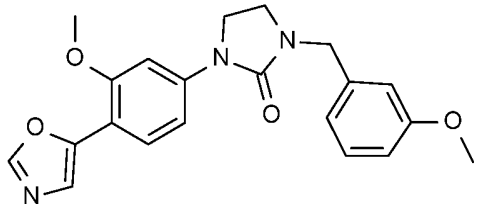
1-[3-Methoxy-4-(1,3-oxazol-5-yl)phenyl]-3-[(2-methoxyphenyl)methyl]imidazolidin-2-one



The title compound was prepared in analogy to Example 59, using 3-methoxy-4-(oxazol-5-yl)aniline in step 1 and 1-(chloromethyl)-2-methoxybenzene in step 3. MS: 380.2 $(M+H)^+$.

Example 68

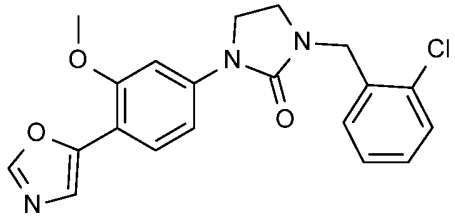
1-[3-Methoxy-4-(1,3-oxazol-5-yl)phenyl]-3-[(3-methoxyphenyl)methyl]imidazolidin-2-one



The title compound was prepared in analogy to Example 59, using 3-methoxy-4-(oxazol-5-yl)aniline in step 1 and 1-(bromomethyl)-3-methoxybenzene in step 3. MS: 380.2 $(M+H)^+$.

Example 69

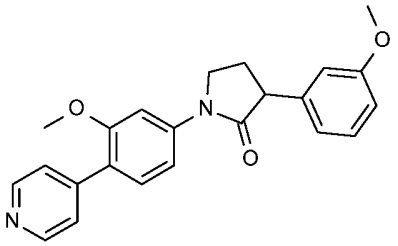
1-[(2-Chlorophenyl)methyl]-3-[3-methoxy-4-(1,3-oxazol-5-yl)phenyl]imidazolidin-2-one



The title compound was prepared in analogy to Example 59, using 3-methoxy-4-(oxazol-5-yl)aniline in step 1 and 1-(bromomethyl)-3-chlorobenzene in step 3. MS: 384.2 $(M+H)^+$.

Example 70

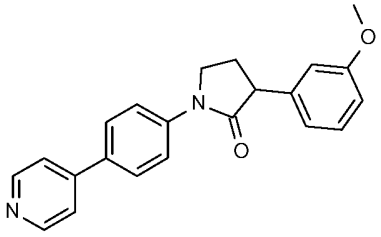
3-(3-Methoxyphenyl)-1-(3-methoxy-4-pyridin-4-ylphenyl)pyrrolidin-2-one



The title compound was prepared in analogy to Example 12, using 3-methylphenyl acetic acid in step 1, and pyridin-4-ylboronic acid in step 6. LC-MS: 375.3 $(M+H)^+$.

Example 71

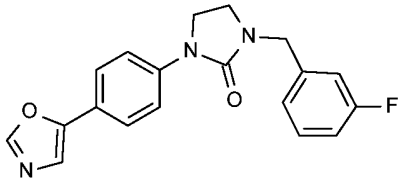
3-(3-Methoxyphenyl)-1-(4-pyridin-4-ylphenyl)pyrrolidin-2-one



The title compound was prepared in analogy to Example 12, using 3-methylphenyl acetic acid in step 1, 4-bromoaniline in Step 2, and pyridin-4-ylboronic acid in step 6. LC-MS: 345.3 $(M+H)^+$.

Example 72

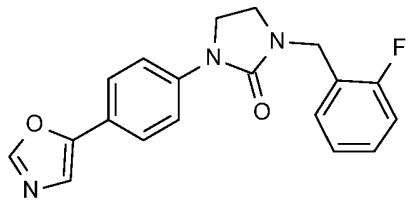
1-[(3-Fluorophenyl)methyl]-3-[4-(1,3-oxazol-5-yl)phenyl]imidazolidin-2-one



The title compound was prepared in analogy to Example 59, using 1-(bromomethyl)-3-fluorobenzene in step 3. MS: 338.2 $(M+H)^+$.

Example 73

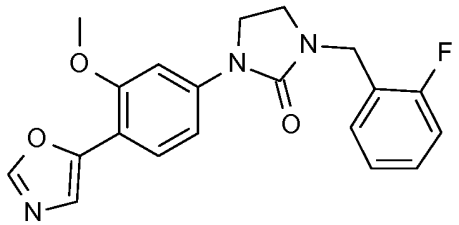
1-[(2-Fluorophenyl)methyl]-3-[4-(1,3-oxazol-5-yl)phenyl]imidazolidin-2-one



The title compound was prepared in analogy to Example 59, using 1-(bromomethyl)-2-fluorobenzene in step 3. MS: 338.2 $(M+H)^+$.

Example 74

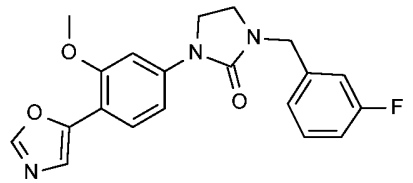
1-[(2-Fluorophenyl)methyl]-3-[3-methoxy-4-(1,3-oxazol-5-yl)phenyl]imidazolidin-2-one



The title compound was prepared in analogy to Example 59, using 3-methoxy-4-(oxazol-5-yl)aniline in step 1 and 1-(bromomethyl)-2-fluorobenzene in step 3. MS: 368.2 $(M+H)^+$.

Example 75

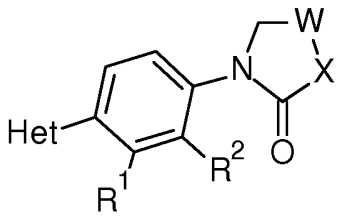
1-[(3-Fluorophenyl)methyl]-3-[3-methoxy-4-(1,3-oxazol-5-yl)phenyl]imidazolidin-2-one



The title compound was prepared in analogy to Example 59, using 3-methoxy-4-(oxazol-5-yl)aniline in step 1 and 1-(bromomethyl)-3-fluorobenzene in step 3. MS: 368.2 $(M+H)^+$.

Claims

1. A compound of formula I



I

wherein

Het is oxazole-5-yl, pyridin-4-yl, or pyrazol-4-yl;

R^1/ R^2 are, independently from each other, hydrogen, lower alkyl, lower alkoxy, or halogen;

W is $-CH_2-$ or $-CH_2CH_2-$;

X is CR^3R^4 or NR^5;

R^3 is hydrogen or lower alkyl;

R^4 is $-(CH_2)_n$-phenyl, optionally substituted by halogen, lower alkoxy, lower alkyl substituted by halogen, lower alkoxy substituted by halogen or lower alkyl;

R^5 is CHR-phenyl or CH_2CHR-phenyl, optionally substituted by halogen, lower alkoxy, lower alkyl substituted by halogen, lower alkoxy substituted by halogen or lower alkyl, or is

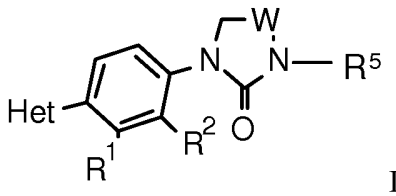
CHR-pyridin-2, 3 or 4 –yl;

R is hydrogen or lower alkyl;

n is 0 or 1;

or a pharmaceutically acceptable acid addition salt, a racemic mixture or its corresponding enantiomer and/or optical isomer thereof.

2. A compound of formula Ia according to claim 1,



Ia

wherein

Het is oxazole-5-yl, pyridin-4-yl, or pyrazol-4-yl;

R^1/ R^2 are, independently from each other, hydrogen, lower alkyl, lower alkoxy, or halogen;

W is $-CH_2-$ or $-CH_2CH_2-$;

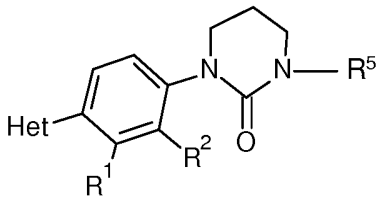
R^5 is CHR-phenyl or CH_2CHR-phenyl, optionally substituted by halogen, lower alkoxy, lower alkyl substituted by halogen, lower alkoxy substituted by halogen or lower alkyl, or is

CHR-pyridin-2, 3 or 4 –yl;

R is hydrogen or lower alkyl;

or a pharmaceutically acceptable acid addition salt, a racemic mixture or its corresponding enantiomer and/or optical isomer thereof.

3. A compound of formula Ia-1 according to claim 2,



Ia-1

wherein

Het is oxazole-5-yl, pyridin-4-yl, or pyrazol-4-yl;

R^1/ R^2 are, independently from each other, hydrogen, lower alkyl, lower alkoxy, or halogen;

R^5 is CHR-phenyl or CH_2CHR-phenyl, optionally substituted by halogen, lower alkoxy, lower alkyl substituted by halogen, lower alkoxy substituted by halogen or lower alkyl, or is

CHR-pyridin-2, 3 or 4 –yl;

R is hydrogen or lower alkyl;

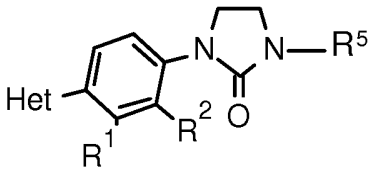
or a pharmaceutically acceptable acid addition salt, a racemic mixture or its corresponding enantiomer and/or optical isomer thereof.

4. A compound of formula Ia-1 according to any one of claims 2 and 3, which compounds are

1-benzyl-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]hexahydropyrimidin-2-one

1-[(2-chlorophenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]hexahydropyrimidin-2-one or
1-[(3-methoxyphenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]hexahydropyrimidin-2-one.

5. A compound of formula Ia-2 according to claim 2,



Ia-2

wherein

Het is oxazole-5-yl, pyridin-4-yl, or pyrazol-4-yl;

R^1/ R^2 are, independently from each other, hydrogen, lower alkyl, lower alkoxy, or halogen;

R^5 is CHR-phenyl or CH_2CHR-phenyl, optionally substituted by halogen, lower alkoxy, lower alkyl substituted by halogen, lower alkoxy substituted by halogen or lower alkyl, or is
CHR-pyridin-2, 3 or 4 –yl;
R is hydrogen or lower alkyl;

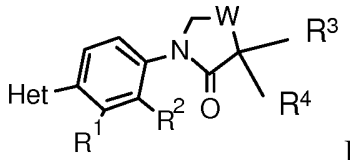
or a pharmaceutically acceptable acid addition salt, a racemic mixture or its corresponding enantiomer and/or optical isomer thereof.

6. A compound of formula Ia-2 according to claims 2 and 5, wherein the compounds are
1-benzyl-3-(4-(pyridin-4-yl)phenyl)imidazolidin-2-one
1-benzyl-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one
1-[(2-chlorophenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one
1-[(3-methoxyphenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one
1-[(3-chlorophenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one
1-[(3-fluorophenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one
1-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-[[3-(trifluoromethyl)phenyl]methyl]imidazolidin-2-one
1-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-[[3-(trifluoromethoxy)phenyl]methyl]imidazolidin-2-one

1-[(3-ethoxyphenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one
1-[(3-methoxyphenyl)methyl]-3-[4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one
1-[(3-methoxyphenyl)methyl]-3-[3-methyl-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one
1-[3-chloro-4-(1H-pyrazol-4-yl)phenyl]-3-[(3-methoxyphenyl)methyl]imidazolidin-2-one
1-[2-fluoro-4-(1H-pyrazol-4-yl)phenyl]-3-[(3-methoxyphenyl)methyl]imidazolidin-2-one
1-[3-fluoro-4-(1H-pyrazol-4-yl)phenyl]-3-[(3-methoxyphenyl)methyl]imidazolidin-2-one
1-[3-ethoxy-4-(1H-pyrazol-4-yl)phenyl]-3-[(3-methoxyphenyl)methyl]imidazolidin-2-one
1-[(2-fluorophenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one
1-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-(o-tolylmethyl)imidazolidin-2-one
1-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-(m-tolylmethyl)imidazolidin-2-one
1-[(3-methoxyphenyl)methyl]-3-[2-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one
1-[(2-methoxyphenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one
1-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-(2-phenylethyl)imidazolidin-2-one
1-[2-(2-methoxyphenyl)ethyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one
1-[2-(2-chlorophenyl)ethyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one
1-[2-chloro-4-(1H-pyrazol-4-yl)phenyl]-3-[(3-methoxyphenyl)methyl]imidazolidin-2-one
1-[(4-fluorophenyl)methyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one
1-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-(3-pyridylmethyl)imidazolidin-2-one
1-[2-(3-chlorophenyl)ethyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one
1-[2-(4-chlorophenyl)ethyl]-3-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]imidazolidin-2-one
1-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-(1-phenylpropyl)imidazolidin-2-one
1-[3-methoxy-4-(4-pyridyl)phenyl]-3-[[2-(trifluoromethyl)phenyl]methyl]imidazolidin-2-one
1-[3-methoxy-4-(4-pyridyl)phenyl]-3-(4-pyridylmethyl)imidazolidin-2-one
1-[(3-methoxyphenyl)methyl]-3-[4-(1,3-oxazol-5-yl)phenyl]imidazolidin-2-one
1-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-(4-pyridylmethyl)imidazolidin-2-one
1-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-(2-pyridylmethyl)imidazolidin-2-one
1-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-(2-phenylpropyl)imidazolidin-2-one
1-[3-methoxy-4-(4-pyridyl)phenyl]-3-(m-tolylmethyl)imidazolidin-2-one
1-[3-methoxy-4-(4-pyridyl)phenyl]-3-(3-pyridylmethyl)imidazolidin-2-one
1-[3-methoxy-4-(1,3-oxazol-5-yl)phenyl]-3-[(2-methoxyphenyl)methyl]imidazolidin-2-one
1-[3-methoxy-4-(1,3-oxazol-5-yl)phenyl]-3-[(3-methoxyphenyl)methyl]imidazolidin-2-one
1-[(2-chlorophenyl)methyl]-3-[3-methoxy-4-(1,3-oxazol-5-yl)phenyl]imidazolidin-2-one
1-[(3-fluorophenyl)methyl]-3-[4-(1,3-oxazol-5-yl)phenyl]imidazolidin-2-one
1-[(2-fluorophenyl)methyl]-3-[4-(1,3-oxazol-5-yl)phenyl]imidazolidin-2-one

1-[(2-fluorophenyl)methyl]-3-[3-methoxy-4-(1,3-oxazol-5-yl)phenyl]imidazolidin-2-one or 1-[(3-fluorophenyl)methyl]-3-[3-methoxy-4-(1,3-oxazol-5-yl)phenyl]imidazolidin-2-one.

7. A compound of formula Ib according to claim 1,



Ib

wherein

Het is oxazole-5-yl, pyridin-4-yl, or pyrazol-4-yl;

R^1/ R^2 are, independently from each other, hydrogen, lower alkyl, lower alkoxy, or halogen;

W is $-CH_2-$ or $-CH_2CH_2-$;

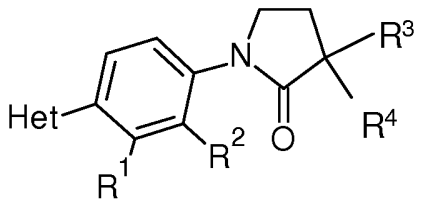
R^3 is hydrogen or lower alkyl;

R^4 is $-(CH_2)_n$-phenyl, optionally substituted by halogen, lower alkoxy, lower alkyl substituted by halogen, lower alkoxy substituted by halogen or lower alkyl;

n is 0 or 1;

or a pharmaceutically acceptable acid addition salt, a racemic mixture or its corresponding enantiomer and/or optical isomer thereof.

8. A compound of formula Ib-1 according to claim 7



Ib-1

wherein

Het is oxazole-5-yl, pyridin-4-yl, or pyrazol-4-yl;

R^1/ R^2 are, independently from each other, hydrogen, lower alkyl, lower alkoxy, or halogen;

R^3 is hydrogen or lower alkyl;

R^4 is $-(CH_2)_n$-phenyl, optionally substituted by halogen, lower alkoxy, lower alkyl substituted by halogen, lower alkoxy substituted by halogen or lower alkyl;

n is 0 or 1;

or a pharmaceutically acceptable acid addition salt, a racemic mixture or its corresponding enantiomer and/or optical isomer thereof.

9. A compound of formula Ib-1 according to claim 8, which compounds are

3-ethyl-1-(3-methoxy-4-(oxazol-5-yl)phenyl)-3-phenylpyrrolidin-2-one

1-(3-methoxy-4-oxazol-5-yl-phenyl)-3-(3-methoxyphenyl)pyrrolidin-2-one

3-(2-chlorophenyl)-1-(3-methoxy-4-oxazol-5-yl-phenyl)pyrrolidin-2-one

1-(3-methoxy-4-oxazol-5-yl-phenyl)-3-phenyl-pyrrolidin-2-one

1-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]-3-phenyl-pyrrolidin-2-one

3-phenyl-1-[4-(1H-pyrazol-4-yl)phenyl]pyrrolidin-2-one

3-(3-methoxyphenyl)-1-[4-(1H-pyrazol-4-yl)phenyl]pyrrolidin-2-one

3-(4-chlorophenyl)-1-[4-(1H-pyrazol-4-yl)phenyl]pyrrolidin-2-one

3-(4-fluorophenyl)-1-[4-(1H-pyrazol-4-yl)phenyl]pyrrolidin-2-one

3-(3-chlorophenyl)-1-[4-(1H-pyrazol-4-yl)phenyl]pyrrolidin-2-one

3-benzyl-1-(3-methoxy-4-(1H-pyrazol-4-yl)phenyl)pyrrolidin-2-one

1-(3-methoxy-4-(1H-pyrazol-4-yl)phenyl)-3-(3-methoxyphenyl)pyrrolidin-2-one

3-(3-chlorophenyl)-1-(3-methoxy-4-(1H-pyrazol-4-yl)phenyl)pyrrolidin-2-one

3-(3-fluorophenyl)-1-(3-methoxy-4-(1H-pyrazol-4-yl)phenyl)pyrrolidin-2-one

3-[(3-chlorophenyl)methyl]-1-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]pyrrolidin-2-one

3-[(2-chlorophenyl)methyl]-1-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]pyrrolidin-2-one

3-(3-chlorophenyl)-1-[3-methoxy-4-(1,3-oxazol-5-yl)phenyl]pyrrolidin-2-one

3-[(3-methoxyphenyl)methyl]-1-[3-methoxy-4-(1H-pyrazol-4-yl)phenyl]pyrrolidin-2-one

1-[3-methoxy-4-(1,3-oxazol-5-yl)phenyl]-3-(2-methoxyphenyl)pyrrolidin-2-one

3-(3-methoxyphenyl)-1-[4-(1,3-oxazol-5-yl)phenyl]pyrrolidin-2-one

1-[4-(1,3-oxazol-5-yl)phenyl]-3-phenylpyrrolidin-2-one

1-[3-methoxy-4-(1,3-oxazol-5-yl)phenyl]-3-[3-(trifluoromethyl)phenyl]pyrrolidin-2-one

3-(2-fluorophenyl)-1-[4-(1,3-oxazol-5-yl)phenyl]pyrrolidin-2-one

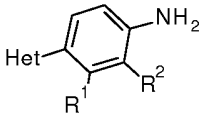
3-(2-fluorophenyl)-1-[3-methoxy-4-(1,3-oxazol-5-yl)phenyl]pyrrolidin-2-one

3-(3-fluorophenyl)-1-[4-(1,3-oxazol-5-yl)phenyl]pyrrolidin-2-one

3-(3-fluorophenyl)-1-[3-methoxy-4-(1,3-oxazol-5-yl)phenyl]pyrrolidin-2-one
3-(3-methoxyphenyl)-1-(3-methoxy-4-pyridin-4-ylphenyl)pyrrolidin-2-one or
3-(3-methoxyphenyl)-1-(4-pyridin-4-ylphenyl)pyrrolidin-2-one.

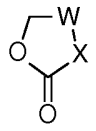
10. A process for the manufacture of a compound of formula I as defined in any one of claims 1 to 9, which process comprises

a) reacting a compound of formula



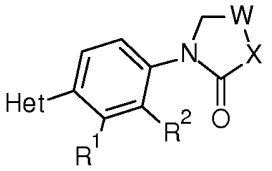
1

with a compound of formula



2

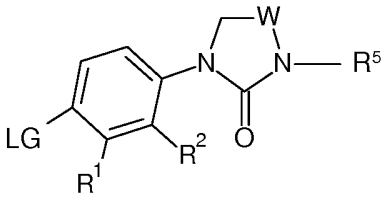
to a compound of formula



I

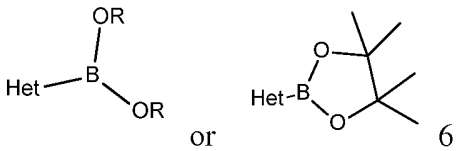
and, if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts, or

b) reacting a compound of formula



5

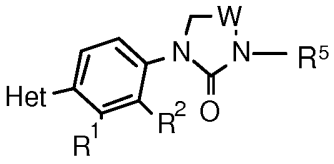
with a compound of formula



6

for R being hydrogen or lower alkyl,

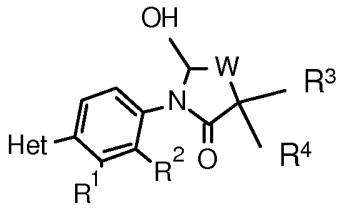
to a compound of formula



Ia

and, if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts, or

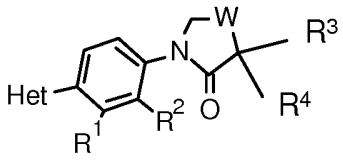
c) reacting a compound of formula



14

with a reducing agent, selected from Et_3SiH

to a compound of formula



Ib

and, if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

11. A compound of formula I according to any one of claims 1 – 9 for use as therapeutically active substances.

12. A compound of formula I according to any one of claims 1- 9 for use in the treatment of schizophrenia, obsessive-compulsive personality disorder, depression, bipolar disorders, anxiety disorders, normal aging, epilepsy, retinal degeneration, traumatic brain injury, spinal cord injury, post-traumatic stress disorder, panic disorder, Parkinson's disease, dementia, Alzheimer's disease, cognitive impairment, chemotherapy-induced cognitive dysfunction, Down syndrome, autism spectrum disorders, hearing loss, tinnitus, spinocerebellar ataxia, amyotrophic lateral sclerosis, multiple sclerosis, Huntington's disease, stroke, radiation therapy, chronic stress, abuse of neuro-active drugs, selected from alcohol, opiates, methamphetamine, phencyclidine and cocaine.

