HETEROARYL DIAZACYCLOALKANES AS CHOLINERGIC LIGANDS AT NICOTINIC ACETYLCHOLINE RECEPTORS

The present invention relates to novel heteroaryl diazacycloalkane derivatives which are cholinergic ligands at nicotinic ACh receptors. The compounds of the invention are useful for the treatment of conditions or disorders or diseases involving the cholinergic system of the central or peripheral nervous system, pain, inflammatory diseases, diseases caused by smooth muscle contractions and as assistance in the cessation of chemical substance abuse.

## Background

The endogenous cholinergic neurotransmitter, acetylcholine, exert its biological effect via two types of cholinergic receptors; the muscarinic ACh receptors and the nicotinic ACh receptors. As it is well established that muscarinic ACh receptors dominate quantitatively over nicotinic ACh receptors in the brain area important to memory and cognition, much research aimed at the development of agents for the treatment of memory related disorders have focused on the synthesis of muscarinic ACh receptor modulators. Recently, however, an interest in the development of nicotinic ACh receptor modulators has emerged. Several diseases are associated with degeneration of the cholinergic system i.e. senile dementia of the Alzheimer type, vascular dementia and cognitive impairment due to the organic brain damage disease related directly to alcoholism. Indeed several CNS disorders can be attributed to a cholinergic deficiency, a dopaminergic deficiency, an adrenergic deficiency or a serotonergic deficiency. Alzheimer's disease is characterised by a profound loss of memory and cognitive functions caused by a severe depletion of cholinergic neurons, i.e. neurons that release acetylcholine. A reduction in the number of nicotinic ACh receptors are also observed with the progression of Alzheimer's disease. It is believed that the neurons in the cortex that die with the progression of Alzheimer's disease do so because of lack of stimulation of the nicotinic ACh receptors. It is predicted that treatment of Alzheimer's patients with nicotinic ACh receptor modulators will not only improve the memory of patients but in addition act to keep these neurons alive. Smoking actually seems to protect individuals against neurodegeneration and compounds behaving on these receptor may very likely have a generally neuroprotective effect.
However degeneration of the cholinergic system is not limited to individuals suffering from i.e. Alzheimers disease but is also seen in healthy aged adults and rats. Therefore it is suggested that the cholinergic system is involved and partly responsible for the memory disturbances seen in aged animals and humans. Nicotine receptor modulator may therefore be useful in the

treatment of Alzheimer's disease, memory loss, memory dysfunction, AIDS-dementia, senile dementia or neurodegenerative disorders.

Parkinsons disease appears to involve degeneration of dopaminergic neurons. One symptom of the disease has been observed to be loss of nicotinic receptors associated with the dopaminergic neurons and possibly interfering with the process of release of dopamine. As sustained nicotine administration increases the number of receptors present, administration of nicotine receptor modulators may ameliorate the symptoms of Parkinson's disease. Other condition or disorders or disease ascribed to deficiencies in the dopaminergic system is: drug addiction, depression, obesity and narcolepsy.

Tourette's syndrome is a neuropsychiatric disorder involving a range of neurological and behavioral symptoms. It is believed that neurotransmitter dysfunction is involved though the pathophysiology is still unknown and that nicotine will be beneficial in the treatment of the disease (Devor et. al. The Lancet, vol. 8670 p. 1046, 1989)

Schizophrenia is a severe psychiatric illness. Neuroleptic compounds has been used in the treatment of the disease, the effect of the compounds is believed to be interaction in the dopaminergic system. Nicotine is proposed to be effective in the treatment of schizophrenia (ie. Adler et. al. Biol. Psychiatry, Vol. 32, p. 607-616, 1992.)