13. A pharmaceutical composition comprising a compound of formula I as claimed in any one of claim 1 – 9 and pharmaceutically acceptable excipients.

14. The use of a compound of formula I according to any one of claims 1 – 9 for the preparation of a medicament for the treatment of schizophrenia, obsessive-compulsive personality disorder, depression, bipolar disorders, anxiety disorders, normal aging, epilepsy, retinal degeneration, traumatic brain injury, spinal cord injury, post-traumatic stress disorder, panic disorder, Parkinson's disease, dementia, Alzheimer's disease, cognitive impairment, chemotherapy-induced cognitive dysfunction, Down syndrome, autism spectrum disorders, hearing loss, tinnitus, spinocerebellar ataxia, amyotrophic lateral sclerosis, multiple sclerosis, Huntington's disease, stroke, radiation therapy, chronic stress, abuse of neuro-active drugs, selected from alcohol, opiates, methamphetamine, phencyclidine and cocaine.

15. A method for the treatment of schizophrenia, obsessive-compulsive personality disorder, depression, bipolar disorders, anxiety disorders, normal aging, epilepsy, retinal degeneration, traumatic brain injury, spinal cord injury, post-traumatic stress disorder, panic disorder, Parkinson's disease, dementia, Alzheimer's disease, cognitive impairment, chemotherapy-induced cognitive dysfunction, Down syndrome, autism spectrum disorders, hearing loss, tinnitus, spinocerebellar ataxia, amyotrophic lateral sclerosis, multiple sclerosis, Huntington's disease, stroke, radiation therapy, chronic stress, abuse of neuro-active drugs, selected from alcohol, opiates, methamphetamine, phencyclidine and cocaine, which method comprises administering an effective amount of a compound of formula I as claimed in any one of claims 1 – 9.

16. The invention as hereinbefore described.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/050521

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/10 A61K31/4155 A61K31/4178 A61K31/422 A61K31/4439
A61K31/513 C07D403/10 C07D413/10 A61P25/00
ADD.
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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 2 455 370 A1 (SHIONOGI & CO [JP]) 23 May 2012 (2012-05-23) Formulae 1, 31-32, (a27), (b6), (c4), (A90), (A91), (C13); page 49, line 10; page 92, lines 16 and 43; claims; compounds 120, 257, 258, 262 -----	1-16
A	WO 2005/090300 A1 (PFIZER PROD INC [US]; BRODNEY MICHAEL AARON [US]; CARON STEPHANE [US];) 29 September 2005 (2005-09-29) Formula (I); claims; examples -----	1-16

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

"E" earlier application or patent 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
23 February 2015	04/03/2015

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	Kirsch, Cécile

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2015/050521

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 2455370 A1	23-05-2012	CN 102482228 A	30-05-2012
		EP 2455370 A1	23-05-2012
		US 2012135997 A1	31-05-2012
		WO 2011007819 A1	20-01-2011
WO 2005090300 A1	29-09-2005	AR 050403 A1	25-10-2006
		AT 533745 T	15-12-2011
		AU 2005223481 A1	29-09-2005
		BR PI0508825 A	14-08-2007
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		CR 8618 A	15-11-2006
		DO P2005000035 A	31-10-2005
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		JP 2007529495 A	25-10-2007
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		NL 1028558 C2	27-06-2006
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		UY 28811 A1	31-10-2005
		WO 2005090300 A1	29-09-2005
		ZA 200607133 A	27-12-2007

(19)中华人民共和国国家知识产权局

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2016.07.05

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WO2015/107053 EN 2015.07.23

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代理人 吴胜周 程金山

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A61K 31/4155(2006.01)
A61K 31/4178(2006.01)
A61K 31/422(2006.01)
A61K 31/4439(2006.01)
A61K 31/513(2006.01)
C07D 403/10(2006.01)
C07D 413/10(2006.01)
A61P 25/00(2006.01)

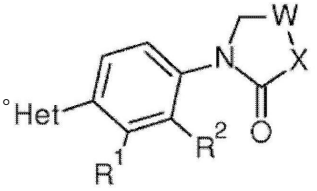
权利要求书7页 说明书44页

(54)发明名称

能够刺激神经发生的N-苯基-内酰胺衍生物及其在神经性病症的治疗中的用途

(57)摘要

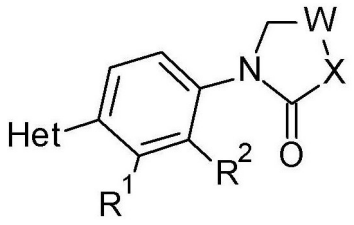
本发明涉及通式I的化合物，其中Het是噁唑-5-基、吡啶-4-基或吡唑-4-基；R^1/R^2彼此独立地是氢、低级烷基、低级烷氧基或卤素；W是-CH_2-或-CH_2CH_2-；X是CR^3R^4或NR^5；R^3是氢或低级烷基；R^4是-$(CH_2)_n$-苯基，其任选地被以下基团取代：卤素、低级烷氧基、被卤素取代的低级烷基、被卤素取代的低级烷氧基或低级烷基；R^5是CHR-苯基或CH2CHR-苯基，其任选地被以下基团取代：卤素、低级烷氧基、被卤素取代的低级烷基、被卤素取代的低级烷氧基或低级烷基，或是CHR-吡啶-2、3或4-基；R是氢或低级烷基；n是0或1；或涉及其药用酸加成盐、外消旋混合物或其相应对映异构体和/或光学异构体。所述化合物可以用于治疗精神分裂症、强迫型人格障碍、抑郁症、双相型精神障碍、焦虑症、正常衰老、癫痫、视网膜变性、创伤性脑损伤、脊髓损伤、创伤后精神紧张性障碍、惊恐症、帕金森病、痴呆、阿尔茨海默病、认知损害、化疗引起的认知功能障碍、唐氏综合征、自闭症谱系障碍、听力损失、耳鸣、脊髓小脑性共济失调、肌萎缩侧索硬化、多发性硬化、亨廷顿病、中风、放射治疗、慢性应激、选自酒精、阿片制剂、去氧麻黄碱、苯环利定和可卡因的神经活性药物的滥用。



I

CN 106061964 A

1.一种式I的化合物



I

其中

Het是噁唑-5-基、吡啶-4-基或吡唑-4-基；

R^1/R^2彼此独立地是氢、低级烷基、低级烷氧基或卤素；

W是$-CH_2-$或$-CH_2CH_2-$；

X是CR^3R^4或NR^5；

R^3是氢或低级烷基；

R^4是$-(CH_2)_n-$苯基，其任选地被以下基团取代：卤素、低级烷氧基、被卤素取代的低级烷基、被卤素取代的低级烷氧基或低级烷基；

R^5是CHR-苯基或CH_2CHR-苯基，其任选地被以下基团取代：卤素、低级烷氧基、被卤素取代的低级烷基、被卤素取代的低级烷氧基或低级烷基，或者是

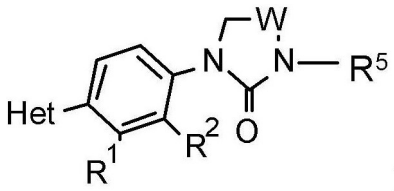
CHR-吡啶-2、3或4-基；

R是氢或低级烷基；

n是0或1；

或其药用酸加成盐、外消旋混合物或其相应对映异构体和/或光学异构体。

2.根据权利要求1的式Ia的化合物，



Ia

其中

Het是噁唑-5-基、吡啶-4-基或吡唑-4-基；

R^1/R^2彼此独立地是氢、低级烷基、低级烷氧基或卤素；

W是$-CH_2-$或$-CH_2CH_2-$；

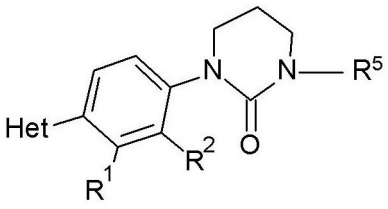
R^5是CHR-苯基或CH_2CHR-苯基，其任选地被以下基团取代：卤素、低级烷氧基、被卤素取代的低级烷基、被卤素取代的低级烷氧基或低级烷基，或者是

CHR-吡啶-2、3或4-基；

R是氢或低级烷基；

或其药用酸加成盐、外消旋混合物或其相应对映异构体和/或光学异构体。

3.根据权利要求2的式Ia-1的化合物，



Ia-1

其中

Het是噁唑-5-基、吡啶-4-基或吡唑-4-基；

R^1/R^2彼此独立地是氢、低级烷基、低级烷氧基或卤素；

R^5是CHR-苯基或CH_2CHR-苯基，其任选地被以下基团取代：卤素、低级烷氧基、被卤素取代的低级烷基、被卤素取代的低级烷氧基或低级烷基，或者是

CHR-吡啶-2、3或4-基；

R是氢或低级烷基；

或其药用酸加成盐、外消旋混合物或其相应对映异构体和/或光学异构体。

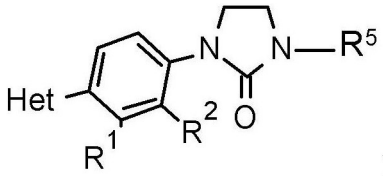
4.根据权利要求2和3中任一项的式Ia-1的化合物，所述化合物是

1-苄基-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]六氢嘧啶-2-酮

1-[(2-氯苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]六氢嘧啶-2-酮或

1-[(3-甲氧基苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]六氢嘧啶-2-酮。

5.根据权利要求2的式Ia-2的化合物，



Ia-2

其中

Het是噁唑-5-基、吡啶-4-基或吡唑-4-基；

R^1/R^2彼此独立地是氢、低级烷基、低级烷氧基或卤素；

R^5是CHR-苯基或CH_2CHR-苯基，其任选地被以下基团取代：卤素、低级烷氧基、被卤素取代的低级烷基、被卤素取代的低级烷氧基或低级烷基，或者是

CHR-吡啶-2、3或4-基；

R是氢或低级烷基；

或其药用酸加成盐、外消旋混合物或其相应对映异构体和/或光学异构体。

6.根据权利要求2和5的式Ia-2的化合物，其中所述化合物是

1-苄基-3-(4-(吡啶-4-基)苯基)咪唑烷-2-酮

1-苄基-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮

1-[(2-氯苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮

1-[(3-甲氧基苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮

1-[(3-氯苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮

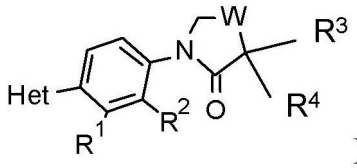
1-[(3-氟苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮

1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-[[3-(三氟甲基)苯基]甲基]咪唑烷-2-酮

1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-[[3-(三氟甲氧基)苯基]甲基]咪唑烷-2-酮

1-[(3-乙氧基苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮
1-[(3-甲氧基苯基)甲基]-3-[4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮
1-[(3-甲氧基苯基)甲基]-3-[3-甲基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮
1-[3-氯-4-(1H-吡唑-4-基)苯基]-3-[(3-甲氧基苯基)甲基]咪唑烷-2-酮
1-[2-氟-4-(1H-吡唑-4-基)苯基]-3-[(3-甲氧基苯基)甲基]咪唑烷-2-酮
1-[3-氟-4-(1H-吡唑-4-基)苯基]-3-[(3-甲氧基苯基)甲基]咪唑烷-2-酮
1-[3-乙氧基-4-(1H-吡唑-4-基)苯基]-3-[(3-甲氧基苯基)甲基]咪唑烷-2-酮
1-[(2-氟苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮
1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-(邻甲苯基甲基)咪唑烷-2-酮
1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-(间甲苯基甲基)咪唑烷-2-酮
1-[(3-甲氧基苯基)甲基]-3-[2-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮
1-[(2-甲氧基苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮
1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-(2-苯基乙基)咪唑烷-2-酮
1-[2-(2-甲氧基苯基)乙基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮
1-[2-(2-氯苯基)乙基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮
1-[2-氯-4-(1H-吡唑-4-基)苯基]-3-[(3-甲氧基苯基)甲基]咪唑烷-2-酮
1-[(4-氟苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮
1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-(3-吡啶基甲基)咪唑烷-2-酮
1-[2-(3-氯苯基)乙基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮
1-[2-(4-氯苯基)乙基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮
1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-(1-苯基丙基)咪唑烷-2-酮
1-[3-甲氧基-4-(4-吡啶基)苯基]-3-[[2-(三氟甲基)苯基]甲基]咪唑烷-2-酮
1-[3-甲氧基-4-(4-吡啶基)苯基]-3-(4-吡啶基甲基)咪唑烷-2-酮
1-[(3-甲氧基苯基)甲基]-3-[4-(1,3-噁唑-5-基)苯基]咪唑烷-2-酮
1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-(4-吡啶基甲基)咪唑烷-2-酮
1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-(2-吡啶基甲基)咪唑烷-2-酮
1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-(2-苯基丙基)咪唑烷-2-酮
1-[3-甲氧基-4-(4-吡啶基)苯基]-3-(间甲苯基甲基)咪唑烷-2-酮
1-[3-甲氧基-4-(4-吡啶基)苯基]-3-(3-吡啶基甲基)咪唑烷-2-酮
1-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]-3-[(2-甲氧基苯基)甲基]咪唑烷-2-酮
1-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]-3-[(3-甲氧基苯基)甲基]咪唑烷-2-酮
1-[(2-氯苯基)甲基]-3-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]咪唑烷-2-酮
1-[(3-氟苯基)甲基]-3-[4-(1,3-噁唑-5-基)苯基]咪唑烷-2-酮
1-[(2-氟苯基)甲基]-3-[4-(1,3-噁唑-5-基)苯基]咪唑烷-2-酮
1-[(2-氟苯基)甲基]-3-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]咪唑烷-2-酮或
1-[(3-氟苯基)甲基]-3-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]咪唑烷-2-酮。

7.根据权利要求1的式Ib的化合物，



Ib

其中

Het是噁唑-5-基、吡啶-4-基或吡唑-4-基；

R^1/R^2彼此独立地是氢、低级烷基、低级烷氧基或卤素；

W是$-CH_2-$或$-CH_2CH_2-$；

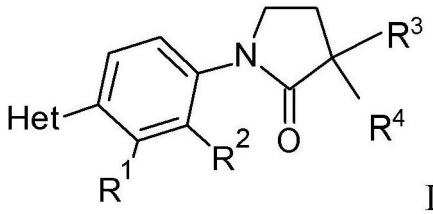
R^3是氢或低级烷基；

R^4是$-(CH_2)_n-$苯基，其任选地被以下基团取代：卤素、低级烷氧基、被卤素取代的低级烷基、被卤素取代的低级烷氧基或低级烷基；

n是0或1；

或其药用酸加成盐、外消旋混合物或其相应对映异构体和/或光学异构体。

8.根据权利要求7的式Ib-1的化合物



Ib-1

其中

Het是噁唑-5-基、吡啶-4-基或吡唑-4-基；

R^1/R^2彼此独立地是氢、低级烷基、低级烷氧基或卤素；

R^3是氢或低级烷基；

R^4是$-(CH_2)_n-$苯基，其任选地被以下基团取代：卤素、低级烷氧基、被卤素取代的低级烷基、被卤素取代的低级烷氧基或低级烷基；

n是0或1；

或其药用酸加成盐、外消旋混合物或其相应对映异构体和/或光学异构体。

9.根据权利要求8的式Ib-1的化合物，所述化合物是

3-乙基-1-(3-甲氧基-4-(噁唑-5-基)苯基)-3-苯基吡咯烷-2-酮

1-(3-甲氧基-4-噁唑-5-基-苯基)-3-(3-甲氧基苯基)吡咯烷-2-酮

3-(2-氯苯基)-1-(3-甲氧基-4-噁唑-5-基-苯基)吡咯烷-2-酮

1-(3-甲氧基-4-噁唑-5-基-苯基)-3-苯基-吡咯烷-2-酮

1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-苯基-吡咯烷-2-酮

3-苯基-1-[4-(1H-吡唑-4-基)苯基]吡咯烷-2-酮

3-(3-甲氧基苯基)-1-[4-(1H-吡唑-4-基)苯基]吡咯烷-2-酮

3-(4-氯苯基)-1-[4-(1H-吡唑-4-基)苯基]吡咯烷-2-酮

3-(4-氟苯基)-1-[4-(1H-吡唑-4-基)苯基]吡咯烷-2-酮

3-(3-氯苯基)-1-[4-(1H-吡唑-4-基)苯基]吡咯烷-2-酮

3-苄基-1-(3-甲氧基-4-(1H-吡唑-4-基)苯基)吡咯烷-2-酮

1-(3-甲氧基-4-(1H-吡唑-4-基)苯基)-3-(3-甲氧基苯基)吡咯烷-2-酮

3-(3-氯苯基)-1-(3-甲氧基-4-(1H-吡唑-4-基)苯基)吡咯烷-2-酮

3-(3-氟苯基)-1-(3-甲氧基-4-(1H-吡唑-4-基)苯基)吡咯烷-2-酮

3-[(3-氯苯基)甲基]-1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]吡咯烷-2-酮

3-[(2-氯苯基)甲基]-1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]吡咯烷-2-酮

3-(3-氯苯基)-1-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]吡咯烷-2-酮

3-[(3-甲氧基苯基)甲基]-1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]吡咯烷-2-酮

1-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]-3-(2-甲氧基苯基)吡咯烷-2-酮

3-(3-甲氧基苯基)-1-[4-(1,3-噁唑-5-基)苯基]吡咯烷-2-酮

1-[4-(1,3-噁唑-5-基)苯基]-3-苯基吡咯烷-2-酮

1-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]-3-[3-(三氟甲基)苯基]吡咯烷-2-酮

3-(2-氟苯基)-1-[4-(1,3-噁唑-5-基)苯基]吡咯烷-2-酮

3-(2-氟苯基)-1-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]吡咯烷-2-酮

3-(3-氟苯基)-1-[4-(1,3-噁唑-5-基)苯基]吡咯烷-2-酮

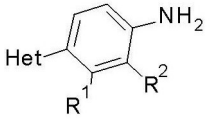
3-(3-氟苯基)-1-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]吡咯烷-2-酮

3-(3-甲氧基苯基)-1-(3-甲氧基-4-吡啶-4-基苯基)吡咯烷-2-酮或

3-(3-甲氧基苯基)-1-(4-吡啶-4-基苯基)吡咯烷-2-酮。

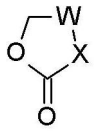
10.一种用于制备权利要求1至9中任一项所定义的式I的化合物的方法,所述方法包括

a)将式1的化合物



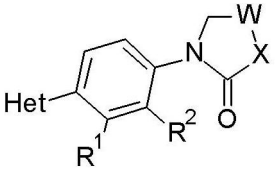
1

与式2的化合物反应



2

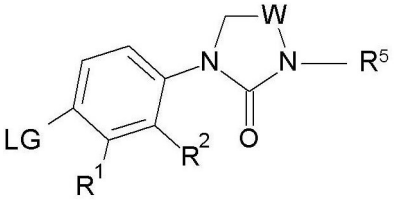
得到式I的化合物



I

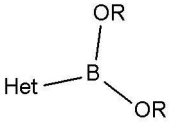
并且,如果需要,将获得的化合物转化为药用酸加成盐,或

b)将式5的化合物

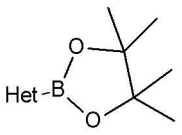


5

与式6的化合物反应



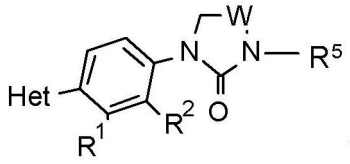
或



6，

其中R为氢或低级烷基，

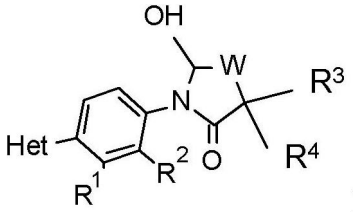
得到式Ia的化合物



Ia

并且，如果需要，将获得的化合物转化为药用酸加成盐，或

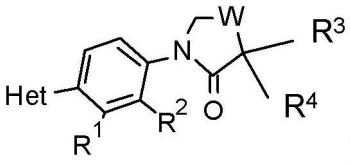
c)将式14的化合物



14

与选自Et_3SiH的还原剂反应

得到式Ib的化合物



Ib

并且，如果需要，将获得的化合物转化为药用酸加成盐。

11.根据权利要求1-9中任一项的式I的化合物，其用作治疗活性物质。

12.根据权利要求1-9中任一项的式I的化合物，其用于治疗精神分裂症、强迫型人格障碍、抑郁症、双相型精神障碍、焦虑症、正常衰老、癫痫、视网膜变性、创伤性脑损伤、脊髓损伤、创伤后精神紧张性障碍、惊恐症、帕金森病、痴呆、阿尔茨海默病、认知损害、化疗引起的认知功能障碍、唐氏综合征、自闭症谱系障碍、听力损失、耳鸣、脊髓小脑性共济失调、肌萎缩侧索硬化、多发性硬化、亨廷顿病、中风、放射治疗、慢性应激、选自酒精、阿片制剂、去氧麻黄碱、苯环利定和可卡因的神经活性药物的滥用。

13.一种药物组合物，所述药物组合物包含如权利要求1-9中任一项所述的式I的化合物和药用赋形剂。

14.根据权利要求1-9中任一项的式I的化合物用于制备药物的用途，所述药物用于治疗精神分裂症、强迫型人格障碍、抑郁症、双相型精神障碍、焦虑症、正常衰老、癫痫、视网膜变性、创伤性脑损伤、脊髓损伤、创伤后精神紧张性障碍、惊恐症、帕金森病、痴呆、阿尔茨海默病、认知损害、化疗引起的认知功能障碍、唐氏综合征、自闭症谱系障碍、听力损失、耳鸣、脊髓小脑性共济失调、肌萎缩侧索硬化、多发性硬化、亨廷顿病、中风、放射治疗、慢性应激、选自酒精、阿片制剂、去氧麻黄碱、苯环利定和可卡因的神经活性药物的滥用。

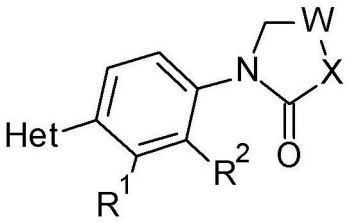
15.一种用于治疗精神分裂症、强迫型人格障碍、抑郁症、双相型精神障碍、焦虑症、正

常衰老、癫痫、视网膜变性、创伤性脑损伤、脊髓损伤、创伤后精神紧张性障碍、惊恐症、帕金森病、痴呆、阿尔茨海默病、认知损害、化疗引起的认知功能障碍、唐氏综合征、自闭症谱系障碍、听力损失、耳鸣、脊髓小脑性共济失调、肌萎缩侧索硬化、多发性硬化、亨廷顿病、中风、放射治疗、慢性应激、选自酒精、阿片制剂、去氧麻黄碱、苯环利定和可卡因的神经活性药物的滥用的方法，所述方法包括施用有效量的如权利要求1-9中任一项所述的式I的化合物。

16.如上所述的本发明。

能够刺激神经发生的N-苯基-内酰胺衍生物及其在神经性病症的治疗中的用途

[0001] 本发明涉及通式I的化合物

[0002] 

I

[0003] 其中

[0004] Het是噁唑-5-基、吡啶-4-基或吡唑-4-基；

[0005] R^1/R^2彼此独立地是氢、低级烷基、低级烷氧基或卤素；

[0006] W是$-CH_2-$或$-CH_2CH_2-$；

[0007] X是CR^3R^4或NR^5；

[0008] R^3是氢或低级烷基；

[0009] R^4是$-(CH_2)_n-$苯基，其任选地被以下基团取代：卤素、低级烷氧基、被卤素取代的低级烷基、被卤素取代的低级烷氧基或低级烷基；

[0010] R^5是CHR-苯基或CH_2CHR-苯基，其任选地被以下基团取代：卤素、低级烷氧基、被卤素取代的低级烷基、被卤素或低级烷基取代的低级烷氧基，或是

[0011] CHR-吡啶-2、3或4-基；

[0012] R是氢或低级烷基；

[0013] n是0或1；

[0014] 或其药用酸加成盐、外消旋混合物或其相应对映异构体和/或光学异构体。

[0015] 现在已经显示，本发明的化合物刺激从神经干细胞(NSC)的神经发生。神经发生在发育过程中和成人脑中发生。概念上，该神经发生过程可以分为四个步骤：(i)NSC的增殖；(ii)NSC的神经元命运决定；(iii)新的神经元的存活和成熟；和(iv)新神经元功能性整合入神经元网络。

[0016] 成人神经发生是整个生命中成人脑中发生的发育过程，借此，新的功能神经元从成人神经干细胞产生。在生理条件下组成型成人神经发生主要发生在两个“神经源性的”脑区域，1)海马齿状回中的亚颗粒区(SGZ)，在那里产生新的齿状颗粒细胞，2)侧脑室的亚脑室区(SVZ)，在那里新的神经元产生并且随后通过嘴侧迁移流(RMS)迁移至嗅球，从而成为中间神经元。

[0017] 广泛的证据提示，海马的成人神经发生在认知和情绪状态中发挥重要作用，尽管精确的功能仍然难以描述。已经主张，相对小量的新生颗粒神经元可以影响整个脑功能，因为它们使齿状回内的很多中间神经元受神经支配，其每个抑制数百个成熟颗粒细胞，导致神经发生依赖性的反馈抑制。与低激发阈值联合，所述新生神经元针对环境中非常细微的变化引发响应。该过程中的失调可以在行为上表明与精神疾病相关的模式分离上的短缺。例如，成人海马的神经发生与认知和情感能力相关，例如，体育锻炼，暴露于丰富的外界环

境和典型的抗抑郁药并发地促进成人海马神经发生和认知和/或情绪状态,同时慢性应激(chronic stress),抑郁症,睡眠剥夺和衰老减少成人神经发生并且与负面的认知和/或情绪状态相关(Neuron 70,2011年5月26日,pp 582-588和pp 687-702;WO 2008/046072)。令人关注的是,抗抑郁药促进海马成人神经发生并且其对某些行为的影响需要刺激神经发生。通常相信,在其它成人CNS区域中的神经发生在正常生理条件下是非常有限的,但在损伤诸如中风(stroke),和中枢和外周脑损伤之后可以被诱导。

[0018] 因此,据信,成人神经发生的刺激代表了用于正常衰老、尤其是用于多种神经变性疾病和神经精神疾病的神经再生治疗靶点,所述神经变性疾病和神经精神疾病包括精神分裂症(schizophrenia),强迫型人格障碍(obsessive-compulsive personality disorder),重度抑郁症(major depression),双相型精神障碍(bipolar disorders),焦虑症(anxiety disorders),癫痫(epilepsy),视网膜变性(retinal degeneration),创伤性脑损伤(traumatic brain injury),脊髓损伤(spinal cord injury),创伤后精神紧张性障碍(post-traumatic stress disorder),惊恐症(panic disorder),帕金森病(Parkinson's disease),痴呆(dementia),阿尔茨海默病(Alzheimer's disease),轻度认知损害(mild cognitive impairment),化疗引起的认知功能障碍(chemotherapy-induced cognitive dysfunction)("化疗后大脑(chemobrain)"),唐氏综合征(Down syndrome),自闭症谱系障碍(autism spectrum disorders),听力损失(hearing loss)(Neuroscience,167(2010)1216-1226;Nature Medicine,第11卷,第3期,(2005),271-276)耳鸣(tinnitus),脊髓小脑性共济失调(spinocerebellar ataxia),肌萎缩侧索硬化(amyotrophic lateral sclerosis),多发性硬化(multiple sclerosis),亨廷顿病(Huntington's disease),中风(stroke),和由放射治疗(radiation therapy),慢性应激(chronic stress),或神经活性药物如酒精、阿片制剂、去氧麻黄碱、苯环利定和可卡因的滥用导致的失调(US 2012/0022096)。

[0019] 成人神经发生的刺激也代表用于以下治疗靶点:视神经病变(S.Isenmann,A.Kretz,A.Cellerino,Progress in Retinal and Eye Research,22,(2003)483)和黄斑变性(G.Landa,O.Butovsky,J.Shoshani,M.Schwartz,A.Pollack,Current Eye Research 33,(2008)1011)。

[0020] 因此,化学刺激成人神经发生提供新的再生手段和机会,以开发用于治疗神经系统疾病和神经精神障碍的新药。

[0021] 因此,本发明的目的是鉴定调节神经发生的化合物。已经发现,式I的化合物在该区域有活性并且它们可以因此用于治疗精神分裂症(schizophrenia)、强迫型人格障碍(obsessive-compulsive personality disorder)、抑郁症(depression)、双相型精神障碍(bipolar disorders)、焦虑症(anxiety disorders)、正常衰老、癫痫(epilepsy)、视网膜变性(retinal degeneration)、创伤性脑损伤(traumatic brain injury)、脊髓损伤(spinal cord injury)、创伤后精神紧张性障碍(post-traumatic stress disorder)、惊恐症(panic disorder)、帕金森病(Parkinson's disease)、痴呆(dementia)、阿尔茨海默病(Alzheimer's disease)、轻度认知损害(mild cognitive impairment)、化疗引起的认知功能障碍(chemotherapy-induced cognitive dysfunction)("chemobrain (化疗后大脑)")、唐氏综合征(Down syndrome)、自闭症谱系障碍(autism spectrum disorders)、听

力损失(hearing loss)、耳鸣(tinnitus)、脊髓小脑性共济失调(spinocerebellar ataxia)、肌萎缩侧索硬化(amyotrophic lateral sclerosis)、多发性硬化(multiple sclerosis)、亨廷顿病(Huntington's disease)、中风(stroke)和由放射治疗(radiation therapy)、慢性应激(chronic stress)、视神经病变(optic neuropathy)或黄斑变性(macular degeneration)或神经活性药物如酒精、阿片制剂、去氧麻黄碱、苯环利定或可卡因的滥用导致的失调。

[0022] 式I的化合物的最优选的适应症是阿尔茨海默病(Alzheimer's disease),抑郁症(depression),焦虑症(anxiety disorders)和中风(stroke)。

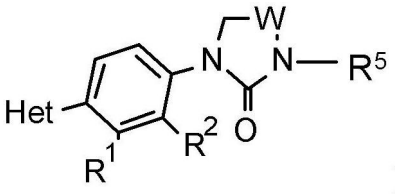
[0023] 本发明涉及式I的化合物和它们的药用盐,条件是其应用于对映异构体或非对映异构体的混合物或它们的对映异构纯或对映异构纯形式,涉及作为药学活性物质的这些化合物,涉及它们的制造方法,以及涉及在治疗或预防与以下各项相关的病症中的用途:神经发生、精神分裂症、强迫型人格障碍、抑郁症、双相型精神障碍、焦虑症、正常衰老、癫痫、视网膜变性、创伤性脑损伤、脊髓损伤、创伤后精神紧张性障碍、惊恐症、帕金森病、痴呆、阿尔茨海默病、轻度认知损害、化疗引起的认知功能障碍(″化疗后大脑″)、唐氏综合征、自闭症谱系障碍、听力损失、耳鸣、脊髓小脑性共济失调、肌萎缩侧索硬化、多发性硬化、亨廷顿病、中风、由放射治疗、慢性应激、视神经病变或黄斑变性、选自酒精、阿片制剂、去氧麻黄碱、苯环利定或可卡因的神经活性药物的滥用导致的失调。

[0024] 本发明的另一个目的是包含式I的化合物的药物组合物。

[0025] 本发明的另一个目的是式I的化合物用于制备药物的用途,所述药物用于治疗性和/或预防性治疗上述疾病。

[0026] 本发明的另一个目的是一种用于治疗精神分裂症、强迫型人格障碍、重度抑郁症、双相型精神障碍、焦虑症、正常衰老、癫痫、视网膜变性、创伤性脑损伤、脊髓损伤、创伤后精神紧张性障碍、惊恐症、帕金森病、痴呆、阿尔茨海默病、认知损害、化疗引起的认知功能障碍、唐氏综合征、自闭症谱系障碍、听力损失、耳鸣、脊髓小脑性共济失调、肌萎缩侧索硬化、多发性硬化、亨廷顿病、中风、放射治疗、慢性应激、神经活性药物如酒精、阿片制剂、去氧麻黄碱、苯环利定和可卡因的滥用的方法,所述方法包括施用有效量的式I的化合物。

[0027] 本发明的一个实施方案是式Ia的化合物

[0028] 

Ia

[0029] 其中

[0030] Het是噁唑-5-基、吡啶-4-基或吡唑-4-基;

[0031] R^1/R^2彼此独立地是氢、低级烷基、低级烷氧基或卤素;

[0032] W是$-CH_2-$或$-CH_2CH_2-$;

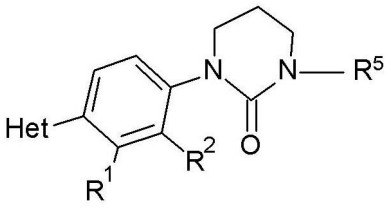
[0033] R^5是CHR-苯基或CH_2CHR-苯基,其任选地被以下基团取代:卤素、低级烷氧基、被卤素取代的低级烷基、被卤素取代的低级烷氧基或低级烷基,或是

[0034] CHR-吡啶-2、3或4-基;

[0035] R是氢或低级烷基；

[0036] 或其药用酸加成盐、外消旋混合物或其相应对映异构体和/或光学异构体。

[0037] 本发明的一个实施方案进一步是式Ia-1的化合物，

[0038] 

Ia-1

[0039] 其中

[0040] Het是噁唑-5-基、吡啶-4-基或吡唑-4-基；

[0041] R^1/R^2彼此独立地是氢、低级烷基、低级烷氧基或卤素；

[0042] R^5是CHR-苯基或CH_2CHR-苯基，其任选地被以下基团取代：卤素、低级烷氧基、被卤素取代的低级烷基、被卤素取代的低级烷氧基或低级烷基，或是

[0043] CHR-吡啶-2、3或4-基；

[0044] R是氢或低级烷基；

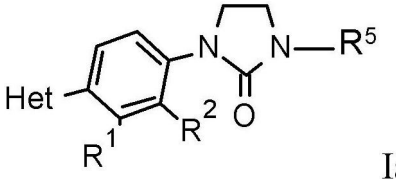
[0045] 或其药用酸加成盐、外消旋混合物或其相应对映异构体和/或光学异构体，例如以下化合物

[0046] 1-苄基-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]六氢嘧啶-2-酮

[0047] 1-[(2-氯苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]六氢嘧啶-2-酮或

[0048] 1-[(3-甲氧基苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]六氢嘧啶-2-酮。

[0049] 本发明的一个目的进一步是式Ia-2的化合物，

[0050] 

Ia-2

[0051] 其中

[0052] Het是噁唑-5-基、吡啶-4-基或吡唑-4-基；

[0053] R^1/R^2彼此独立地是氢、低级烷基、低级烷氧基或卤素；

[0054] R^5是CHR-苯基或CH_2CHR-苯基，其任选地被以下基团取代：卤素、低级烷氧基、被卤素取代的低级烷基、被卤素取代的低级烷氧基或低级烷基，或是

[0055] CHR-吡啶-2、3或4-基；

[0056] R是氢或低级烷基；

[0057] 或其药用酸加成盐、外消旋混合物或其相应对映异构体和/或光学异构体，例如以下化合物

[0058] 1-苄基-3-(4-(吡啶-4-基)苯基)咪唑烷-2-酮

[0059] 1-苄基-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮

[0060] 1-[(2-氯苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮

[0061] 1-[(3-甲氧基苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮

[0062] 1-[(3-氯苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮

[0063] 1-[(3-氟苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮

[0064] 1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-[[3-(三氟甲基)苯基]甲基]咪唑烷-2-酮

[0065] 1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-[[3-(三氟甲氧基)苯基]甲基]咪唑烷-2-酮

[0066] 1-[(3-乙氧基苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮

[0067] 1-[(3-甲氧基苯基)甲基]-3-[4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮

[0068] 1-[(3-甲氧基苯基)甲基]-3-[3-甲基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮

[0069] 1-[3-氯-4-(1H-吡唑-4-基)苯基]-3-[(3-甲氧基苯基)甲基]咪唑烷-2-酮

[0070] 1-[2-氟-4-(1H-吡唑-4-基)苯基]-3-[(3-甲氧基苯基)甲基]咪唑烷-2-酮

[0071] 1-[3-氟-4-(1H-吡唑-4-基)苯基]-3-[(3-甲氧基苯基)甲基]咪唑烷-2-酮

[0072] 1-[3-乙氧基-4-(1H-吡唑-4-基)苯基]-3-[(3-甲氧基苯基)甲基]咪唑烷-2-酮

[0073] 1-[(2-氟苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮

[0074] 1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-(邻甲苯基甲基)咪唑烷-2-酮

[0075] 1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-(间甲苯基甲基)咪唑烷-2-酮

[0076] 1-[(3-甲氧基苯基)甲基]-3-[2-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮

[0077] 1-[(2-甲氧基苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮

[0078] 1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-(2-苯基乙基)咪唑烷-2-酮

[0079] 1-[2-(2-甲氧基苯基)乙基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮

[0080] 1-[2-(2-氯苯基)乙基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮

[0081] 1-[2-氯-4-(1H-吡唑-4-基)苯基]-3-[(3-甲氧基苯基)甲基]咪唑烷-2-酮

[0082] 1-[(4-氟苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮

[0083] 1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-(3-吡啶基甲基)咪唑烷-2-酮

[0084] 1-[2-(3-氯苯基)乙基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮

[0085] 1-[2-(4-氯苯基)乙基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮

[0086] 1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-(1-苯基丙基)咪唑烷-2-酮

[0087] 1-[3-甲氧基-4-(4-吡啶基)苯基]-3-[[2-(三氟甲基)苯基]甲基]咪唑烷-2-酮

[0088] 1-[3-甲氧基-4-(4-吡啶基)苯基]-3-(4-吡啶基甲基)咪唑烷-2-酮

[0089] 1-[(3-甲氧基苯基)甲基]-3-[4-(1,3-噁唑-5-基)苯基]咪唑烷-2-酮

[0090] 1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-(4-吡啶基甲基)咪唑烷-2-酮

[0091] 1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-(2-吡啶基甲基)咪唑烷-2-酮

[0092] 1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-(2-苯基丙基)咪唑烷-2-酮

[0093] 1-[3-甲氧基-4-(4-吡啶基)苯基]-3-(间甲苯基甲基)咪唑烷-2-酮

[0094] 1-[3-甲氧基-4-(4-吡啶基)苯基]-3-(3-吡啶基甲基)咪唑烷-2-酮

[0095] 1-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]-3-[(2-甲氧基苯基)甲基]咪唑烷-2-酮

[0096] 1-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]-3-[(3-甲氧基苯基)甲基]咪唑烷-2-酮

[0097] 1-[(2-氯苯基)甲基]-3-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]咪唑烷-2-酮

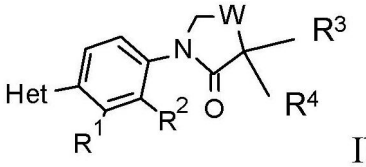
[0098] 1-[(3-氟苯基)甲基]-3-[4-(1,3-噁唑-5-基)苯基]咪唑烷-2-酮

[0099] 1-[(2-氟苯基)甲基]-3-[4-(1,3-噁唑-5-基)苯基]咪唑烷-2-酮

[0100] 1-[(2-氟苯基)甲基]-3-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]咪唑烷-2-酮或

[0101] 1-[(3-氟苯基)甲基]-3-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]咪唑烷-2-酮。

[0102] 本发明的另一个目的是式Ib的化合物。

[0103] 

Ib

[0104] 其中

[0105] Het是噁唑-5-基、吡啶-4-基或吡唑-4-基；

[0106] R^1/R^2彼此独立地是氢、低级烷基、低级烷氧基或卤素；

[0107] W是$-CH_2-$或$-CH_2CH_2-$；

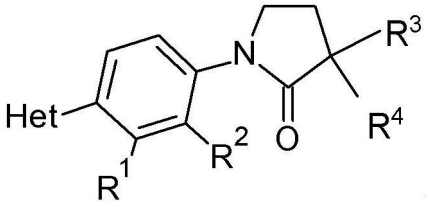
[0108] R^3是氢或低级烷基；

[0109] R^4是$-(CH_2)_n-$苯基，其任选地被以下基团取代：卤素、低级烷氧基、被卤素取代的低级烷基、被卤素取代的低级烷氧基或低级烷基；

[0110] n是0或1；

[0111] 或其药用酸加成盐、外消旋混合物或其相应对映异构体和/或光学异构体。

[0112] 本发明的另一个目的是式Ib-1的化合物

[0113] 

Ib-1

[0114] 其中

[0115] Het是噁唑-5-基、吡啶-4-基或吡唑-4-基；

[0116] R^1/R^2彼此独立地是氢、低级烷基、低级烷氧基或卤素；

[0117] R^3是氢或低级烷基；

[0118] R^4是$-(CH_2)_n-$苯基，其任选地被以下基团取代：卤素、低级烷氧基、被卤素取代的低级烷基、被卤素取代的低级烷氧基或低级烷基；

[0119] n是0或1；

[0120] 或其药用酸加成盐、外消旋混合物或其相应对映异构体和/或光学异构体，例如以下化合物

[0121] 3-乙基-1-(3-甲氧基-4-(噁唑-5-基)苯基)-3-苯基吡咯烷-2-酮

[0122] 1-(3-甲氧基-4-噁唑-5-基-苯基)-3-(3-甲氧基苯基)吡咯烷-2-酮

[0123] 3-(2-氯苯基)-1-(3-甲氧基-4-噁唑-5-基-苯基)吡咯烷-2-酮

[0124] 1-(3-甲氧基-4-噁唑-5-基-苯基)-3-苯基-吡咯烷-2-酮

[0125] 1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-苯基-吡咯烷-2-酮

[0126] 3-苯基-1-[4-(1H-吡唑-4-基)苯基]吡咯烷-2-酮

[0127] 3-(3-甲氧基苯基)-1-[4-(1H-吡唑-4-基)苯基]吡咯烷-2-酮

[0128] 3-(4-氯苯基)-1-[4-(1H-吡唑-4-基)苯基]吡咯烷-2-酮

[0129] 3-(4-氟苯基)-1-[4-(1H-吡唑-4-基)苯基]吡咯烷-2-酮

[0130] 3-(3-氯苯基)-1-[4-(1H-吡唑-4-基)苯基]吡咯烷-2-酮

[0131] 3-苄基-1-(3-甲氧基-4-(1H-吡唑-4-基)苯基)吡咯烷-2-酮

[0132] 1-(3-甲氧基-4-(1H-吡唑-4-基)苯基)-3-(3-甲氧基苯基)吡咯烷-2-酮

[0133] 3-(3-氯苯基)-1-(3-甲氧基-4-(1H-吡唑-4-基)苯基)吡咯烷-2-酮

[0134] 3-(3-氟苯基)-1-(3-甲氧基-4-(1H-吡唑-4-基)苯基)吡咯烷-2-酮

[0135] 3-[(3-氯苯基)甲基]-1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]吡咯烷-2-酮

[0136] 3-[(2-氯苯基)甲基]-1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]吡咯烷-2-酮

[0137] 3-(3-氯苯基)-1-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]吡咯烷-2-酮

[0138] 3-[(3-甲氧基苯基)甲基]-1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]吡咯烷-2-酮

[0139] 1-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]-3-(2-甲氧基苯基)吡咯烷-2-酮

[0140] 3-(3-甲氧基苯基)-1-[4-(1,3-噁唑-5-基)苯基]吡咯烷-2-酮

[0141] 1-[4-(1,3-噁唑-5-基)苯基]-3-苯基吡咯烷-2-酮

[0142] 1-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]-3-[3-(三氟甲基)苯基]吡咯烷-2-酮

[0143] 3-(2-氟苯基)-1-[4-(1,3-噁唑-5-基)苯基]吡咯烷-2-酮

[0144] 3-(2-氟苯基)-1-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]吡咯烷-2-酮

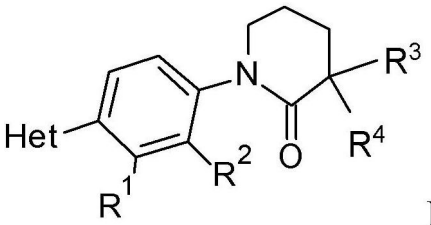
[0145] 3-(3-氟苯基)-1-[4-(1,3-噁唑-5-基)苯基]吡咯烷-2-酮

[0146] 3-(3-氟苯基)-1-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]吡咯烷-2-酮

[0147] 3-(3-甲氧基苯基)-1-(3-甲氧基-4-吡啶-4-基苯基)吡咯烷-2-酮或

[0148] 3-(3-甲氧基苯基)-1-(4-吡啶-4-基苯基)吡咯烷-2-酮。

[0149] 本发明的另一个目的是式Ib-2的化合物

[0150] 