Nicotine has been reported to have en effect on neurotransmitter release in several systems. Release of acetylcholine and dopamine by neurons upon administration of nicotine has been reported (J. Neurochem. vol. 43, 1593-1598, 1984) and release of norepinephrine by Hall et. al. (Biochem. Pharmacol. vol. 21, 1829-1838, 1972) Release of serotonin by Hery et. al. (Arch. Int. Pharmacodyn. Ther. vol. 296. p. 91-97, 1977). Release of glutamate by Toth et. al (Neurochem. Res. vol. 17, p. 265-271, 1992)

The serotonin system and dysfunction's of the serotonergic system is believed to be involved in diseases or conditions or disorders like: anxiety, depression, eating disorders, obsessive compulsive disorder, panic disorders, chemical substance abuse, alcoholism, pain, memory deficits and anxiety, pseudodementia, Ganser's syndrome, migraine pain, bulimia, obesity, pre-menstrual syndrome or late luteal phase syndrome, tobacco abuse, post-traumatic syndrome, social phobia, chronic fatigue syndrome, premature ejaculation, erectile difficulty, anorexia nervosa, disorders of sleep, autism, mutism or trichotillomania.

Nicotine improves concentration and task performance. Therefore compounds exhibiting nicotine receptor modulating properties will be likely to be useful compounds in the treatment of learning deficit, cognition deficit, attention deficit, attention deficit hyperactivity disorder and dyslexia.

Tobacco use and especially cigarette smoking is recognised as a serious health problem. However nicotine withdrawal symptoms associated with smoking cessation makes it difficult to

break this habit. Withdrawal symptoms include anger, anxiety, difficulties in concentrating, restlessness, decreased heart rate and increased appetite and weight gain. Nicotine itself has shown to ease the withdrawal symptoms.

Withdrawal from addictive substances, i.e. opiates, benzodiazepines, ethanol, tobacco or nicotine, is in general a traumatic experience characterised by anxiety and frustration. Nicotine has been found to be effective in reducing anger, irritability, frustration and feelings of tension without causing general response depression, drowsiness or sedation and compounds having same characteristics as nicotine is likely to have same effects.

Mild to moderate pain is normally treatable with NSAID's (non-steroidal anti-inflammatory drugs) while opiates are used preferentially for moderate to severe pain. The opiates have some well-known side-effects, including chemical dependence and abuse potential as well as a depressive effect on the respiratory and gastrointestinal system. There exists therefore a strong need for analgesic compounds that do not exhibit these side effects and which can relieve mild, moderate and severe pain of acute, chronic or recurrent character as well as migraine pain and postoperative pain, phantom limb pain.
Epibatidine, a compound isolated from the skin of a poison frog, is a very potent analgesic with an approximate potency of 500 times that of morphine. The analgesic effect is not affected by naloxone, which is an indication of a negligible affinity for the opiate receptors. Epibatidine is an nicotinic cholinergic receptor agonist and it is therefore very likely, that compounds possessing this receptor modulating character will also show a strong analgesic response.
The compounds of the present invention has proven useful for modulation of smooth muscle contractions and may therefore be used in the treatment or prevention of condition or disorders or diseases inherent from smooth muscle contractions like i.e. convulsive disorders, angina pectoris, premature labor, convulsions, diarrhoea, asthma, epilepsy, tardive dyskinesia, hyperkinesia.

Further, it is well known that nicotine has an effect on appetite and it is predicted that modulators at the nicotine ACh receptor may be useful as appetite suppressants in the treatment of obesity and eating disorders.
The cholinergic receptors play an important role in the functioning of muscles, organs and generally in the central or peripheral system. There are also complex interactions between cholinergic receptors and the function of receptors of other neurotransmitters such as dopamine, serotonin and noradrenaline.

It is likely that nicotine receptor modulator compounds can be effective in preventing or treating conditions or disorders or diseases like: inflammation, inflammatory skin conditions, Chron's disease, inflammatory bowel disease, irritable colon, ulcerative collitis, irritable colon, diarrhoea, neurodegeneration, perpherical neuropathy, amyotrophic lateral sclerosis, nociception, endocrine disorders, thyrotoxicosis, pheochromocytoma, hypertension, arrhytmias, mania, manic depression, Huntington's disease, jetlag.