Ib-2

[0151] 其中

[0152] Het是噁唑-5-基、吡啶-4-基或吡唑-4-基；

[0153] R^1/R^2彼此独立地是氢、低级烷基、低级烷氧基或卤素；

[0154] R^3是氢或低级烷基；

[0155] R^4是-$(CH_2)_n$-苯基，其任选地被以下基团取代：卤素、低级烷氧基、被卤素取代的低级烷基、被卤素取代的低级烷氧基或低级烷基；

[0156] n是0或1；

[0157] 或其药用酸加成盐、外消旋混合物或其相应对映异构体和/或光学异构体。

[0158] 不论讨论的术语单独或组合出现，以下用于本说明书的通用术语的定义都适用。

[0159] 如本文使用的，术语“低级烷基”表示包括具有1-7个碳原子的直链或支链碳链的饱和的，即脂族的烃基团。“烷基”的实例是甲基、乙基、正丙基和异丙基。

[0160] 术语“烷氧基”表示基团-O-R’，其中R’是如上所定义的低级烷基。

[0161] 术语“被卤素取代的低级烷基”表示如上所定义的低级烷基基团，其中至少一个氢原子被卤素原子替代。优选的基团是CF_3。

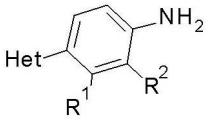
[0162] 术语“被卤素取代的低级烷氧基”表示如上所定义的低级烷氧基，其中至少一个氢原子被卤素原子替代。优选的基团是OCF_3。

[0163] 术语“卤素”表示氯、溴、氟或碘。

[0164] 式I的化合物可以根据下文的方法步骤并且根据方案1-7制备。

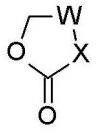
[0165] 本发明的新的式I化合物及其药用盐可以通过本领域中已知的方法制备，例如，通过下文描述的方法制备，所述方法包括

[0166] a)将式1的化合物

[0167] 

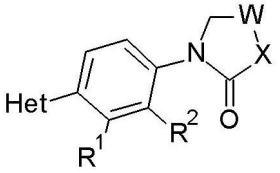
1

[0168] 与式2的化合物反应

[0169] 

2

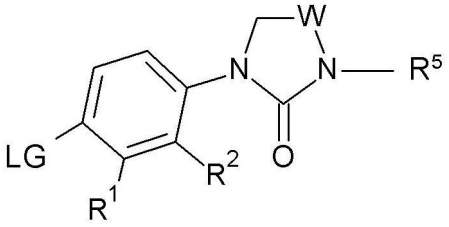
[0170] 得到式I的化合物

[0171] 

I

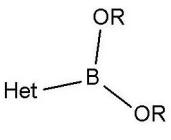
[0172] 并且，如果需要，将获得的化合物转化为药用酸加成盐，或

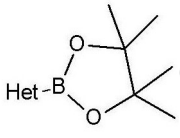
[0173] b)将式5的化合物

[0174] 

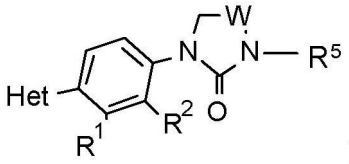
5

[0175] 与式6的化合物反应

[0176] 

或 

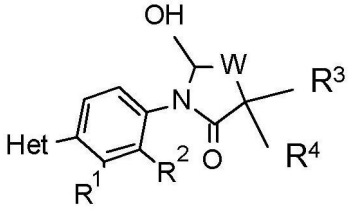
6，其中R是氢或低级烷基，得到式Ia的化合物

[0177] 

Ia

[0178] 并且,如果需要,将获得的化合物转化为药用酸加成盐,或

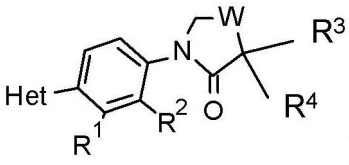
[0179] c)将式14的化合物

[0180] 

14

[0181] 与选自Et_3SiH的还原剂反应

[0182] 得到式Ib的化合物

[0183] 

Ib

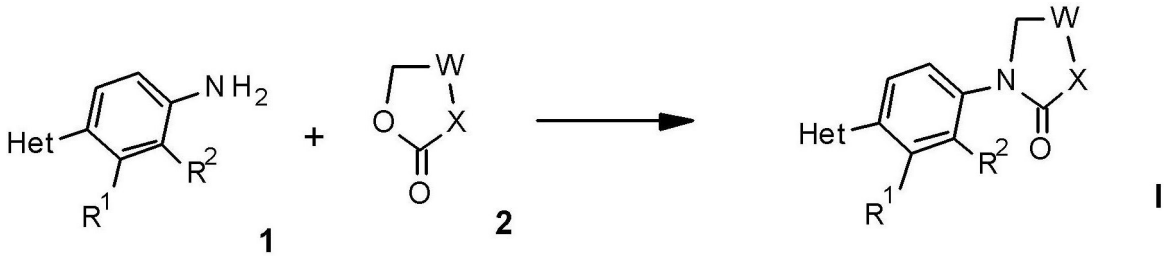
[0184] 并且,如果需要,将获得的化合物转化为药用酸加成盐。

[0185] 取代基的定义如上文所述。

[0186] 本发明式I的化合物的制备可以以顺序或会聚的合成途径进行。本发明化合物的合成显示在以下方案1中。进行所述反应和纯化产生的产物的技术对于本领域技术人员已知。除非有相反说明,以下方法描述中使用的取代基和标记具有上文中给出的意义。

[0187] 更详细地,可以通过下文给出的方法,通过实施例中给出的方法或通过类似方法制造式I的化合物。各个反应步骤的适当反应条件是本领域技术人员已知的。反应顺序不限于方案1中显示的顺序,而是依赖于起始材料和其相应反应性,反应步骤的顺序可以随意改变。起始材料是可商购的或可以通过与下文给出的方法类似的方法,通过说明书引用的参考文献中或实施例中描述的方法,或通过本领域已知的方法制备。

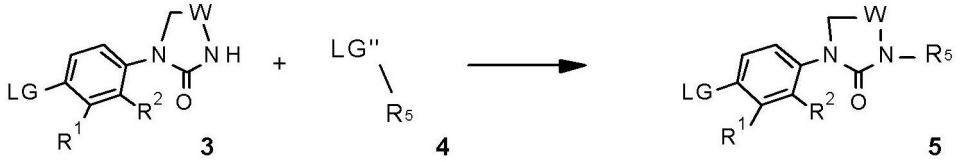
[0188] 方案1

[0189] 

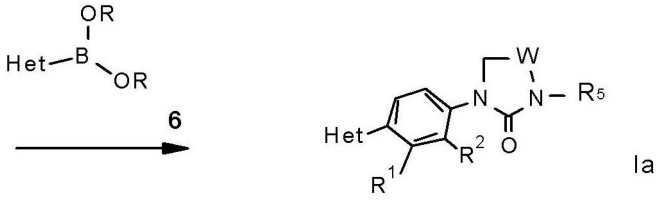
1 2 I

[0190] 根据方案1,通过将芳族胺1与内酯2反应可以制备式I的化合物。胺1可以用合适的碱如三甲基铝处理,用于增加的反应性。合适的起始材料1和2可商购获得或可以通过本领域中已知的方法制备。

[0191] 方案2



[0192]

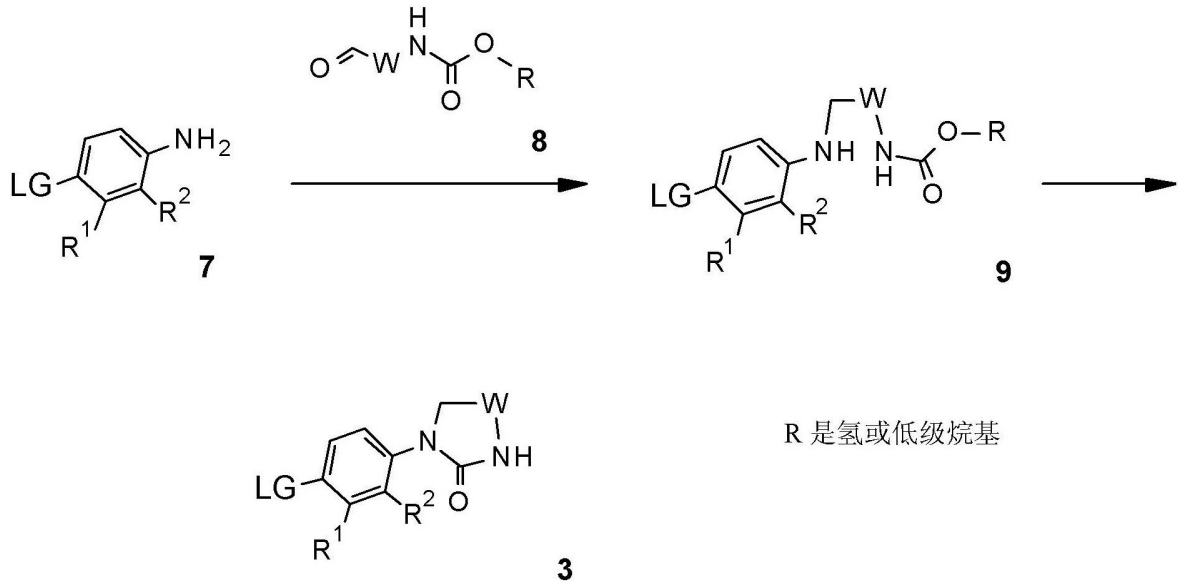


R 是氢或低级烷基

[0193] 式Ia的化合物可以根据方案2制备。其中LG是合适的离去基团如Br的芳基咪唑3，首先与合适的碱如氢化钠反应，然后与其中LG”是合适的离去基团如Br的化合物4反应。然后在合适的催化剂如四(三苯基膦)钯和合适的碱如碳酸钠的存在下，将得到的化合物5与硼酸或硼酸酯6反应，得到化合物Ia。芳基咪唑3可商购获得，可以通过本领域中已知的方法制备，或可以根据方案3制备。

[0194] 方案3

[0195]

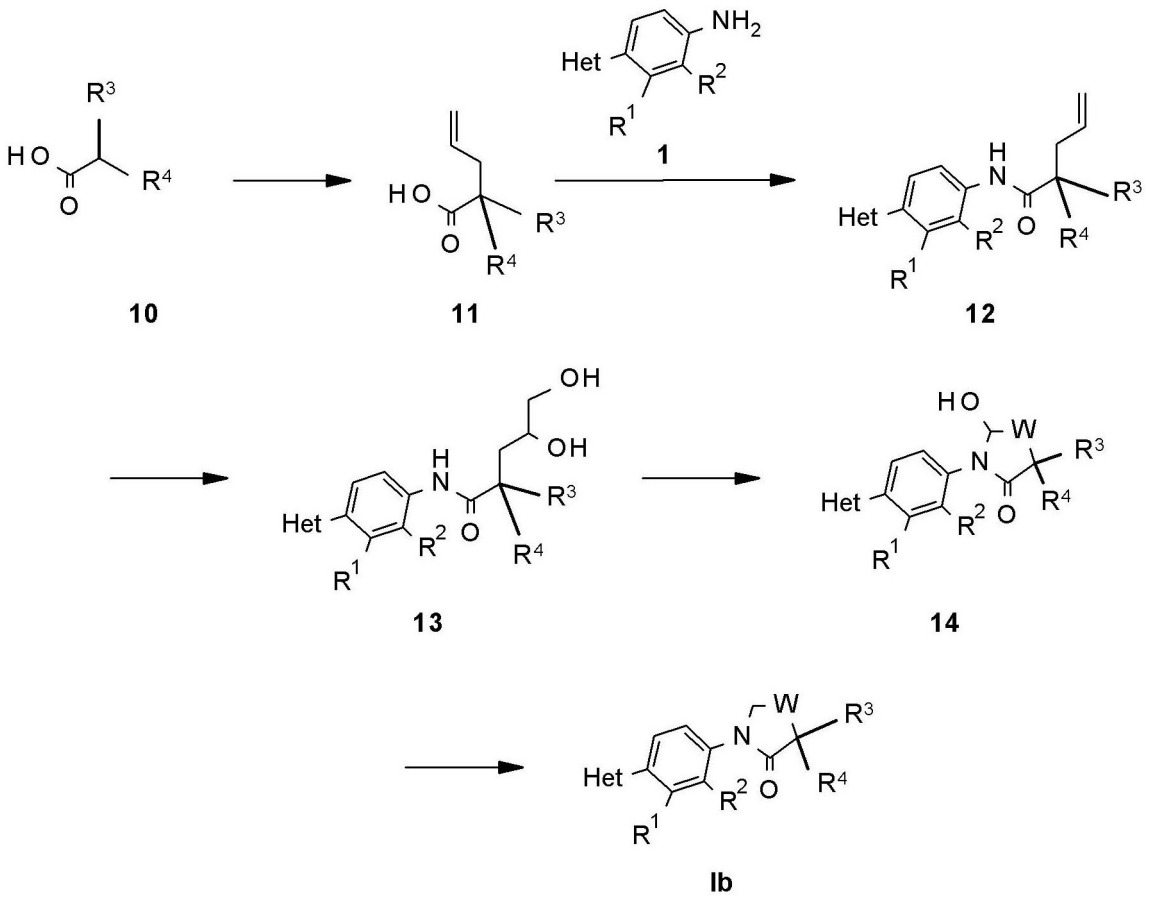


R 是氢或低级烷基

[0196] 式3的化合物可以根据方案3制备：在称为还原胺化的方法中，将其中LG是合适的离去基团如Br的芳基胺7，与烷氧基羰基氨基醛8和还原剂如$NaBH(OAc)_3/AcOH$反应，得到9。可以通过用合适的碱如KOtBu处理来将化合物9转化为3。

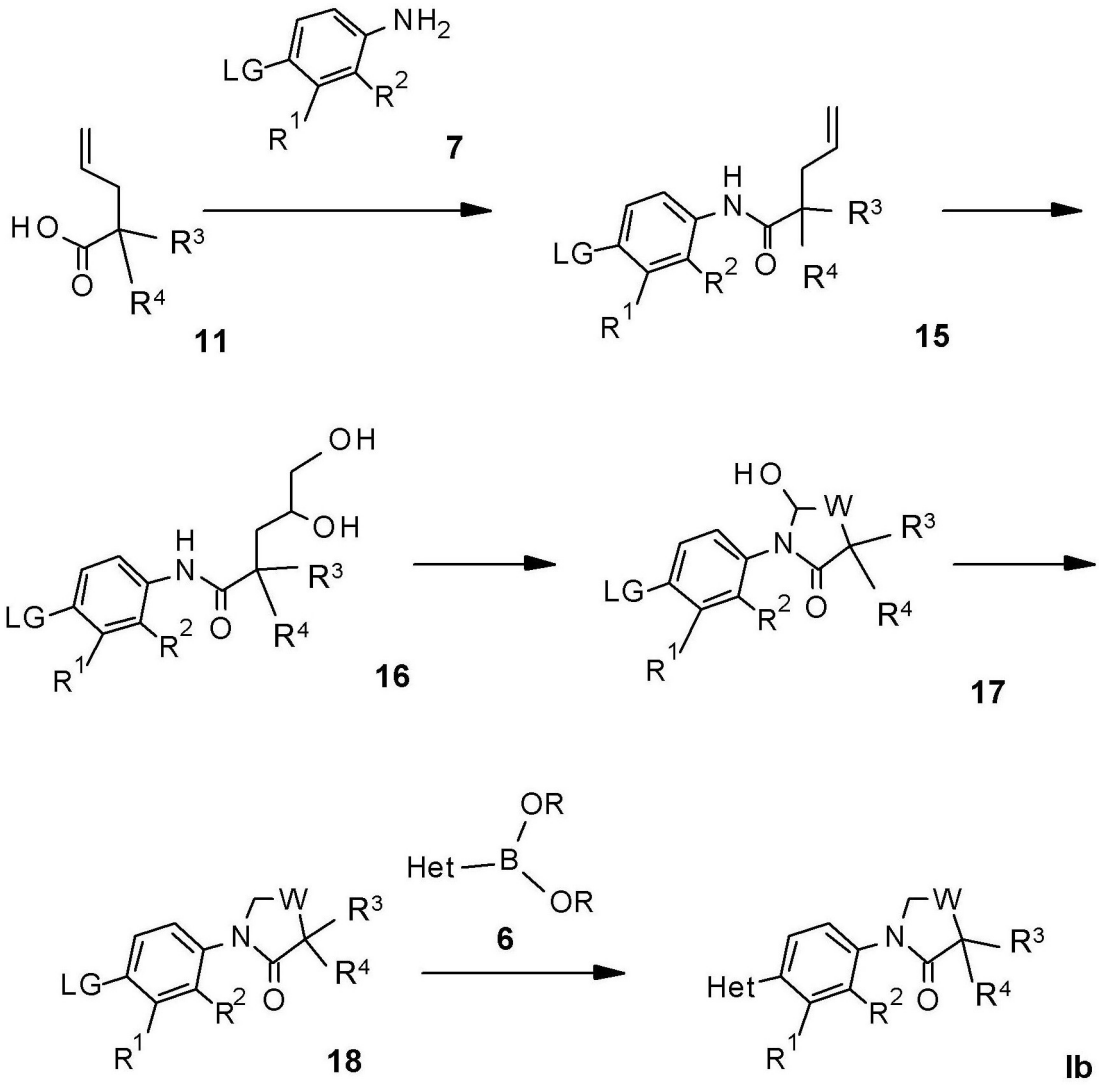
[0197] 方案4

[0198]



[0199] 式Ib的化合物可以根据方案4制备。将芳基乙酸10用合适的碱如LiHMDS处理，并且随后用烯丙基碘处理，得到11。将酸11用活化剂如PyBOP处理，并用芳族胺1转化为12。然后化合物12通过合适的氧化剂如NMO、OsO_4和$NaIO_4$氧化，可能经由二醇中间体13，得到14。然后将化合物14用合适的还原剂，如Et_3SiH还原为化合物Ib。

[0200] 方案5

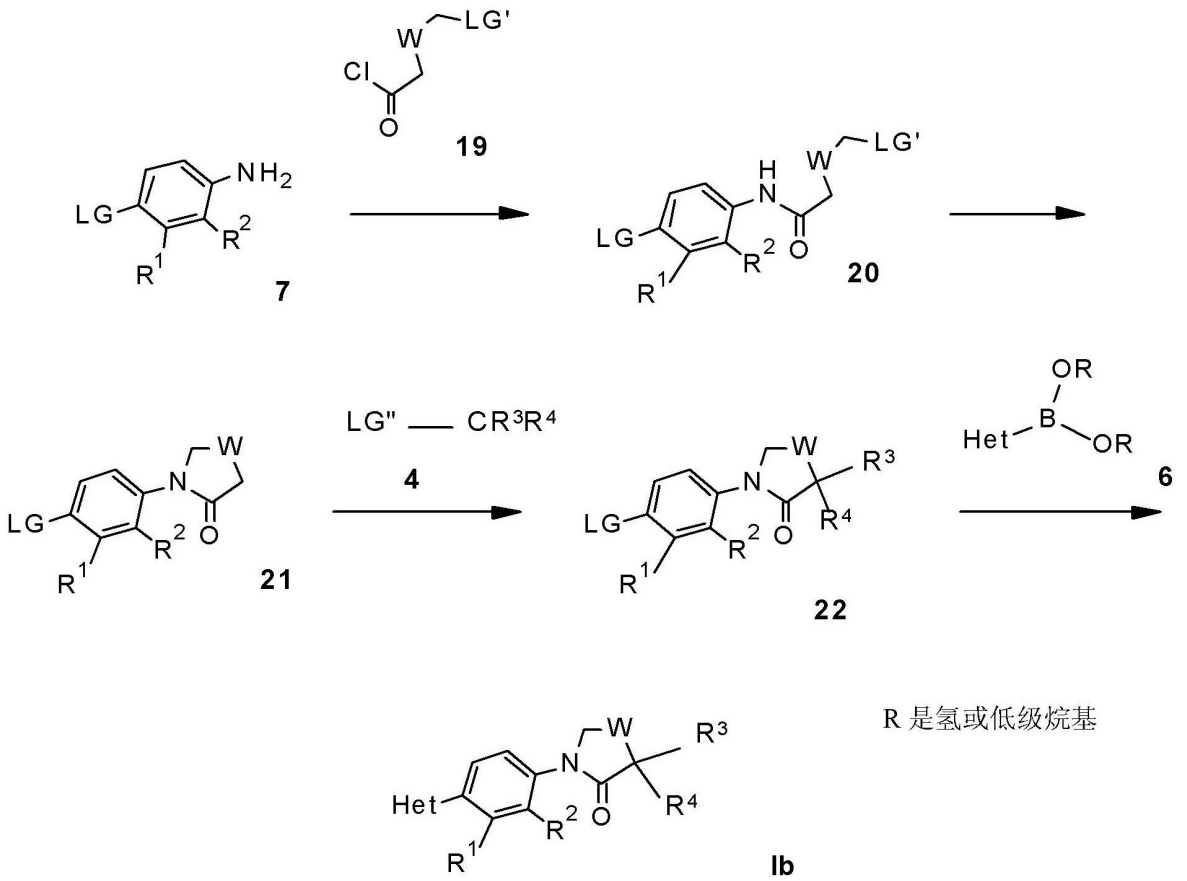
[0201] 

R 是氢或低级烷基

[0202] 备选地，式Ib的化合物可以根据方案5制备。将烯丙基芳基乙酸11用活化剂如PyBOP处理，并用其中LG是合适的离去基团如Br的芳族胺7转化为15。与方案4类似，然后化合物15通过合适的氧化剂如NMO、OsO_4和$NaIO_4$氧化，可能经二醇中间体16，得到17。然后用合适的还原剂如Et_3SiH将化合物17还原为化合物18。然后在合适的催化剂如四(三苯基膦)钯和合适的碱如碳酸钠的存在下，将化合物18与硼酸或硼酸酯6反应，得到化合物Ib。

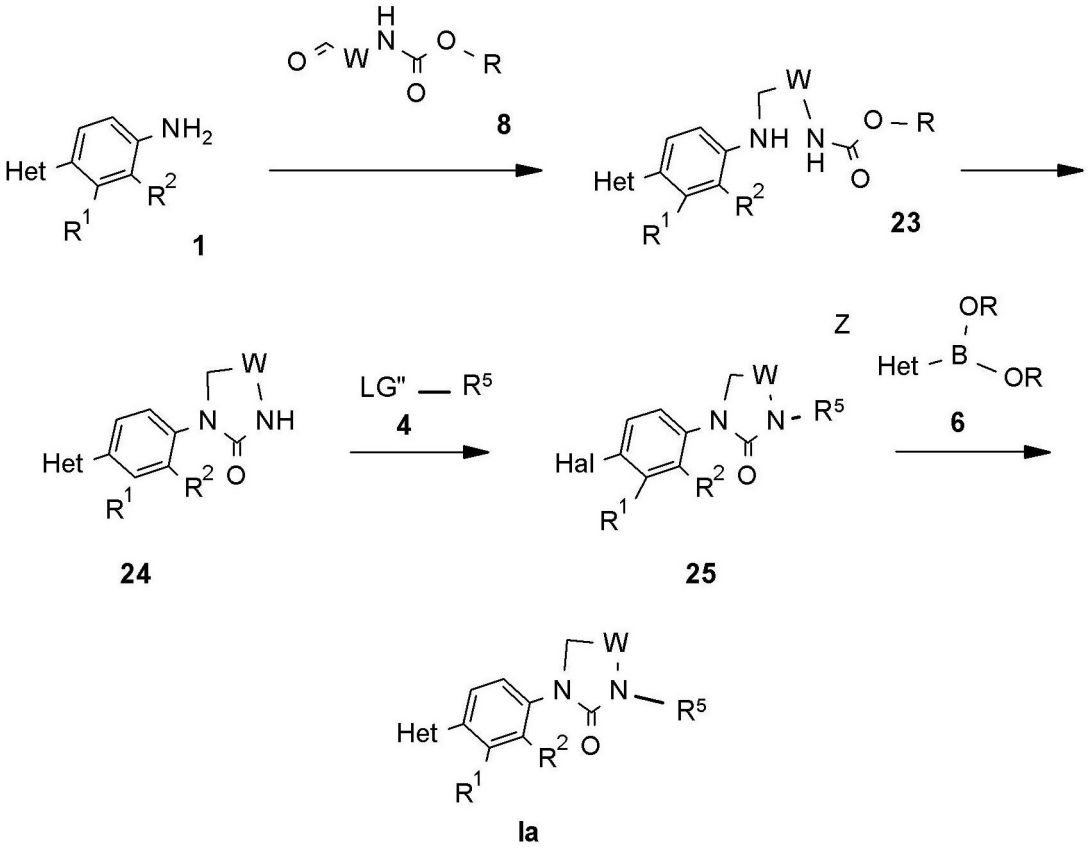
[0203] 方案6

[0204]

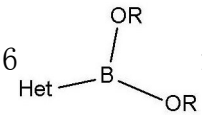
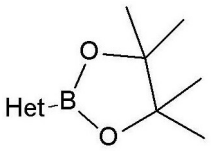


[0205] 式Ib的化合物可以根据方案6制备。将其中LG是合适的离去基团如Br的芳基胺7，与酰氯19，或其中LG'是合适的离去基团如Br的类似活化的酸反应，得到20。用合适的碱如KOH处理，得到21。用另一种合适的碱如酰胺锂和其中LG"是合适的离去基团如溴的化合物4处理，得到22。然后在合适的催化剂如四(三苯基膦)钯和合适的碱如碳酸钠的存在下，将化合物22与硼酸或硼酸酯6反应，得到化合物Ib。

[0206] 方案7

[0207] 

[0208] 式Ia的化合物还可以根据方案7制备。在称为还原胺化的方法中，将芳基胺1与烷氧基羰基氨基醛8和还原剂如$NaBH(OAc)_3$/AcOH反应，得到23。可以通过用合适的碱如KOtBu处理将化合物23转化为24。将23首先与合适的碱如氢化钠反应，然后与其中LG是合适的离去基团如Br的化合物4反应。然后在合适的催化剂如四(三苯基膦)钯和合适的碱如碳酸钠的存在下，将得到的化合物25与硼酸或硼酸酯6反应，得到化合物I-a。

[0209] 方案中的结构6  还包括以下结构：。

[0210] 化合物的分离和纯化

[0211] 如果需要，本文中描述的化合物和中间体的分离和纯化可以通过任意合适的分离或纯化方法进行，所述方法诸如，例如，过滤，萃取，结晶，柱层析，薄层层析，厚层层析，制备型低或高压液相色谱或这些方法的组合。可以通过参考下文的制备和实施例获得适当的分离和离析方法的具体说明。然而，当然可以使用其它相当的分离或离析方法。可以使用手性HPLC分离式I的手性化合物的外消旋混合物。

[0212] 式I的化合物的盐

[0213] 式I的化合物是碱性的并且可以被转化为相应的酸加成盐。通过用至少化学计量的量的适当酸诸如盐酸，氢溴酸，硫酸，硝酸，磷酸等，和有机酸诸如乙酸，丙酸，乙醇酸，丙酮酸，草酸，苹果酸，丙二酸，琥珀酸，马来酸，富马酸，酒石酸，柠檬酸，苯甲酸，肉桂酸，扁桃酸，甲磺酸，乙磺酸，对甲苯磺酸，水杨酸等处理实现转变。典型地，将游离碱溶解在惰性有机溶剂诸如二乙醚，乙酸乙酯，氯仿，乙醇或甲醇等中，并且将酸加入类似的溶剂中。将温度

维持在0℃和50℃之间。产生的盐自发沉淀或可以用较小极性的溶剂带出溶液。

[0214] 式I的碱性化合物的酸加成盐可以通过用至少化学计量当量的适当碱诸如氢氧化钠或氢氧化钾,碳酸钾,碳酸氢钠,氨水等处理转化为相应的游离碱。

[0215] 式I的化合物和其药用加成盐具有有益的药学性质。具体地,已经发现本发明的化合物具有作为神经源性剂的活性。

[0216] 根据下文给出的测试研究所述化合物。

[0217] 神经发生测定

[0218] 神经干细胞增殖测定

[0219] 小分子的神经源性性质基于通过之前描述的双重smad抑制衍生的人胚胎干细胞衍生的神经干细胞(NSC)的增殖而确定(Chambers,S.M.,等人,Highly efficient neural conversion of human ES and iPS cells by dual inhibition of SMAD signaling,Nature biotechnology,2009.27(3):p.275-80.)

[0220] 4天的孵育期之后,通过基于ATP水平的细胞增加(Promega:CellTiterGlo®)测量化合物响应。

[0221] 将NSC解冻并扩充3代。在第14天,将NSC以38μl培养基体积中21'000个细胞/cm^2的细胞密度接种入Polyornithin/Laminin包被的384孔板中。

[0222] 细胞接种后4小时,以2μl的体积添加化合物溶液。将化合物的储液(水,5%DMSO)稀释以获得剂量响应(11个点,稀释因子是2),范围从8μM至8nM。运行对照以不断确定细胞的神经源性性质:

[0223] 阴性(中性)对照是细胞培养基(最终DMSO浓度:0.25%)。

[0224] 阳性对照是:

[0225] 1.细胞培养基+100ng/ml FGF2(最终DMSO浓度:0.1%)

[0226] 2.细胞培养基+20ng/ml EGF(最终DMSO浓度:0.1%)

[0227] 3.细胞培养基+100ng/ml Wnt3a(最终DMSO浓度:0.1%)

[0228] 在37℃,5%CO_2孵育4天之后,定量每孔的ATP量。ATP浓度与细胞数量成比例。通过使用Promega CellTiterGlo®试剂盒定量ATP。CellTiterGlo®试剂含有细胞溶解缓冲液,热稳定荧光素酶(UltraGlo™重组荧光素酶),镁和荧光素。荧光素与ATP反应产生氧化荧光素,AMP和光。发光信号与ATP含量成比例。

[0229] 对于各个测定板,通过采用16个阴性对照孔的平均确定阴性(中性)对照值。对于各个化合物,将神经源性化合物响应计算为(化合物/阴性对照)*100。

[0230] 对于各个测试化合物,确定来自剂量响应曲线的EC_{150}值。EC150是达到对照(100%)的150%活性的化合物浓度。

[0231] 优选的化合物显示在<3.0μM的范围内的EC_{150}(μM),如表1中所示。

[0232] 表1

[0233] 实施例和EC_{150}数据的列表

[0234]

实施例编号	化合物名称	EC_{150} (uM)
1	3-乙基-1-(3-甲氧基-4-(噁唑-5-基)苯基)-3-苯基吡咯烷-2-酮	3.2257
2	1-苄基-3-(4-(吡啶-4-基)苯基)咪唑烷-2-酮	1.0425
3	1-(3-甲氧基-4-噁唑-5-基-苯基)-3-(3-甲氧基苯基)吡咯烷-2-	0.0814

[0235]

	酮	
4	3-(2-氯苯基)-1-(3-甲氧基-4-噁唑-5-基-苯基)吡咯烷-2-酮	0.6783
5	1-苄基-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]六氢嘧啶-2-酮	1.3254
6	1-[(2-氯苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]六氢嘧啶-2-酮	1.9918
7	1-[(3-甲氧基苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]六氢嘧啶-2-酮	0.1144
8	1-(3-甲氧基-4-噁唑-5-基-苯基)-3-苯基-吡咯烷-2-酮	0.4712
9	1-苄基-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮	0.1612
10	1-[(2-氯苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮	0.2695
11	1-[(3-甲氧基苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮	0.0239
12	1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-苯基-吡咯烷-2-酮	0.0414
13	3-苯基-1-[4-(1H-吡唑-4-基)苯基]吡咯烷-2-酮	0.2048
14	3-(3-甲氧基苯基)-1-[4-(1H-吡唑-4-基)苯基]吡咯烷-2-酮	0.0405
15	3-(4-氯苯基)-1-[4-(1H-吡唑-4-基)苯基]吡咯烷-2-酮	0.384
16	3-(4-氟苯基)-1-[4-(1H-吡唑-4-基)苯基]吡咯烷-2-酮	0.0417
17	3-(3-氯苯基)-1-[4-(1H-吡唑-4-基)苯基]吡咯烷-2-酮	0.2304
18	1-[(3-氯苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮	0.3946
19	1-[(3-氟苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮	0.047
20	1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-[[3-(三氟甲基)苯基]甲基]咪唑烷-2-酮	0.0086
21	1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-[[3-(三氟甲氧基)苯基]甲基]咪唑烷-2-酮	0.0092
22	1-[(3-乙氧基苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮	0.0739
23	3-苄基-1-(3-甲氧基-4-(1H-吡唑-4-基)苯基)吡咯烷-2-酮	0.6122

[0236]

24	1-(3-甲氧基-4-(1H-吡唑-4-基)苯基)-3-(3-甲氧基苯基)吡咯烷-2-酮	0.0299
25	3-(3-氯苯基)-1-(3-甲氧基-4-(1H-吡唑-4-基)苯基)吡咯烷-2-酮	0.0659
26	3-(3-氟苯基)-1-(3-甲氧基-4-(1H-吡唑-4-基)苯基)吡咯烷-2-酮	0.0776
27	1-[(3-甲氧基苯基)甲基]-3-[4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮	0.2944
28	1-[(3-甲氧基苯基)甲基]-3-[3-甲基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮	1.2174
29	1-[3-氯-4-(1H-吡唑-4-基)苯基]-3-[(3-甲氧基苯基)甲基]咪唑烷-2-酮	0.3664
30	1-[2-氟-4-(1H-吡唑-4-基)苯基]-3-[(3-甲氧基苯基)甲基]咪唑烷-2-酮	0.0416
31	1-[3-氟-4-(1H-吡唑-4-基)苯基]-3-[(3-甲氧基苯基)甲基]咪唑烷-2-酮	0.0157
32	1-[3-乙氧基-4-(1H-吡唑-4-基)苯基]-3-[(3-甲氧基苯基)甲基]咪唑烷-2-酮	0.8349
33	1-[(2-氟苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮	0.2246
34	1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-(邻甲苯基甲基)咪唑烷-2-酮	0.2004
35	1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-(间甲苯基甲基)咪唑烷-2-酮	2.6464
36	3-[(3-氯苯基)甲基]-1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]吡咯烷-2-酮	1.6485
37	3-[(2-氯苯基)甲基]-1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]吡咯烷-2-酮	1.1254
38	3-(3-氯苯基)-1-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]吡咯烷-2-酮	1.3515

[0237]

39	1-[(3-甲氧基苯基)甲基]-3-[2-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮	0.393
40	3-[(3-甲氧基苯基)甲基]-1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]吡咯烷-2-酮	0.334
41	1-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]-3-(2-甲氧基苯基)吡咯烷-2-酮	2.9106
42	1-[(2-甲氧基苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮	0.3085
43	1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-(2-苯基乙基)咪唑烷-2-酮	0.3093
44	1-[2-(2-甲氧基苯基)乙基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮	1.9784
45	1-[2-(2-氯苯基)乙基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮	0.1358
46	1-[2-氯-4-(1H-吡唑-4-基)苯基]-3-[(3-甲氧基苯基)甲基]咪唑烷-2-酮	1.8344
47	1-[(4-氟苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮	0.7685
48	1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-(3-吡啶基甲基)咪唑烷-2-酮	0.1195
49	1-[2-(3-氯苯基)乙基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮	1.7318
50	1-[2-(4-氯苯基)乙基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮	2.0118
51	1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-(1-苯基丙基)咪唑烷-2-酮	0.5942
52	3-(3-甲氧基苯基)-1-[4-(1,3-噁唑-5-基)苯基]吡咯烷-2-酮	0.5169
53	1-[4-(1,3-噁唑-5-基)苯基]-3-苯基吡咯烷-2-酮	2.2077
54	1-[3-甲氧基-4-(4-吡啶基)苯基]-3-[[2-(三氟甲基)苯基]甲基]咪唑烷-2-酮	0.0351

[0238]

55	1-[3-甲氧基-4-(4-吡啶基)苯基]-3-(4-吡啶基甲基)咪唑烷-2-酮	0.3765
56	1-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]-3-[3-(三氟甲基)苯基]吡咯烷-2-酮	1.8592
57	3-(2-氟苯基)-1-[4-(1,3-噁唑-5-基)苯基]吡咯烷-2-酮	0.525
58	3-(2-氟苯基)-1-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]吡咯烷-2-酮	0.2297
59	1-[(3-甲氧基苯基)甲基]-3-[4-(1,3-噁唑-5-基)苯基]咪唑烷-2-酮	0.1225
60	3-(3-氟苯基)-1-[4-(1,3-噁唑-5-基)苯基]吡咯烷-2-酮	0.6045
61	3-(3-氟苯基)-1-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]吡咯烷-2-酮	0.2623
62	1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-(4-吡啶基甲基)咪唑烷-2-酮	0.042
63	1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-(2-吡啶基甲基)咪唑烷-2-酮	0.2551
64	1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-(2-苯基丙基)咪唑烷-2-酮	0.3873
65	1-[3-甲氧基-4-(4-吡啶基)苯基]-3-(间甲苯基甲基)咪唑烷-2-酮	0.0298
66	1-[3-甲氧基-4-(4-吡啶基)苯基]-3-(3-吡啶基甲基)咪唑烷-2-酮	0.4002
67	1-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]-3-[(2-甲氧基苯基)甲基]咪唑烷-2-酮	0.7015
68	1-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]-3-[(3-甲氧基苯基)甲基]咪唑烷-2-酮	0.3158
69	1-[(2-氯苯基)甲基]-3-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]咪唑烷-2-酮	2.2373
70	3-(3-甲氧基苯基)-1-(3-甲氧基-4-吡啶-4-基苯基)吡咯烷-2-酮	0.0613
71	3-(3-甲氧基苯基)-1-(4-吡啶-4-基苯基)吡咯烷-2-酮	0.0155

[0239]

72	1-[(3-氟苯基)甲基]-3-[4-(1,3-噁唑-5-基)苯基]咪唑烷-2-酮	1.0717
73	1-[(2-氟苯基)甲基]-3-[4-(1,3-噁唑-5-基)苯基]咪唑烷-2-酮	1.492
74	1-[(2-氟苯基)甲基]-3-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]咪唑烷-2-酮	2.6998
75	1-[(3-氟苯基)甲基]-3-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]咪唑烷-2-酮	0.5973

[0240] 式I的化合物和式I的化合物的药用盐可以用作药物，例如药物制剂形式的药物。所述药物制剂可以口服施用，例如以片剂、包衣片剂、糖衣丸(dragées)、硬和软明胶胶囊、溶液、乳液或混悬剂的形式施用。然而，施用还可以经直肠(例如以栓剂的形式)或经肠胃外(例如以注射液的形式)实现。

[0241] 式I的化合物可以用药学上惰性的、无机或有机载体处理以用于生产药物制剂。例如，可以使用乳糖、玉米淀粉或其衍生物、滑石、硬脂酸或其盐等作为此种载体用于片剂、包衣片剂、糖衣丸和硬明胶胶囊。用于软明胶胶囊的合适的载体是例如，植物油、蜡、脂肪、半固体和液体多元醇等。然而，根据活性物质的性质，在软明胶胶囊的情形下，通常不需要载体。用于生产溶液和糖浆的适当载体是，例如，水、多元醇、甘油、植物油等。用于栓剂的适当载体是例如，天然或硬化油、蜡、脂肪、半液体或液体多元醇等。

[0242] 此外，药物制剂可以含有防腐剂、增溶剂、稳定剂、湿润剂、乳化剂、甜味剂、着色剂、香料、改变渗透压的盐、缓冲剂、掩蔽剂或抗氧化剂。它们还可以含有其它治疗上有价值的物质。

[0243] 含有式I的化合物或其药用盐和治疗上惰性的载体的药物也是本发明的目的，其制备方法也是本发明的目的，所述方法包括将一种或多种式I的化合物和/或药用酸加成盐和(如果需要)一种或多种其它治疗上有价值的物质与一种或多种治疗惰性载体一起制成盖伦制剂施用形式。

[0244] 根据本发明的最优选的适应证是包括中枢神经系统的病症的那些，例如治疗或预防抑郁、精神病、帕金森病、焦虑、注意力缺陷多动症(ADHD)和糖尿病。

[0245] 剂量可以在宽范围内改变并且当然将适于各个特定案例中的个体需求。在口服施用的情况下，成人的剂量可以在约0.01mg至约1000mg/天的通式I的化合物或相应量的其药用盐的范围内变化。每日剂量可以作为单剂或以分开的多剂施用，此外，当发现必要时，也可以超过所述上限。

[0246] 片剂制剂(湿法制粒)

[0247]

项目	成分	mg/片			
		5 mg	25 mg	100 mg	500 mg
1.	式 I 的化合物	5	25	100	500
2.	乳糖无水 DTG	125	105	30	150
3.	Sta-Rx 1500	6	6	6	30
4.	微晶纤维素	30	30	30	150
5.	硬脂酸镁	1	1	1	1
	总量	167	167	167	831

[0248] 制造过程

[0249] 1.混合项目1、2、3和4并用净化水制粒。

[0250] 2.在50℃干燥颗粒。

[0251] 3.将颗粒通过合适的研磨装置。

[0252] 4.添加项目5并混合三分钟;在合适的压力机上压制。

[0253] 胶囊制剂

[0254]

项目	成分	mg/胶囊			
		5 mg	25 mg	100 mg	500 mg
1.	式 I 的化合物	5	25	100	500
2.	含水乳糖	159	123	148	---
3.	玉米淀粉	25	35	40	70
4.	滑石	10	15	10	25
5.	硬脂酸镁	1	2	2	5
	总量	200	200	300	600

[0255] 制造过程

[0256] 1.在适当的混合器中混合项目1、2和3达30分钟。

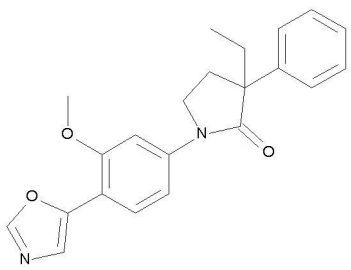
[0257] 2.添加项目4和5并混合3分钟。

[0258] 3.装入适当的胶囊中。

[0259] 实施例1

[0260] 3-乙基-1-(3-甲氧基-4-(噁唑-5-基)苯基)-3-苯基吡咯烷-2-酮

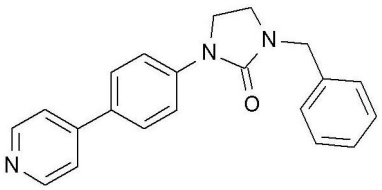
[0261]



[0262] 在10ml圆底烧瓶中，将3-甲氧基-4-(噁唑-5-基)苯胺(可商购获得，CAS:198821-79-3;200mg，1.05mmol)与二噁烷(4ml)混合，得到浅褐色溶液。加入三甲基铝(2M，在庚烷中，1.05ml，2.1mmol)。将反应混合物加热至50℃并且搅拌30min。加入3-乙基-3-苯基二氢呋喃-2(3H)-酮(可商购获得，CAS:4064-16-8;400mg，2.1mmol)。将反应混合物加热至100℃并且搅拌2d。将反应混合物倒入水/Na_2CO_3中并用EtOAc(2x25ml)萃取。将有机层用Na_2SO_4干燥并在真空中浓缩。将粗制物料通过急骤色谱(硅胶，20g，在庚烷中的0％至50％EtOAc)纯化，得到标题化合物，为浅黄色蜡状固体(221mg，58.0％)。MS(m/e)＝363.17$[M+H]^+$。

[0263] 实施例2

[0264] 1-苄基-3-(4-(吡啶-4-基)苯基)咪唑烷-2-酮

[0265] 

[0266] 步聚1:1-苄基-3-(4-溴苯基)咪唑烷-2-酮

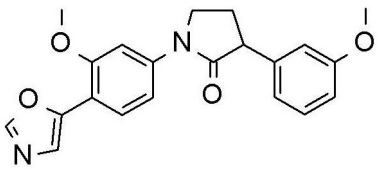
[0267] 在25ml圆底烧瓶中，将1-(4-溴苯基)咪唑烷-2-酮(可商购获得，CAS:530081-14-2;480mg，1.99mmol)与DMF(10ml)混合，得到浅黄色溶液。将反应混合物冷却至0℃。加入氢化钠(159mg，3.98mmol)。将反应混合物在0℃搅拌20min。允许反应混合物温热至室温。加入(溴甲基)苯(521mg，362μl，2.99mmol)。将反应混合物在室温搅拌过夜。将反应混合物倒入水(40ml)中并且用EtOAc(3x40ml)萃取。合并有机层，用饱和NaCl(1x40ml)洗涤，用Na_2SO_4干燥并在真空中浓缩。将粗制物料通过急骤色谱(硅胶，20g，在庚烷中的0％至50％EtOAc)纯化，得到标题化合物，为白色固体(629mg，95.4％)。MS(m/e)＝333.4$[M+H]^+$。