The compounds of the present invention are nicotine receptor modulators and has the potential to exhibit nicotinic pharmacology, preferentially without the side effects associated with nicotine itself. Additionally, the compounds are expected to have the potential as enhancers of neurotransmitter secretion and suppress symptoms associated with a low activity of neurotransmitters.

**Objects of the Invention**

It is an object of the present invention to provide novel heteroaryl diazacycloalkane derivatives which are useful for the treatment of a range of diseases and disorders characterized by decreased cholinergic function or responsive to the activity of nicotinic ACh receptor agonists.

Another object of the present invention is to provide novel pharmaceutical compositions containing these compounds, as well as methods for the preparation thereof and methods for the treatment therewith.

It is yet another object of the invention to provide novel compounds that have some if not all of the following favourable characteristics:

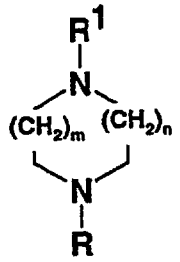
- A selective binding to the receptor subtypes of neuronal nAChR's, e.g. the non-α7 subtypes.
- A low affinity for the muscular subtype.
- A oral efficacy in an *in vivo* (rat model) of arousal/attention.
- A low toxicity *in vivo*.
- No adverse effects on heart rate or blood pressure *in vivo*.
- Compounds that are non-mutagenic.

Other objects will become apparent hereinafter to one skilled in the art.

## Summary of the Invention

The invention then, inter alia, comprises the following, alone or in combination:

A compound represented by the general formula



(I)

any of its enantiomers or any mixture thereof, isotopes thereof or a pharmaceutically acceptable salt thereof;

wherein

n is 1, 2 or 3;

m is 0,1 or 2;

R represents hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, or aralkyl; and

$R^1$ represents **aminophenyl; nitrophenyl; hydroxyphenyl, alkoxyphenyl; a monocyclic 5 to 6 membered heterocyclic group** which may be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, alkoxy, cycloalkoxy, alkenoxy, alkynoxy, alkynoxy, methylenedioxy, halogen, $CF_3$, $OCF_3$, CN, amino, nitro, $-COOR^3$, $-CONR^2R^3$, $-NH-CO_2R^2$, $NHCO-R^2$, $-OCO-NR^2R^3$; wherein $R^2$ and $R^3$ independently represents hydrogen or alkyl;

aryl optionally substituted one or more times with alkyl, cycloalkyl, cycloalkylalkyl alkenyl, alkynyl, alkoxy, cycloalkoxy, alkenoxy, alkynoxy, methylenedioxy, halogen, $CF_3$, $OCF_3$, CN, amino and nitro;

-X-alkyl-Y-alkyl wherein X and Y independently represents O, S, NH, N-alkyl or Se; and alkyl is optionally substituted with alkoxy or thioalkoxy;

$-X-(alkyl)_o$-aryl wherein o is 0 or 1 and X represents O, S, NH, N-alkyl or Se; optionally substituted one or more times with alkyl, cycloalkyl, cycloalkylalkyl alkenyl, alkynyl, alkoxy, cycloalkoxy, alkenoxy, alkynoxy, methylenedioxy, halogen, $CF_3$, $OCF_3$, CN, amino and nitro;

-X-(alkyl)$_o$-Z wherein o is 0 or 1 and X represents O, S, NH, N-alkyl or Se and Z represents a 5- or 6- membered monocyclic heterocyclic group; optionally substituted one or more times with alkyl, cycloalkyl, cycloalkylalkyl alkenyl, alkynyl, alkoxy, cycloalkoxy, alkenoxy, alkynoxy, methylenedioxy, halogen, $CF_3$, $OCF_3$, CN, amino and nitro;

- a monocyclic 5 to 6 membered heterocyclic group optionally substituted one or more times with alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, alkoxy, cycloalkoxy, alkenoxy, alkynoxy, methylenedioxy, halogen, $CF_3$, $OCF_3$, CN, amino and nitro;

or $R^1$ represents **a bicyclic heterocyclic group,** composed of a 5 to 6 membered monocyclic heterocyclic group fused to a benzene ring, and which may be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl alkenyl, alkynyl, alkoxy, alkoxy-alkoxy, cycloalkoxy, alkenoxy, alkynoxy, methylenedioxy, halogen, $CF_3$, $OCF_3$, CN, amino, nitro, aryl optionally substituted one or more times with alkyl, cycloalkyl, cycloalkylalkyl alkenyl, alkynyl, alkoxy, cycloalkoxy, alkenoxy, alkynoxy, methylenedioxy, halogen, $CF_3$, $OCF_3$, CN, amino and nitro; and a monocyclic 5 to 6 membered heterocyclic group optionally substituted one or more times with alkyl, cycloalkyl, cycloalkylalkyl alkenyl, alkynyl, alkoxy, cycloalkoxy, alkenoxy, alkynoxy, methylenedioxy, halogen, $CF_3$, $OCF_3$, CN, amino and nitro;

with the proviso that when $R^1$ is hydroxyphenyl, alkoxyphenyl, nitrophenyl or aminophenyl, then m and n are not both 2;

A pharmaceutical composition, comprising a therapeutically effective amount of a compound of above, or a pharmaceutically acceptable addition salt thereof, together with at least one pharmaceutically acceptable carrier or diluent.

The use of a compound as above for the manufacture of a medicament for the treatment of a disease of a living animal body, including a human, which disease is responsive to the activity of nicotinic ACh receptor modulators.

A compound as above for use as a medicament for treatment of a disease of a living animal body, including a human, which disease is responsive to the activity of nicotinic Ach receptors modulators;

A method of treating a disease of a living animal body, including a human, which disease is responsive to the activity of nicotinic ACh receptor modulators, comprising the step of administering to such a living animal body, including a human, in need thereof a therapeutically effective amount of a compound as above;

**Detailed disclosure of the invention**

A preferred aspect of the invention comprises a compound of formula (I) as above wherein the group bridging R and $R^1$ is a piperazine, a homopiperazine, a 1,4-di-azacyclooctane, a 1,5-di-azacyclooctane, a 1,3-diazacyclohexane or an imidazolidine;

Another preferred aspect of the invention comprises compounds of formula (I) as above wherein R is as defined above and $R^1$ represents an optionally substituted heteroaryl attached to a piperazine, a homopiperazine, a 1,4-diazacyclooctane, a 1,5-diazacyclooctane, an imidazolidine or a 1,3-diazacyclohexane;

Another preferred aspect of the invention comprises compound of formula (I), as above wherein $R^1$ represents **isoquinolinyl;** or
**phenyl** optionally substituted with nitro, hydroxy, amino or alkoxy; or
**pyridyl, quinolinyl, pyridazinyl or pyridinyl** all of which may be optionally substituted one or more times with alkoxy, cycloalkoxy, alkoxyalkoxy, alkoxycycloalkyl, hydroxyalkoxy, thioalkoxy, thioalkylaryl, alkenoxy, alkynoxy, carboxylamido, a bicyclic heterocyclic group, thioalkoxyaryl, thioaryl, hydroxy or trifluoromethanesulfonyloxy; halogen, phenyl optionally substituted with nitro; a monocyclic 5 to 6 membered heterocyclic group optionally substituted with alkyl;

Yet another aspect of the invention comprises a compound of formula (I) as above, wherein $R^1$ represents 3-pyridyl, 3-quinolinyl, 5-methoxy-3-pyridyl, 5-chloro-3-pyridyl, 5-(4-methyl-1-piperazinyl)-3-pyridyl, 5-ethoxy-3-pyridyl, 6-methoxy-3-pyridyl, 5-propyloxy-3-pyridinyl, 5-phenyl-3-pyridyl, 5-(2-methyl-propyloxy)-3-pyridyl, 5-propyl-1-en-oxy-3-pyridyl, 2-chloro-5-methoxy-3-pyridyl, 6-chloro-5-methoxy-3-pyridyl, 6-bromo-5-ethoxy-3-pyridyl, 6-(N-pyrrolidinyl)-3-pyridyl, 6-phenyl-3-pyridyl, 5-(3-nitrophenyl)-3-pyridyl, 5-butoxy-3-pyridyl, 5-methoxyethoxy-3-pyridyl, 5-(2-methyl-propoxy)-3-pyridyl, 5-(2-hydroxy-ethoxy)-3-pyridyl, 5-(3-methyl-butoxy)-3-pyridyl, 5-cyclopropylmethoxy-3-pyridyl, 5-propyloxy-3-pyridyl, 5-hexyloxy-3-pyridyl, 5-cyclohexylmethoxy-3-pyridyl, 6-thioethoxy-3-pyridyl, 5-(2-ethoxy-ethoxy)-3-pyridyl, 5-pentyloxy-3-pyridyl, 5-heptyloxy-3-pyridyl, 5-(propyl-1-en-oxy)-3-pyridyl, 5-thiobenzyl-3-pyridyl,