[0268] 步骤2:1-苄基-3-(4-(吡啶-4-基)苯基)咪唑烷-2-酮

[0269] 在50ml圆底烧瓶中，将DMF/水(7:2)的混合物(22.5ml)用氩气脱氧。加入1-苄基-3-(4-溴苯基)咪唑烷-2-酮(200mg，604μmol)、吡啶-4-基硼酸(148mg，1.21mmol)、碳酸钠(224mg，2.11mmol)和四(三苯基膦)钯(907μg，0.785μmol)。将反应混合物加热至回流并搅拌过夜。将反应混合物倒入水(50ml)并用EtOAc(3x50ml)萃取。将有机层用Na_2SO_4干燥并在真空中浓缩。将黄色固体残余物与MeOH(2ml)混合并在超声浴中处理5min。将悬浮液过滤。将白色固体在真空中干燥，得到标题化合物，为灰白色固体(89mg，44.6％)。MS(m/e)＝330.16$[M+H]^+$。

[0270] 实施例3

[0271] 1-(3-甲氧基-4-噁唑-5-基-苯基)-3-(3-甲氧基苯基)吡咯烷-2-酮

[0272] 

[0273] 步骤1:2-(3-甲氧基苯基)戊-4-烯酸

[0274] 在-78℃向3-甲氧基苯基乙酸(30.08mmol)在THF(150ml)中的溶液中加入LiHMDS(在THF中的1M溶液;66.19ml，66.19mmol)，并将反应混合物在-78℃搅拌0.5h。在-78℃将烯

丙基碘(2.75ml,30.08mmol)加入反应混合物中,并且在3h的时间内将混合物缓慢温热至25℃,然后在25℃继续搅拌12h。将反应混合物用饱和氯化铵溶液猝灭,使用1N HCl水溶液酸化,并用EtOAc(2x130ml)萃取。将合并的有机层用无水Na_2SO_4干燥,过滤,并在减压下浓缩。将得到的粗制物料通过柱色谱用硅胶(10-20%EtOAc/己烷)纯化,得到2-(3-甲氧基苯基)戊-4-烯酸(5.3g,85.48%),为浅黄色油状物。

[0275] 步骤2:N-(3-甲氧基-4-噁唑-5-基-苯基)-2-(3-甲氧基苯基)戊-4-烯酰胺

[0276] 在氩气氛下向2-(3-甲氧基苯基)戊-4-烯酸(1.5g,7.28mmol)在DCM(80ml)中的溶液中加入PyBOP(5.68g,10.92mmol)和DIPEA(3.71ml,21.84mmol)并且将反应混合物在25℃搅拌0.5h。将3-甲氧基-4-噁唑-5-基-苯基胺(1.66g,8.73mmol)加入至反应混合物中,并将得到的混合物在25℃搅拌16h。将混合物用水洗涤,分离有机层并且将水层用DCM(60ml)萃取。将合并的有机层用无水Na_2SO_4干燥,过滤,并在真空中蒸。将得到的粗制物质通过柱色谱用普通硅胶(30-40%EtOAc/己烷)纯化,得到N-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]-2-(3-甲氧基苯基)戊-4-烯酰胺(2.3g,83.47%),为白色固体。LC-MS:379.4$(M+H)^+$。

[0277] 步骤3:4,5-二羟基-N-(3-甲氧基-4-噁唑-5-基-苯基)-2-(3-甲氧基苯基)戊酰胺

[0278] 在25℃向N-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]-2-(3-甲氧基苯基)戊-4-烯酰胺(2.3g,6.08mmol)和NMO(1.42g,12.16mmol)在丙酮(100ml)和水(16.6ml)中的溶液中加入OsO_4(4%,在水中;0.15ml),并且将得到的混合物在25℃搅拌16h。将饱和硫代硫酸钠水溶液(60ml)加入至反应混合物中并用EtOAc(2x150ml)萃取。将合并的有机层用无水Na_2SO_4干燥,过滤,并在真空中浓缩。将得到的粗制物质通过柱色谱用普通硅胶(70-80%EtOAc/己烷)纯化,得到4,5-二羟基-N-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]-2-(3-甲氧基苯基)戊酰胺(1.89g,75.31%),为黄色固体。LC-MS:413.1$(M+H)^+$。

[0279] 步骤4:5-羟基-1-(3-甲氧基-4-噁唑-5-基-苯基)-3-(3-甲氧基苯基)吡咯烷-2-酮

[0280] 向4,5-二羟基-N-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]-2-(3-甲氧基苯基)戊酰胺(1.89g,4.58mmol)在THF(90ml)中的溶液中加入$NaIO_4$(1.95g,9.17mmol)在水(42ml)中的溶液,并且将得到的混合物在25℃搅拌2h。将反应混合物使用饱和$Na_2S_2O_3$水溶液猝灭,并且用EtOAc(2x100ml)萃取。将合并的有机层用水洗涤,用无水Na_2SO_4干燥,过滤,并在真空中蒸发,得到5-羟基-1-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]-3-(3-甲氧基苯基)吡咯烷-2-酮(1.63g),为白色固体,在未经任何进一步纯化的情况下将其用于下一步骤。LC-MS:381.2$(M+H)^+$。

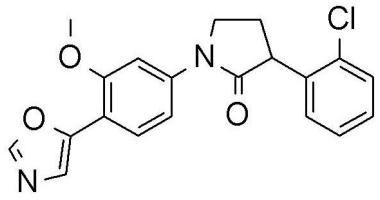
[0281] 步骤5:1-(3-甲氧基-4-噁唑-5-基-苯基)-3-苯基-吡咯烷-2-酮

[0282] 在0℃向5-羟基-1-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]-3-(3-甲氧基苯基)吡咯烷-2-酮(1.63g,4.28mmol)在DCM(150ml)中的溶液中加入Et_3SiH(8ml)和TFA(8ml),并且将反应混合物在25℃搅拌2h。在真空中除去挥发物。将得到的残余物用DCM(120ml)稀释并用饱和$NaHCO_3$水溶液洗涤。将有机层用无水Na_2SO_4干燥,过滤,并在减压下蒸发。将得到的粗制物质通过柱色谱用普通硅胶(50%EtOAc/己烷)纯化,得到1-[3-甲氧基-4-(1,3-噁唑-5-

基)苯基]-3-(3-甲氧基苯基)吡咯烷-2-酮(950mg,56.92%,来自步骤3),为灰白色固体。LC-MS:365.3(M+H)$^+$。

[0283] 实施例4

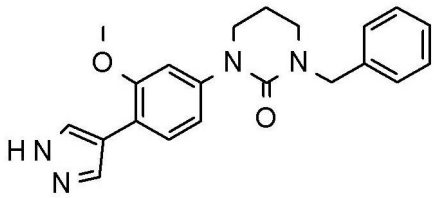
[0284] 3-(2-氯苯基)-1-(3-甲氧基-4-噁唑-5-基-苯基)吡咯烷-2-酮

[0285] 

[0286] 与实施例3类似,在步骤1中使用2-氯苯乙酸,制备标题化合物。LC-MS:369.0(M+H)$^+$。

[0287] 实施例5

[0288] 1-苄基-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]六氢嘧啶-2-酮

[0289] 

[0290] 步骤1:N-{3-[(4-溴-3-甲氧基苯基)氨基]丙基}氨基甲酸苄酯

[0291] 在0℃向4-溴-3-甲氧基-苯基胺(2g,9.90mmol)在DCM(100ml)中的溶液中加入3-[(苄氧基羰基)氨基]丙醛(2.46g,11.88mmol)和AcOH(0.57ml,9.90mmol),并且将得到的反应混合物在0℃搅拌0.5h。然后将$NaBH(OAc)_3$(3.14g,14.85mmol)加入至反应混合物中,再次在25℃搅拌12h。将混合物用水(40ml)稀释,分离有机层并且将水层用DCM(2x40ml)再次萃取。将合并的有机层在真空中蒸发。将得到的粗制物料通过柱色谱用普通硅胶(25-30%EtOAc/己烷)纯化,得到N-{3-[(4-溴-3-甲氧基苯基)氨基]丙基}氨基甲酸苄酯(1.4g,36.21%),为黄色粘性固体。LC-MS:395.2(M+H)$^+$。

[0292] 步骤2:1-(4-溴-3-甲氧基苯基)-1,3-二嗪农(diazinan)-2-酮

[0293] 在0℃向KOtBu(799mg,7.12mmol)在THF(30ml)中的溶液中加入N-{3-[(4-溴-3-甲氧基苯基)氨基]丙基}氨基甲酸苄酯(1.4g,3.56mmol)在THF(30ml)中的溶液,并且将得到的混合物在25℃搅拌12h。将混合物用饱和氯化铵水溶液猝灭并用EtOAc(2x80ml)萃取。将合并的有机层用无水Na_2SO_4干燥,过滤,并在真空中蒸发。使用30%EtOAc/己烷将得到的残余物研磨,得到1-(4-溴-3-甲氧基苯基)-1,3-二嗪农-2-酮(667mg,65.67%),为黄色固体。LC-MS:284.8(M+H)$^+$。

[0294] 步骤3:1-苄基-3-(4-溴-3-甲氧基苯基)-1,3-二嗪农-2-酮

[0295] 在0℃向NaH(60%,在矿物油中)(31.57mg,0.78mmol)在DMF(2ml)中的悬浮液中加入1-(4-溴-3-甲氧基苯基)-1,3-二嗪农-2-酮(150mg,0.52mmol)在DMF(5ml)中的溶液,并且将得到的混合物在0℃搅拌0.5h。然后将苄基溴(0.094ml,0.78mmol)加入至混合物中,将其在25℃搅拌另外的12h。将混合物用水(15ml)稀释并用EtOAc(2x40ml)萃取。将合并的有机层用无水Na_2SO_4干燥,过滤,并在真空中蒸发,得到1-苄基-3-(4-溴-3-甲氧基苯基)-1,3-二嗪农-2-酮(244mg,粗制),为浅黄色粘性固体,在未经任何进一步纯化的情况下将其用于

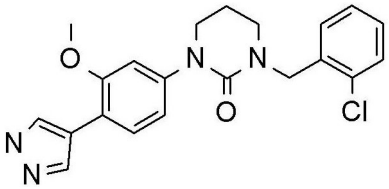
下一步骤。LC-MS:374.8(M+H)$^+$。

[0296] 步骤4:1-苄基-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]六氢嘧啶-2-酮

[0297] 向1-苄基-3-(4-溴-3-甲氧基苯基)-1,3-二嗪农-2-酮(240mg,0.64mmol)在二噁烷(16ml)和水(4ml)中的溶液中加入K_2CO_3(265mg,1.92mmol)。将混合物用氩气吹扫10min。然后向该混合物中加入[1-(叔丁氧基羰基)-1H-吡唑-4-基]硼酸频哪醇酯(282mg,0.96mmol)和$Pd(dppf)_2Cl_2$.DCM(20.90mg,0.02mmol),再用氩气吹扫另外的10min,并随后在80℃加热16h。将混合物用水稀释,并用EtOAc(2x30ml)萃取。将合并的有机层用无水Na_2SO_4干燥,过滤,并在真空中蒸发。将得到的粗制物料通过柱色谱用普通硅胶(55-65%EtOAc/己烷)纯化,得到1-苄基-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-1,3-二嗪农-2-酮(44mg,23.09%from 4),为灰白色固体。LC-MS:363.0(M+H)$^+$。

[0298] 实施例6

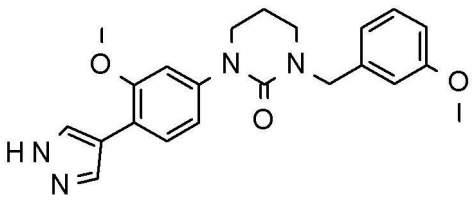
[0299] 1-[(2-氯苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]六氢嘧啶-2-酮

[0300] 

[0301] 与实施例5类似,在步骤3中使用1-(溴甲基)-2-氯-苯制备标题化合物。LC-MS:397.0(M+H)$^+$。

[0302] 实施例7

[0303] 1-[(3-甲氧基苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]六氢嘧啶-2-酮

[0304] 

[0305] 与实施例5类似,在步骤3中使用1-(溴甲基)-3-甲氧基-苯制备标题化合物。LC-MS:393.0(M+H)$^+$。

[0306] 实施例8

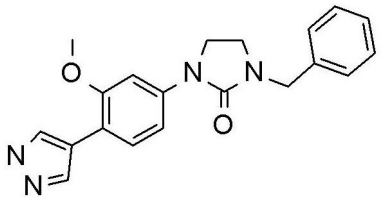
[0307] 1-(3-甲氧基-4-噁唑-5-基-苯基)-3-苯基-吡咯烷-2-酮

[0308] 

[0309] 与实施例3类似,在步骤1中使用苯基乙酸制备标题化合物。LC-MS:335.0(M+H)$^+$。

[0310] 实施例9

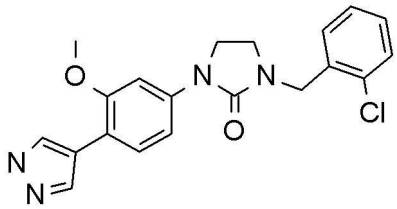
[0311] 1-苄基-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮

[0312] 

[0313] 与实施例5类似，在步骤1中使用N-(2-氧代乙基)氨基甲酸叔丁酯制备标题化合物。LC-MS:349.0(M+H)$^+$。

[0314] 实施例10

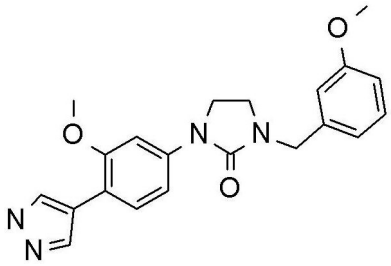
[0315] 1-[(2-氯苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮

[0316] 

[0317] 与实施例5类似，在步骤1中使用N-(2-氧代乙基)氨基甲酸叔丁酯并且在步骤3中使用1-(溴甲基)-2-氯-苯制备标题化合物。LC-MS:383.0(M+H)$^+$。

[0318] 实施例11

[0319] 1-[(3-甲氧基苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮

[0320] 

[0321] 与实施例5类似，在步骤1中使用N-(2-氧代乙基)氨基甲酸叔丁酯并且在步骤3中使用1-(溴甲基)-3-甲氧基-苯制备标题化合物。LC-MS:379.0(M+H)$^+$。

[0322] 实施例12

[0323] 1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-苯基-吡咯烷-2-酮

[0324] 

[0325] 步骤1:2-苯基戊-4-烯酸

[0326] 在-78℃向苯基乙酸(2g,14.7mmol)在THF(60ml)中的溶液中加入LiHMDS(1M溶液，在THF中)(32.35ml,32.35mmol)，并且将反应混合物在-78℃搅拌0.5h。在-78℃将烯丙基碘(1.34ml,14.7mmol)加入至反应混合物中，并且在3h的时间内将混合物缓慢温热至25℃。将其用饱和氯化铵水溶液猝灭，使用1N HCl水溶液酸化并且用EtOAc(2x80ml)萃取。将合并的有机层用无水Na_2SO_4干燥，过滤，并在减压下浓缩。将得到的粗制物料通过柱色谱用普通硅胶(10-20%EtOAc/己烷)纯化，得到2-苯基戊-4-烯酸(2.26g,87.21%)，为浅黄色油状物。LC-MS:175.2(M-H$^+$)。

[0327] 步骤2:N-(4-溴-3-甲氧基苯基)-2-苯基戊-4-烯酰胺

[0328] 在0℃向2-苯基戊-4-烯酸(1.5g,8.52mmol)在DCM(30ml)中的溶液中加入草酰氯(1.10ml,12.78mmol),并且将混合物在25℃搅拌3h。在真空中除去挥发物。在0℃将得到的酰氯溶解在DCM(10ml)中并且加入至4-溴-3-甲氧基苯胺(1.71g,8.50mmol)和Et_3N(2.37ml,8.50mmol)在DCM(20ml)的溶液中。将反应混合物在25℃搅拌16h。将溶剂在真空中蒸发,并且将得到的粗制物料通过柱色谱用普通硅胶(10-15%EtOAc/己烷)纯化,得到N-(4-溴-3-甲氧基苯基)-2-苯基戊-4-烯酰胺(1.9g,62.01%),为黄色粘性固体。LC-MS:359.8($M+H^+$)。

[0329] 步骤3:N-(4-溴-3-甲氧基苯基)-4,5-二羟基-2-苯基戊酰胺

[0330] 在25℃向N-(4-溴-3-甲氧基苯基)-2-苯基戊-4-烯酰胺(1g,2.77mmol)和NMO(976mg,8.33mmol)在丙酮(35ml)和水(4.5ml)中的溶液中加入OsO_4(4%,在水中)(0.144ml),并且将混合物在25℃搅拌12h。将其用1N硫代硫酸钠水溶液(20ml)猝灭,并用EtOAc(2x80ml)萃取。将合并的有机层用无水Na_2SO_4干燥,过滤,并且在真空中浓缩。将得到的粗制物料通过柱色谱用普通硅胶(70%EtOAc/己烷)纯化,得到N-(4-溴-3-甲氧基苯基)-4,5-二羟基-2-苯基戊酰胺(538mg,49.12%),为白色固体。LC-MS:394.2($M+H^+$)。

[0331] 步骤4:1-(4-溴-3-甲氧基苯基)-5-)羟基-3-苯基吡咯烷-2-酮

[0332] 向N-(4-溴-3-甲氧基苯基)-4,5-二羟基-2-苯基戊酰胺(535mg,1.35mmol)在THF(25ml)中的溶液中加入$NaIO_4$(578mg,2.71mmol)在水(12ml)中的溶液,并且将得到的混合物在25℃搅拌2h。将其用饱和Na_2S2O_4水溶液猝灭并用EtOAc(2x40ml)萃取。将合并的有机层用水洗涤,用无水Na_2SO_4干燥,过滤,并在真空中蒸发,得到1-(4-溴-3-甲氧基苯基)-5-羟基-3-苯基吡咯烷-2-酮(479mg,97.39%),为灰白色固体,在未经任何进一步纯化的情况下将其用于下一步骤。LC-MS:362.0($M+H^+$)。

[0333] 步骤5:1-(4-溴-3-甲氧基苯基)-3-苯基吡咯烷-2-酮

[0334] 在0℃向1-(4-溴-3-甲氧基苯基)-5-羟基-3-苯基吡咯烷-2-酮(475mg,1.31mmol)在DCM(15ml)中的溶液中加入Et_3SiH(2.2ml)和TFA(2.2ml),将得到的混合物在25℃搅拌2h。在真空中除去挥发物。将获得的残余物用DCM(50ml)稀释并且用饱和$NaHCO_3$水溶液洗涤。将有机层用无水Na_2SO_4干燥,过滤,并在真空中蒸发。将得到的粗制物质通过柱色谱用普通硅胶(20-25%EtOAc/己烷)纯化,得到1-(4-溴-3-甲氧基苯基)-3-苯基吡咯烷-2-酮(345mg,75.94%),为灰白色固体。LC-MS:345.8($M+H^+$)。

[0335] 步骤6:1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-苯基吡咯烷-2-酮

[0336] 向1-(4-溴-3-甲氧基苯基)-3-苯基吡咯烷-2-酮(342mg,0.98mmol)在二噁烷(10ml)和水(4ml)中的溶液中加入K_2CO_3(410mg,1.48mmol)。将混合物用氩气吹扫10min。然后将[1-(叔丁氧基羰基)-1H-吡唑-4-基]硼酸频哪醇酯(436mg,1.48mmol)和$Pd(dppf)_2Cl_2$*DCM(32.28mg,0.04mmol)加入至反应混合物中,并且再次用氩气吹扫另外的10min。将反应混合物在80℃加热16h。将混合物用水稀释,并用EtOAc(2x40ml)萃取。将合并的有机层用无水Na_2SO_4干燥,过滤并在真空中蒸发。将得到的粗制物质通过柱色谱用普通硅胶(55-65%EtOAc/己烷)纯化,得到1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-苯基吡咯烷-2-酮(80mg,24.28%),为灰白色固体。LC-MS:334.0($M+H^+$)。

[0337] 实施例13

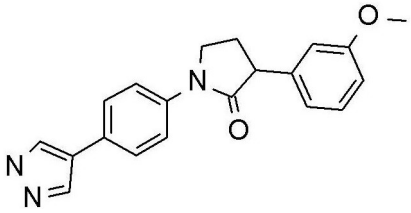
[0338] 3-苯基-1-[4-(1H-吡唑-4-基)苯基]吡咯烷-2-酮

[0339] 

[0340] 与实施例12类似,在步骤2中使用4-溴苯胺制备标题化合物。LC-MS:304.0(M+H)$^+$。

[0341] 实施例14

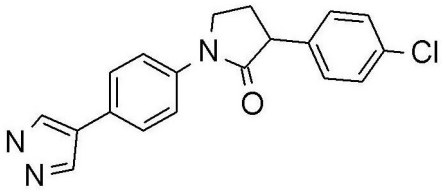
[0342] 3-(3-甲氧基苯基)-1-[4-(1H-吡唑-4-基)苯基]吡咯烷-2-酮

[0343] 

[0344] 与实施例12类似,在步骤1中使用3-甲基苯基乙酸并且在步骤2中使用4-溴苯胺制备标题化合物。LC-MS:334.2(M+H)$^+$。

[0345] 实施例15

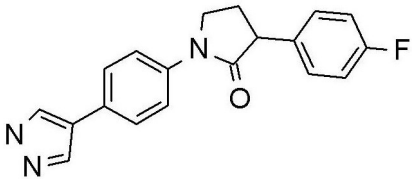
[0346] 3-(4-氯苯基)-1-[4-(1H-吡唑-4-基)苯基]吡咯烷-2-酮

[0347] 

[0348] 与实施例12类似,在步骤1中使用4-氯苯基乙酸并且在步骤2中使用4-溴苯胺制备标题化合物。LC-MS:338.2(M+H)$^+$.

[0349] 实施例16

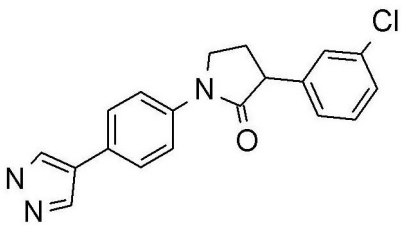
[0350] 3-(4-氟苯基)-1-[4-(1H-吡唑-4-基)苯基]吡咯烷-2-酮

[0351] 

[0352] 与实施例12类似,在步骤1中使用4-氟苯基乙酸并且在步骤2中使用4-溴苯胺制备标题化合物。LC-MS:322.0(M+H)$^+$。

[0353] 实施例17

[0354] 3-(3-氯苯基)-1-[4-(IH-吡唑-4-基)苯基]吡咯烷-2-酮

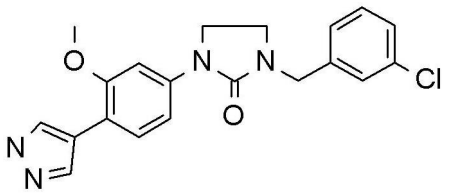
[0355] 

[0356] 与实施例12类似,在步骤1中使用3-氯苯基乙酸并且在步骤2中使用4-溴苯胺制备

标题化合物。LC-MS:338.2(M+H)$^+$。

[0357] 实施例18

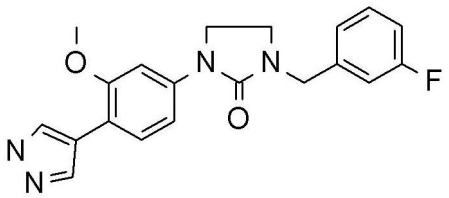
[0358] 1-[(3-氯苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮

[0359] 

[0360] 与实施例5类似,在步骤1中使用N-(2-氧代乙基)氨基甲酸叔丁酯并且在步骤3中使用1-(溴甲基)-3-氯-苯制备标题化合物。LC-MS:383.0(M+H)$^+$。

[0361] 实施例19

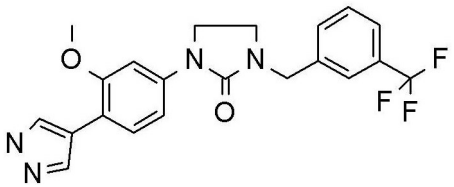
[0362] 1-[(3-氟苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮

[0363] 

[0364] 与实施例5类似,在步骤1中使用N-(2-氧代乙基)氨基甲酸叔丁酯并且在步骤3中1-(溴甲基)-3-氟-苯制备标题化合物。LC-MS:366.9(M+H)$^+$。

[0365] 实施例20

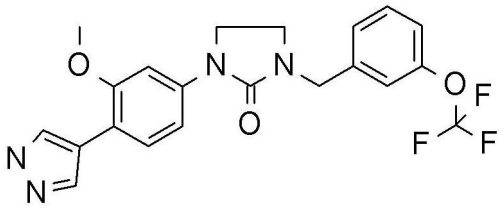
[0366] 1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-[[3-(三氟甲基)苯基]甲基]咪唑烷-2-酮

[0367] 

[0368] 与实施例5类似,在步骤1中使用N-(2-氧代乙基)氨基甲酸叔丁酯并且在步骤3中使用1-(溴甲基)-3-三氟甲基-苯制备标题化合物。LC-MS:417.0(M+H)$^+$。

[0369] 实施例21

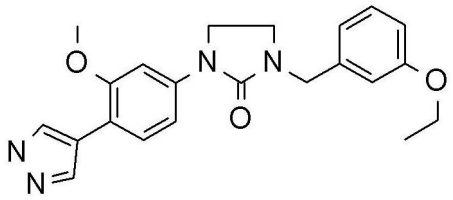
[0370] 1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-[[3-(三氟甲氧基)苯基]甲基]咪唑烷-2-酮

[0371] 

[0372] 与实施例5类似,在步骤1中使用N-(2-氧代乙基)氨基甲酸叔丁酯并且在步骤3中使用1-(溴甲基)-3-三氟甲氧基-苯制备标题化合物。LC-MS:433.1(M+H)$^+$。

[0373] 实施例22

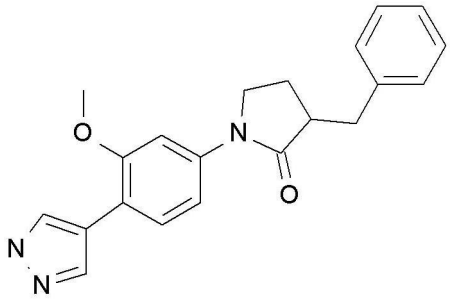
[0374] 1-[(3-乙氧基苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮

[0375] 

[0376] 与实施例5类似，在步骤1中使用N-(2-氧代乙基)氨基甲酸叔丁酯并且在步骤3中使用1-(溴甲基)-3-乙氧基-苯制备标题化合物。LC-MS:393.0(M+H)$^+$。

[0377] 实施例23

[0378] 3-苄基-1-(3-甲氧基-4-(1H-吡唑-4-基)苯基)吡咯烷-2-酮

[0379] 

[0380] 步骤1:1-(4-溴-3-甲氧基苯基)吡咯烷-2-酮

[0381] 在氮气氛下，在0℃在100mL圆底烧瓶中，将4-溴-3-甲氧基苯胺(2g,9.9mmol)和KOH(6.93ml,13.9mmol)与二氯甲烷(30ml)混合，得到浅褐色溶液。然后加入4-溴丁酰氯(1.84g,1.15ml,9.9mmol)。将反应在室温搅拌1h。将反应混合物倒入50ml二氯甲烷中并用水(3x20ml)萃取。将有机层用Na_2SO_4干燥并在真空中浓缩。

[0382] 将残余物溶解在30ml二氯甲烷中。然后加入四丁基溴化铵(63.8mg,198μmol)和KOH(50％,6ml)。将反应在室温搅拌1h。将反应混合物倒入二氯甲烷(50ml)中并用水(3x20ml)萃取。将有机层用Na_2SO_4干燥并在真空中浓缩。将粗制物料通过急骤色谱(硅胶，50g,在庚烷中的20％至50％EtOAc)纯化。获得标题化合物，为灰白色晶体(1.92g,71.8％)。MS(m/e)＝272.1[M+H]$^+$。

[0383] 步骤2:3-苄基-1-(4-溴-3-甲氧基苯基)吡咯烷-2-酮

[0384] 在氮气氛下，在25mL三颈烧瓶中，将2,2,6,6-四甲基哌啶(188mg,1.33mmol)与THF(4ml)混合，得到无色溶液。在0℃，缓慢加入正丁基锂(1.6M于己烷中,833μl,1.33mmol)。将反应在0℃搅拌30min。然后缓慢加入稀释在3ml THF中的1-(4-溴-3-甲氧基苯基)吡咯烷-2-酮(300mg,1.11mmol,Eq:1.00)。将反应在0℃搅拌1h。然后加入(溴甲基)苯(228mg,159μl,1.33mmol)。将反应在0℃搅拌30min。将反应在室温搅拌5d。将反应混合物倒入2x20mL乙酸乙酯中并用水(2x15ml)萃取。将有机层用15ml盐水洗涤。将有机层用Na_2SO_4干燥并在真空中浓缩。将粗制物料通过急骤色谱(硅胶,20g,0％至20％EtOAc,在庚烷中)纯化。获得标题化合物，为浅黄色胶质(120mg,30.0％)。MS(m/e)＝360.06[M+H]$^+$。

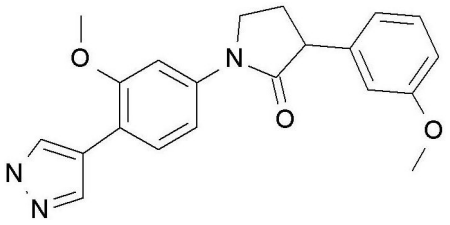
[0385] 步骤3:3-苄基-1-(3-甲氧基-4-(1H-吡唑-4-基)苯基)吡咯烷-2-酮

[0386] 将3-苄基-1-(4-溴-3-甲氧基苯基)吡咯烷-2-酮(120mg,333μmol)、4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)-1H-吡唑-1-甲酸叔丁酯(108mg,366μmol)和碳酸钠(833μl,1.67mmol)与二噁烷(5.00ml)混合。在氮气氛下，加入1,1′-双(二苯基膦)二茂铁-二氯化钯(II)二氯甲烷复合物(27.2mg,33.3μmol)。将反应在80℃搅拌过夜。将反应混

合物倒入25mL乙酸乙酯中并用水(2x15mL)萃取。将有机层用Na_2SO_4干燥并且在真空中浓缩。将粗制物料通过急骤色谱(硅胶,10g,在庚烷中的30％至60％EtOAc)纯化。获得标题化合物,为浅褐色固体(7.3mg,6.31％)。MS(m/e)＝348.17[M+H]$^+$。

[0387] 实施例24

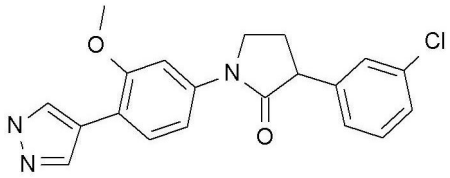
[0388] 1-(3-甲氧基-4-(1H-吡唑-4-基)苯基)-3-(3-甲氧基苯基)吡咯烷-2-酮

[0389] 

[0390] 与实施例12类似,在步骤1中使用2-(3-甲氧基苯基)乙酸并且在步骤2中使用4-溴-3-甲氧基苯胺制备标题化合物。MS(m/e)＝364.17[M+H]$^+$。

[0391] 实施例25

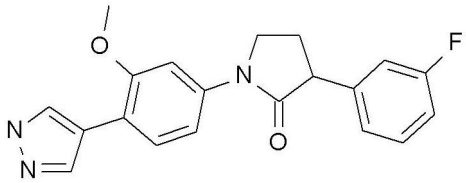
[0392] 3-(3-氯苯基)-1-(3-甲氧基-4-(1H-吡唑-4-基)苯基)吡咯烷-2-酮

[0393] 

[0394] 与实施例12类似,在步骤1中使用2-(3-氯苯基)乙酸并且在步骤2中使用4-溴-3-甲氧基苯胺制备标题化合物。MS(m/e)＝368.11[M+H]$^+$。

[0395] 实施例26

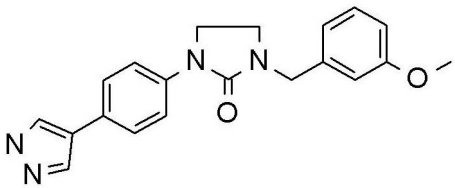
[0396] 3-(3-氟苯基)-1-(3-甲氧基-4-(1H-吡唑-4-基)苯基)吡咯烷-2-酮

[0397] 

[0398] 与实施例12类似,在步骤1中使用2-(3-氟苯基)乙酸并且在步骤2中使用4-溴-3-甲氧基苯胺制备标题化合物。MS(m/e)＝352.14[M+H]$^+$。

[0399] 实施例27

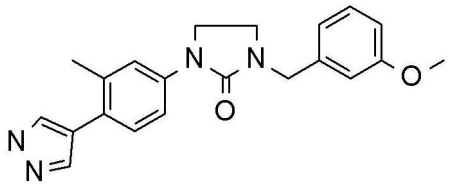
[0400] 1-[(3-甲氧基苯基)甲基]-3-[4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮

[0401] 

[0402] 与实施例5类似,在步骤1中使用N-(2-氧代乙基)氨基甲酸叔丁酯和4-溴苯基胺并且在步骤3中使用1-(溴甲基)-3-甲氧基-苯制备标题化合物。LC-MS:349(M+H)$^+$。

[0403] 实施例28

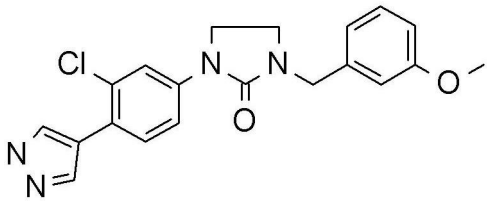
[0404] 1-[(3-甲氧基苯基)甲基]-3-[3-甲基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮

[0405] 

[0406] 与实施例5类似，在步骤1中使用N-(2-氧代乙基)氨基甲酸叔丁酯和4-溴-3-甲基-苯胺并且在步骤3中使用1-(溴甲基)-3-甲氧基-苯制备标题化合物。LC-MS:363(M+H)$^+$。

[0407] 实施例29

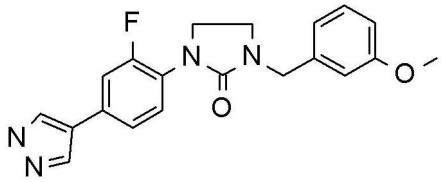
[0408] 1-[3-氯-4-(1H-吡唑-4-基)苯基]-3-[(3-甲氧基苯基)甲基]咪唑烷-2-酮

[0409] 

[0410] 与实施例5类似，在步骤1中使用N-(2-氧代乙基)氨基甲酸叔丁酯和4-溴-3-氯-苯胺并且在步骤3中使用1-(溴甲基)-3-甲氧基-苯制备标题化合物。LC-MS:383(M+H)$^+$。

[0411] 实施例30

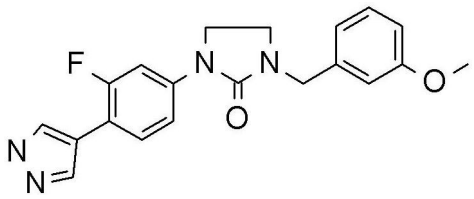
[0412] 1-[2-氟-4-(1H-吡唑-4-基)苯基]-3-[(3-甲氧基苯基)甲基]咪唑烷-2-酮

[0413] 

[0414] 与实施例5类似，在步骤1中使用N-(2-氧代乙基)氨基甲酸叔丁酯和4-溴-2-氟-苯胺，并且在步骤3中使用1-(溴甲基)-3-甲氧基-苯制备标题化合物。LC-MS:367(M+H)$^+$。

[0415] 实施例31

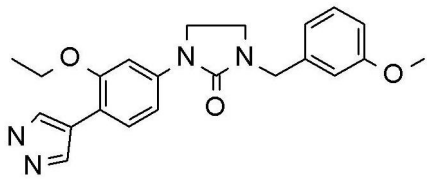
[0416] 1-[3-氟-4-(1H-吡唑-4-基)苯基]-3-[(3-甲氧基苯基)甲基]咪唑烷-2-酮

[0417] 

[0418] 与实施例5类似，在步骤1中使用N-(2-氧代乙基)氨基甲酸叔丁酯和4-溴-3-氟-苯胺并且在步骤3中使用1-(溴甲基)-3-甲氧基-苯制备标题化合物。LC-MS:367(M+H)$^+$。

[0419] 实施例32

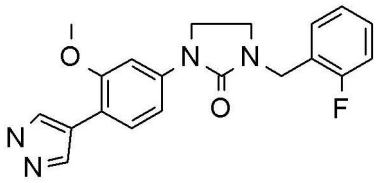
[0420] 1-[3-乙氧基-4-(1H-吡唑-4-基)苯基]-3-[(3-甲氧基苯基)甲基]咪唑烷-2-酮

[0421] 

[0422] 与实施例5类似，在步骤1中使用N-(2-氧代乙基)氨基甲酸叔丁酯和4-溴-3-乙氧基-苯胺并且在步骤3中使用1-(溴甲基)-3-甲氧基-苯制备标题化合物。LC-MS:393(M+H)$^+$。

[0423] 实施例33

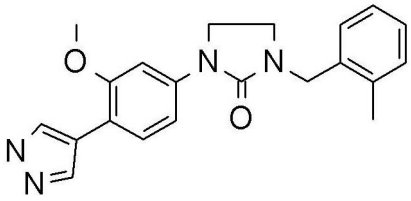
[0424] 1-[(2-氟苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮

[0425] 

[0426] 与实施例5类似,在步骤1中使用N-(2-氧代乙基)氨基甲酸叔丁酯并且在步骤3中使用1-(溴甲基)-2-氟-苯制备标题化合物。LC-MS:367(M+H)$^+$。

[0427] 实施例34

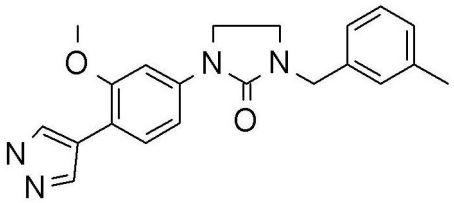
[0428] 1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-(邻甲苯基甲基)咪唑烷-2-酮

[0429] 

[0430] 与实施例5类似,在步骤1中使用N-(2-氧代乙基)氨基甲酸叔丁酯并且在步骤3中使用1-(溴甲基)-2-甲基-苯制备标题化合物。LC-MS:363(M+H)$^+$。

[0431] 实施例35

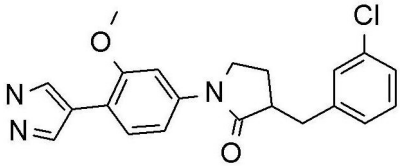
[0432] 1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-(间甲苯基甲基)咪唑烷-2-酮

[0433] 

[0434] 与实施例5类似,在步骤1中使用N-(2-氧代乙基)氨基甲酸叔丁酯并且在步骤3中使用1-(溴甲基)-3-甲基-苯制备标题化合物。LC-MS:363(M+H)$^+$。

[0435] 实施例36

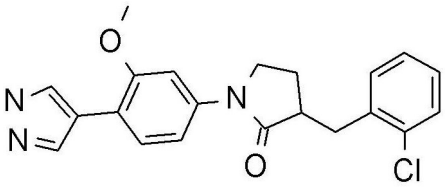
[0436] 3-[(3-氯苯基)甲基]-1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]吡咯烷-2-酮

[0437] 

[0438] 与实施例23类似,在步骤2中使用1-(溴甲基)-3-氯-苯获得标题化合物。MS:382.0(M+H)$^+$。

[0439] 实施例37

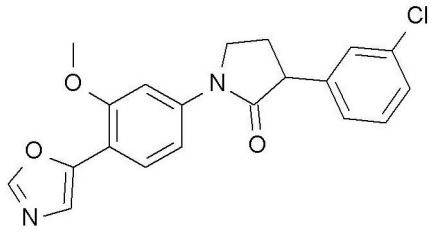
[0440] 3-[(2-氯苯基)甲基]-1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]吡咯烷-2-酮

[0441] 

[0442] 与实施例23类似，在步骤2中使用1-(溴甲基)-2-氯-苯获得标题化合物。MS:382.0 $(M+H)^+$。

[0443] 实施例38

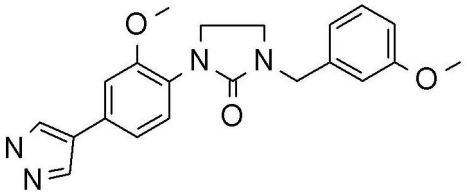
[0444] 3-(3-氯苯基)-1-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]吡咯烷-2-酮

[0445] 

[0446] 与实施例3类似，在步骤1中使用3-氯苯基乙酸制备标题化合物。MS:367.2$(M-H)^+$。

[0447] 实施例39

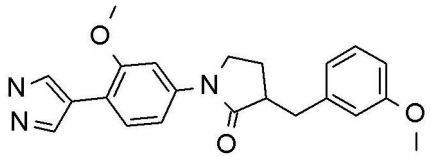
[0448] 1-[(3-甲氧基苯基)甲基]-3-[2-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮

[0449] 

[0450] 与实施例5类似，在步骤1中使用N-(2-氧代乙基)氨基甲酸叔丁酯和4-溴-2-甲氧基-苯胺并且在步骤3中使用1-(溴甲基)-3-甲氧基-苯制备标题化合物。LC-MS:379$(M+H)^+$。

[0451] 实施例40

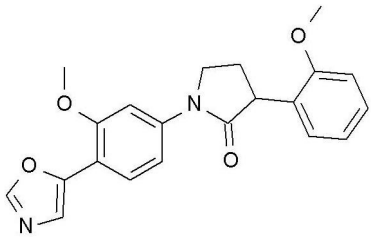
[0452] 3-[(3-甲氧基苯基)甲基]-1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]吡咯烷-2-酮

[0453] 

[0454] 与实施例23类似，在步骤2中使用1-(溴甲基)-3-甲氧基-苯获得标题化合物。MS:378.0$(M+H)^+$。

[0455] 实施例41

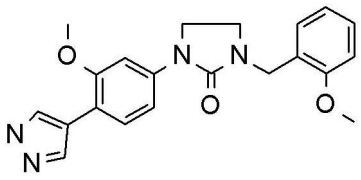
[0456] 1-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]-3-(2-甲氧基苯基)吡咯烷-2-酮

[0457] 

[0458] 与实施例3类似，在步骤1中使用2-甲氧基苯基乙酸制备标题化合物。MS:365.3$(M+H)^+$。

[0459] 实施例42

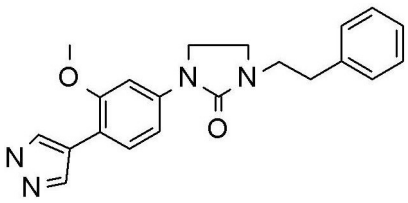
[0460] 1-[(2-甲氧基苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮

[0461] 

[0462] 与实施例5类似，在步骤1中使用N-(2-氧代乙基)氨基甲酸叔丁酯并且在步骤3中使用1-(溴甲基)-2-甲氧基-苯制备标题化合物。LC-MS:379(M+H)$^+$。

[0463] 实施例43

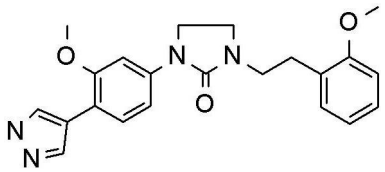
[0464] 1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-(2-苯基乙基)咪唑烷-2-酮

[0465] 

[0466] 与实施例5类似，在步骤1中使用N-(2-氧代乙基)氨基甲酸叔丁酯并且在步骤3中使用2-溴乙基苯制备标题化合物。LC-MS:363(M+H)$^+$。

[0467] 实施例44

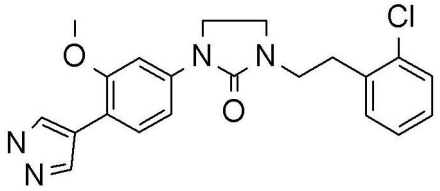
[0468] 1-[2-(2-甲氧基苯基)乙基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮

[0469] 

[0470] 与实施例5类似，在步骤1中使用N-(2-氧代乙基)氨基甲酸叔丁酯并且在步骤3中使用1-(2-溴乙基)-2-甲氧基-苯制备标题化合物。LC-MS:393(M+H)$^+$。

[0471] 实施例45

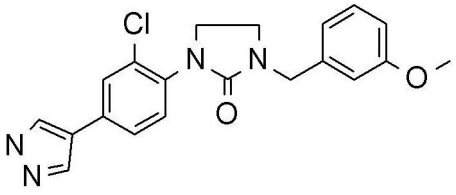
[0472] 1-[2-(2-氯苯基)乙基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮

[0473] 

[0474] 与实施例5类似，在步骤1中使用N-(2-氧代乙基)氨基甲酸叔丁酯并且在步骤3中使用1-(2-溴乙基)-2-氯-苯制备标题化合物。LC-MS:397(M+H)$^+$。