5-carboxylamido-3-pyridyl, 5-thiophenyl-3-pyridyl, 5-methoxy-methoxy)-3-pyridyl, 5-(3-pyridyl)-3-pyridyl, 5-(1-pyrrolyl)-3-pyridyl, 5-(1-indolyl)-3-pyridyl, 5.6-dimethoxy-3-pyridyl, 5-ethenyloxy-3-pyridyl, 5-cyclopentyloxy-3-pyridyl, 5-(ethoxy-d5)-3-pyridyl, 3-chloro-5-pyridyl, 3-bromo-5-pyridyl, 4- isoquinolinyl, 5-hydroxy-3-pyridyl, 5-trifluoromethanesulfonyl-oxy-3-pyridyl, 5-ethynyl-3-pyridyl, 3-nitrophenyl, 3-aminophenyl, 3-methoxyphenyl, 3-hydroxyphenyl, 6-chloro-3-pyridazinyl, 6-phenyl-3-pyridazinyl, 6-chloro-2-pyrazinyl, 3,6-dimethyl-2-pyrazinyl, 6-methyl-3-pyridazinyl, 5-triflouromethyl-3-pyridyl, 6-bromo-3-pyridyl, 6-chloro-3-pyridyl or 3-pyridazinyl;

A preferred aspect of the invention comprises a compound of formula (I) as above wherein R represents hydrogen, lower alkyl or aralkyl;

The most preferred aspect of the invention comprises a compound of formula (I), as above, said compound being:

4-Methyl-1-(3-pyridyl)-piperazine;
4-Methyl-1-(3-pyridyl)-piperazine;
4-Methyl-1-(5-methoxy-3-pyridyl)-piperazine;
3,5-Bis-[4,4´-methyl-1,1´-piperazinyl]pyridine;
1-(5-Chloro-3-pyridyl)-4-Methyl-piperazine;
4-Methyl-1-(5-phenyl-3-pyridyl)-piperazine;
1-(5-Ethoxy-3-pyridyl)-4-methyl-piperazine;
1-(5-Butoxy-3-pyridyl)-4-methyl-piperazine;
4-Methyl-1-[5-(propyl-1-en-oxy)-3-pyridyl]-piperazine;
1-(5-Ethenyloxy-3-pyridyl)-4-methyl-piperazine;
1-(5-Methoxy-3-pyridyl)-4-methyl-1,5-diazacyclooctane;
1-(6-Chloro-3-pyridazinyl)-4-methyl-1,5-diazacyclooctane;
1-(3-Pyridyl)-piperazine;
1-(3-Pyridyl)-piperazine;
1-(5-Methoxy-3-pyridyl)-piperazine;
1-(5-Chloro-3-pyridyl)-piperazine;
1-(5-Phenyl-3-pyridyl)-piperazine;
1-(5-Methoxy-3-pyridyl)-1,5-diazacyclooctane;
1-(6-Chloro-3-pyridazinyl)-1,5-diazacyclooctane;
1-(6-Chloro-3-pyridazinyl)-1,4-diazacyclooctane;
1-(5-Ethoxy-3-pyridyl)piperazine;