[0475] 实施例46

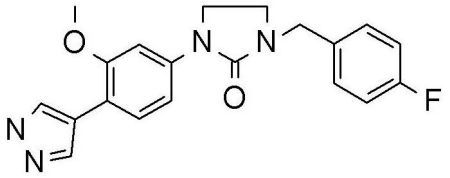
[0476] 1-[2-氯-4-(1H-吡唑-4-基)苯基]-3-[(3-甲氧基苯基)甲基]咪唑烷-2-酮

[0477] 

[0478] 与实施例5类似，在步骤1中使用N-(2-氧代乙基)氨基甲酸叔丁酯和4-溴-2-氯-苯胺并且在步骤3中使用1-(溴甲基)-3-甲氧基-苯制备标题化合物。LC-MS:383(M+H)$^+$。

[0479] 实施例47

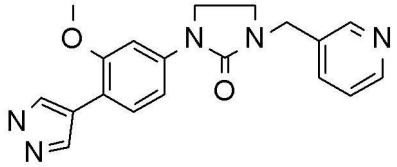
[0480] 1-[(4-氟苯基)甲基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮

[0481] 

[0482] 与实施例5类似,在步骤1中使用N-(2-氧代乙基)氨基甲酸叔丁酯并且在步骤3中使用1-(溴甲基)-4-氟-苯制备标题化合物。LC-MS:367(M+H)$^+$。

[0483] 实施例48

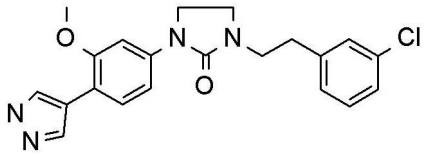
[0484] 1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-(3-吡啶基甲基)咪唑烷-2-酮

[0485] 

[0486] 与实施例5类似,在步骤1中使用N-(2-氧代乙基)氨基甲酸叔丁酯并且在步骤3中使用3-(溴甲基)吡啶制备标题化合物。LC-MS:350(M+H)$^+$。

[0487] 实施例49

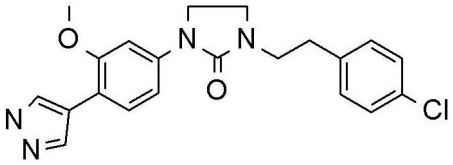
[0488] 1-[2-(3-氯苯基)乙基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮

[0489] 

[0490] 与实施例5类似,在步骤1中使用N-(2-氧代乙基)氨基甲酸叔丁酯并且在步骤3中使用1-(2-溴乙基)-3-氯-苯制备标题化合物。LC-MS:397(M+H)$^+$。

[0491] 实施例50

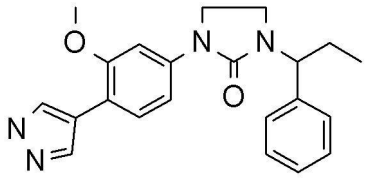
[0492] 1-[2-(4-氯苯基)乙基]-3-[3-甲氧基-4-(1H-吡唑-4-基)苯基]咪唑烷-2-酮

[0493] 

[0494] 与实施例5类似,在步骤1中使用N-(2-氧代乙基)氨基甲酸叔丁酯并且在步骤3中使用1-(2-溴乙基)-4-氯-苯制备标题化合物。LC-MS:397(M+H)$^+$。

[0495] 实施例51

[0496] 1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-(1-苯基丙基)咪唑烷-2-酮

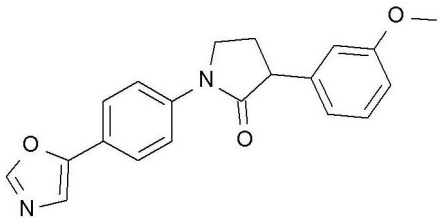
[0497] 

[0498] 与实施例5类似,在步骤4中使用1-(4-溴-3-甲氧基-苯基)-3-(1-苯基-丙基)-咪唑烷-2-酮和4-(4,4,5,5-四甲基-[1,3,2]二氧杂硼杂环戊烷-2-基)-吡唑-1-甲酸叔丁酯

制备标题化合物。LC-MS:377(M+H)$^+$。

[0499] 实施例52

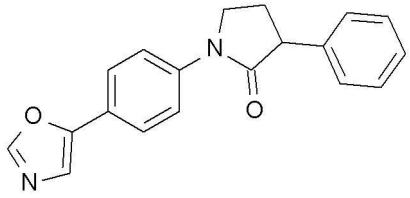
[0500] 3-(3-甲氧基苯基)-1-[4-(1,3-噁唑-5-基)苯基]吡咯烷-2-酮

[0501] 

[0502] 与实施例3类似,在步骤1中使用3-甲氧基苯基乙酸并且在步骤2中使用4-噁唑-5-基苯胺制备标题化合物。MS:335.3(M+H)$^+$。

[0503] 实施例53

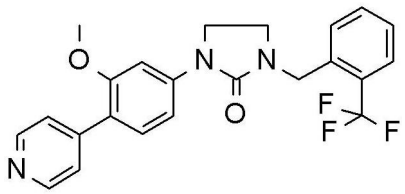
[0504] 1-[4-(1,3-噁唑-5-基)苯基]-3-苯基吡咯烷-2-酮

[0505] 

[0506] 与实施例3类似,在步骤1中使用苯基乙酸并且在步骤2中使用4-噁唑-5-基苯胺制备标题化合物。MS:305.2(M+H)$^+$。

[0507] 实施例54

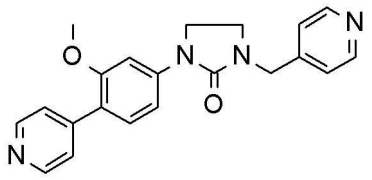
[0508] 1-[3-甲氧基-4-(4-吡啶基)苯基]-3-[[2-(三氟甲基)苯基]甲基]咪唑烷-2-酮

[0509] 

[0510] 与实施例5类似,在步骤1中使用N-(2-氧代乙基)氨基甲酸叔丁酯、在步骤3中使用1-(溴甲基)-2-三氟甲基-苯并且在步骤4中使用吡啶-4-基硼酸制备标题化合物。LC-MS:428(M+H)$^+$。

[0511] 实施例55

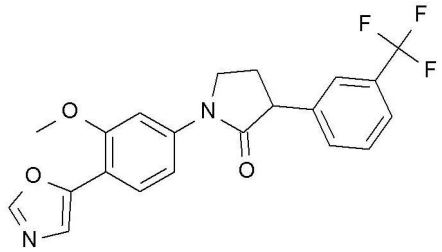
[0512] 1-[3-甲氧基-4-(4-吡啶基)苯基]-3-(4-吡啶基甲基)咪唑烷-2-酮

[0513] 

[0514] 与实施例5类似,在步骤1中使用N-(2-氧代乙基)氨基甲酸叔丁酯、在步骤3中使用4-(溴甲基)吡啶并且在步骤4中使用吡啶-4-基硼酸制备标题化合物。LC-MS:361(M+H)$^+$。

[0515] 实施例56

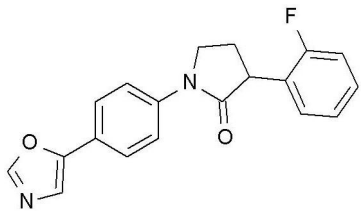
[0516] 1-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]-3-[3-(三氟甲基)苯基]吡咯烷-2-酮

[0517] 

[0518] 与实施例3类似，在步骤1中使用3-三氟甲基苯基乙酸制备标题化合物。MS:403.2 $(M+H)^+$。

[0519] 实施例57

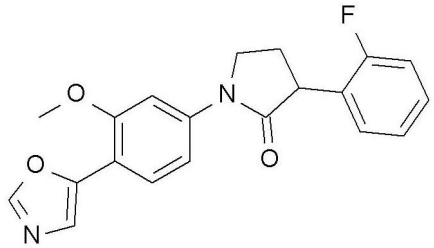
[0520] 3-(2-氟苯基)-1-[4-(1,3-噁唑-5-基)苯基]吡咯烷-2-酮

[0521] 

[0522] 与实施例3类似，在步骤1中使用2-氟苯基乙酸并且在步骤2中使用4-噁唑-5-基苯胺制备标题化合物。MS:323.2 $(M+H)^+$。

[0523] 实施例58

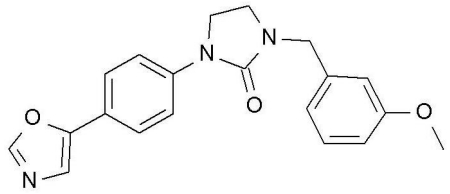
[0524] 3-(2-氟苯基)-1-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]吡咯烷-2-酮

[0525] 

[0526] 与实施例3类似，在步骤1中使用2-氟苯基乙酸制备标题化合物。MS:353.2 $(M+H)^+$。

[0527] 实施例59

[0528] 1-[(3-甲氧基苯基)甲基]-3-[4-(1,3-噁唑-5-基)苯基]咪唑烷-2-酮

[0529] 

[0530] 步骤1:2-(4-(噁唑-5-基)苯基氨基)乙基氨基甲酸叔丁酯

[0531] 在0℃向4-(噁唑-5-基)苯胺(0.5g,3.12mmol,Eq:1.00)在二氯甲烷(31.5ml)中的溶液中加入2-氧代乙基氨基甲酸叔丁酯(628mg,3.75mmol,Eq:1.2)和AcOH(187mg,179μl,3.12mmol,Eq:1.00)。将溶液在0℃搅拌0.5h。然后加入三乙酰氧基硼氢化钠(992mg,4.68mmol),并且将溶液在23℃搅拌6h。将混合物用水(20ml)稀释，分离有机层，并将水层用二氯甲烷萃取。将有机层用盐水洗涤，用$MgSO_4$干燥并蒸发。将粗产物(1.25g)通过急骤色谱纯化，得到标题化合物(0.92g,97％)。MS:304.2 $(M+H)^+$。

[0532] 步骤2:1-(4-(噁唑-5-基)苯基)咪唑烷-2-酮

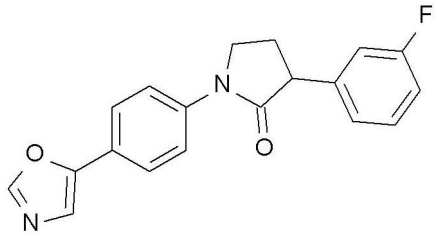
[0533] 在0℃向叔丁醇钾(681mg,6.07mmol)在THF(25.5ml)中的溶液中加入2-(4-(噁唑-5-基)苯基氨基)乙基氨基甲酸叔丁酯(0.92g,3.03mmol)在THF(25.5ml)中的溶液,并且将得到的溶液在23℃搅拌2h。将混合物用100ml饱和NH_4Cl水溶液猝灭并用EtOAc萃取。将有机相用盐水洗涤,用$MgSO_4$干燥并蒸发。将粗产物(0.65g)用3ml AcOEt和10ml庚烷研磨。1/2h后,将混合物过滤,用庚烷洗涤并且在HV干燥,得到标题化合物(560mg,81%)。

[0534] 步骤3:1-[(3-甲氧基苯基)甲基]-3-[4-(1,3-噁唑-5-基)苯基]咪唑烷-2-酮

[0535] 在0℃向氢化钠(21.0mg,525μmol)在DMF(1.35ml)中的悬浮液中加入1-(4-(噁唑-5-基)苯基)咪唑烷-2-酮(80.2mg,0.35mmol)在DMF(3.37ml)中的溶液,并且将得到的混合物在0℃搅拌0.5h。然后将1-(溴甲基)-3-甲氧基苯(106mg,73.5μl,525μmol)加入至混合物中。在23℃将溶液搅拌另外19h。将混合物用20ml水稀释并用EtOAc萃取。将有机层用盐水洗涤,经$MgSO_4$干燥并蒸发。将粗制物料(1.31g)通过柱色谱(硅胶,20g,庚烷/AcOEt 0-50%)纯化。将产物(0.06g)用2ml二氯甲烷和15ml庚烷结晶。1/2h后,将混合物过滤,用庚烷洗涤,并且在HV干燥,得到24mg(20%)的标题化合物。MS:350.2$(M+H)^+$。

[0536] 实施例60

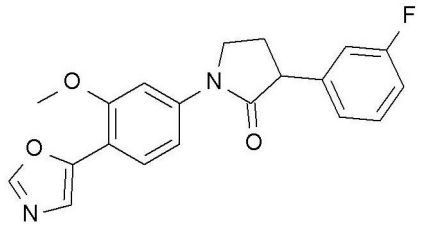
[0537] 3-(3-氟苯基)-1-[4-(1,3-噁唑-5-基)苯基]吡咯烷-2-酮

[0538] 

[0539] 与实施例3类似,在步骤1中使用3-氟苯基乙酸并且在步骤2中使用4-噁唑-5-基苯胺制备标题化合物。MS:323.2$(M+H)^+$。

[0540] 实施例61

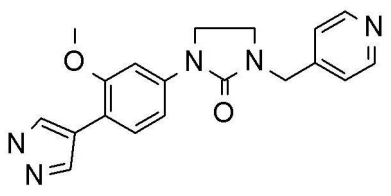
[0541] 3-(3-氟苯基)-1-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]吡咯烷-2-酮

[0542] 

[0543] 与实施例3类似,在步骤1中使用3-氟苯基乙酸制备标题化合物。MS:353.2$(M+H)^+$。

[0544] 实施例62

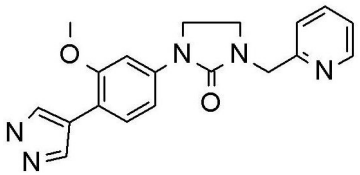
[0545] 1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-(4-吡啶基甲基)咪唑烷-2-酮

[0546] 

[0547] 与实施例5类似，在步骤1中使用N-(2-氧代乙基)氨基甲酸叔丁酯并且在步骤3中使用4-(溴甲基)吡啶制备标题化合物。LC-MS:350(M+H)$^+$。

[0548] 实施例63

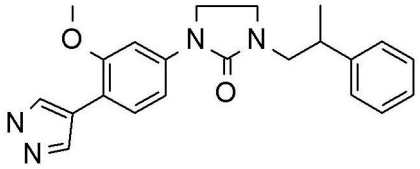
[0549] 1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-(2-吡啶基甲基)咪唑烷-2-酮

[0550] 

[0551] 与实施例5类似，在步骤1中使用N-(2-氧代乙基)氨基甲酸叔丁酯并且在步骤3中使用2-(溴甲基)吡啶制备标题化合物。LC-MS:350(M+H)$^+$。

[0552] 实施例64

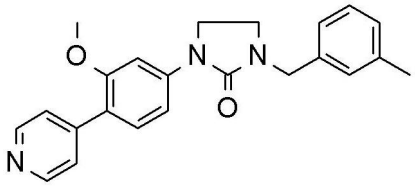
[0553] 1-[3-甲氧基-4-(1H-吡唑-4-基)苯基]-3-(2-苯基丙基)咪唑烷-2-酮

[0554] 

[0555] 与实施例5类似，在步骤1中使用N-(2-氧代乙基)氨基甲酸叔丁酯并且在步骤3中使用(2-溴-1-甲基-乙基)苯制备标题化合物。LC-MS:377(M+H)$^+$。

[0556] 实施例65

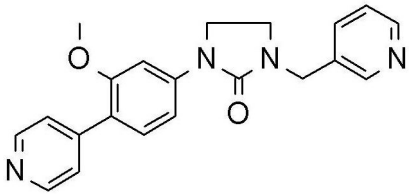
[0557] 1-[3-甲氧基-4-(4-吡啶基)苯基]-3-(间甲苯基甲基)咪唑烷-2-酮

[0558] 

[0559] 与实施例5类似，在步骤1中使用N-(2-氧代乙基)氨基甲酸叔丁酯、在步骤3中使用1-(溴甲基)-3-甲基-苯并且在步骤4中使用吡啶-4-基硼酸制备标题化合物。LC-MS:374(M+H)$^+$。

[0560] 实施例66

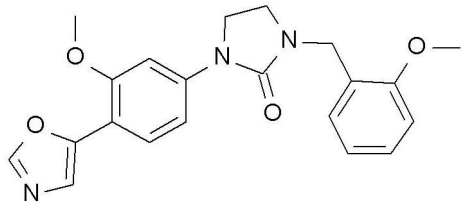
[0561] 1-[3-甲氧基-4-(4-吡啶基)苯基]-3-(3-吡啶基甲基)咪唑烷-2-酮

[0562] 

[0563] 与实施例5类似，在步骤1中使用N-(2-氧代乙基)氨基甲酸叔丁酯、在步骤3中使用3-(溴甲基)吡啶并且在步骤4中使用吡啶-4-基硼酸制备标题化合物。LC-MS:361(M+H)$^+$。

[0564] 实施例67

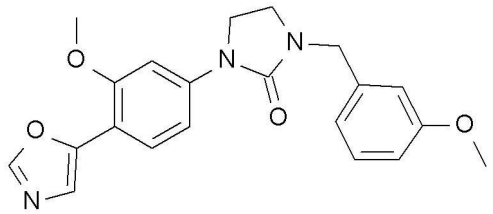
[0565] 1-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]-3-[(2-甲氧基苯基)甲基]咪唑烷-2-酮

[0566] 

[0567] 与实施例59类似，在步骤1中使用3-甲氧基-4-(噁唑-5-基)苯胺并且在步骤3中使用1-(氯甲基)-2-甲氧基苯制备标题化合物。MS:380.2$(M+H)^+$。

[0568] 实施例68

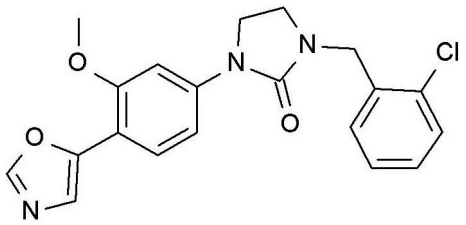
[0569] 1-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]-3-[(3-甲氧基苯基)甲基]咪唑烷-2-酮

[0570] 

[0571] 与实施例59类似，在步骤1中使用3-甲氧基-4-(噁唑-5-基)苯胺并且在步骤3中使用1-(溴甲基)-3-甲氧基苯制备标题化合物。MS:380.2$(M+H)^+$。

[0572] 实施例69

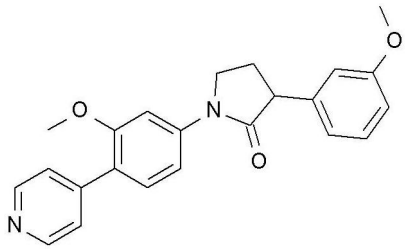
[0573] 1-[(2-氯苯基)甲基]-3-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]咪唑烷-2-酮

[0574] 

[0575] 与实施例59类似，在步骤1中使用3-甲氧基-4-(噁唑-5-基)苯胺并且在步骤3中使用1-(溴甲基)-3-氯苯制备标题化合物。MS:384.2$(M+H)^+$。

[0576] 实施例70

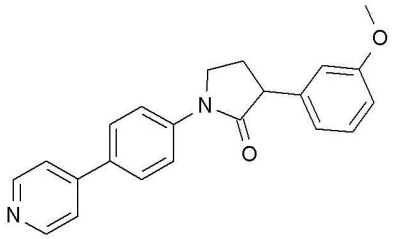
[0577] 3-(3-甲氧基苯基)-1-(3-甲氧基-4-吡啶-4-基苯基)吡咯烷-2-酮

[0578] 

[0579] 与实施例12类似，在步骤1中使用3-甲基苯基乙酸并且在步骤6中使用吡啶-4-基硼酸制备标题化合物。LC-MS:375.3$(M+H)^+$。

[0580] 实施例71

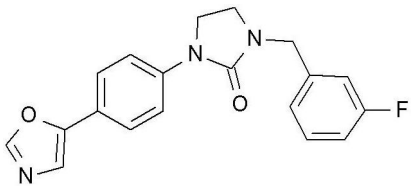
[0581] 3-(3-甲氧基苯基)-1-(4-吡啶-4-基苯基)吡咯烷-2-酮

[0582] 

[0583] 与实施例12类似，在步骤1中使用3-甲基苯基乙酸、在步骤2中使用4-溴苯胺并且在步骤6中使用吡啶-4-基硼酸制备标题化合物。LC-MS:345.3$(M+H)^+$。

[0584] 实施例72

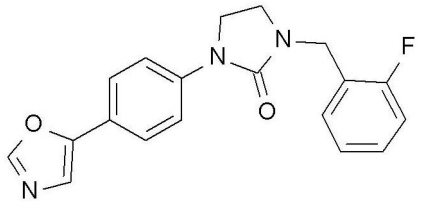
[0585] 1-[(3-氟苯基)甲基]-3-[4-(1,3-噁唑-5-基)苯基]咪唑烷-2-酮

[0586] 

[0587] 与实施例59类似，在步骤3中使用1-(溴甲基)-3-氟苯制备标题化合物。MS:338.2$(M+H)^+$。

[0588] 实施例73

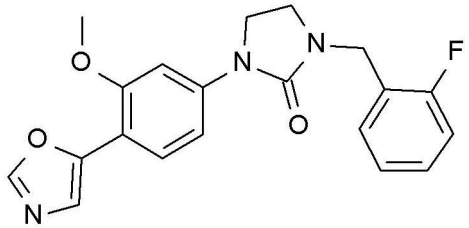
[0589] 1-[(2-氟苯基)甲基]-3-[4-(1,3-噁唑-5-基)苯基]咪唑烷-2-酮

[0590] 

[0591] 与实施例59类似，在步骤3中使用1-(溴甲基)-2-氟苯制备标题化合物。MS:338.2$(M+H)^+$。

[0592] 实施例74

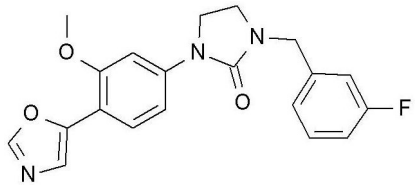
[0593] 1-[(2-氟苯基)甲基]-3-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]咪唑烷-2-酮

[0594] 

[0595] 与实施例59类似，在步骤1中使用3-甲氧基-4-(噁唑-5-基)苯胺并且在步骤3中使用1-(溴甲基)-2-氟苯制备标题化合物。MS:368.2$(M+H)^+$。

[0596] 实施例75

[0597] 1-[(3-氟苯基)甲基]-3-[3-甲氧基-4-(1,3-噁唑-5-基)苯基]咪唑烷-2-酮

[0598] 

[0599] 与实施例59类似，在步骤1中使用3-甲氧基-4-(噁唑-5-基)苯胺并且在步骤3中使用1-(溴甲基)-3-氟苯制备标题化合物。MS:368.2$(M+H)^+$。