1-(5-Butoxy-3-pyridyl)piperazine;
1-[5-(Propyl-1-en-oxy)-3-pyridyl]-piperazine;
1-(5-Ethenyloxy-3-pyridyl)piperazine;
1-(5-Ethoxy-3-pyridyl)-1,5-diazacyclooctane,
1-(5-Propyloxy-3-pyridinyl)-1,5-diazacyclooctane,
1-[5-(Propyl-1-en-oxy)-3-pyridyl]-1,5-diazacyclooctane,
1-(5-Ethenyloxy-3-pyridyl) 1,5-diazacyclooctane;
1-(5-Ethoxy-3-pyridyl)-4-ethyl-piperazine;
4-Methyl-1-(3-pyridyl)-homopiperazine;
4-Methyl-1-(3-pyridyl)-homopiperazine;
1-(5-Methoxy-3-pyridyl)-4-methyl-homopiperazine;
1-(5-Ethoxy-3-pyridyl)-4-methyl-homopiperazine;
4-Methyl-1-(5-phenyl-3-pyridyl)-homopiperazine;
1-(5-Butoxy-3-pyridyl)-4-methyl-homopiperazine;
1-(5-Methoxyethoxy-3-pyridyl)-4-methyl-homopiperazine;
4-Methyl-1-[5-(2-methyl-propyloxy)-3-pyridyl]-homopiperazine;
1-(5-Cyclopropylmethoxy-3-pyridyl)-4-methyl-homopiperazine;
4-Methyl-1-(5-propyloxy-3-pyridyl)-homopiperazine;
1-(5-Hexyloxy-3-pyridyl)-4-methyl-homopiperazine;
4-Methyl-1-[5-(3-methyl-butoxy)-3-pyridyl]-homopiperazine;
4-Methyl-1-(6-thioethoxy-3-pyridyl)-homopiperazine;
1-(5-Cyclohexylmethoxy-3-pyridyl)-4-methyl-homopiperazine;
4-Methyl-1-(5-pentyloxy-3-pyridyl)-homopiperazine;
1-(5-Heptyloxy-3-pyridyl)-4-methyl-homopiperazine;
4-Methyl-1-(5-propyl-1-en-oxy-3-pyridyl)-homopiperazine;
4-Methyl-1-(5-thiobenzyl-3-pyridyl)-homopiperazine;
4-Methyl-1-[5-(3-pyridyl)-3-pyridyl]-homopiperazine;
4-Methyl-1-(3-nitrophenyl)-homopiperazine;
4-Methyl-1-(6-chloro-3-pyridazinyl)-homopiperazine;
4-Methyl-1-(6-phenyl-3-pyridazinyl)-homopiperazine;
4-Methyl-1-(3-pyridazinyl)-homopiperazine;
4-Methyl-1-(6-methyl-3-pyridazinyl)-homopiperazine;
1-(5-Cyclopentyloxy-3-pyridyl)-4-methyl-homopiperazine;
4-Benzyl-1-(3-pyridyl)-homopiperazine;
4-Ethyl-1-(3-pyridyl)-homopiperazine;

1-(3-Pyridyl)-homopiperazine;
1-(3-Pyridyl)-homopiperazine;
1-(6-Methoxy-3-pyridyl)-homopiperazine;
1-(2-Chloro-5-methoxy-3-pyridyl)-homopiperazine;
1-(6-Chloro-5-methoxy-3-pyridyl)-homopiperazine;
1-(6-Bromo-5-ethoxy-3-pyridyl)-homopiperazine;
1-[6-(N-Pyrrolidinyl)-3-pyridyl]-homopiperazine;
1-(6-Phenyl-3-pyridyl)-4-homopiperazine;
1-[5-(3-Nitrophenyl)-3-pyridyl]-4-homopiperazine;
1-(5-Methoxy-3-pyridyl)-homopiperazine;
1-(5-Phenyl-3-pyridyl)-homopiperazine;
1-(5-Ethoxy-3-pyridyl)-homopiperazine;
1-(5-Butoxy-3-pyridyl)-homopiperazine;
1-(5-Methoxyethoxy-3-pyridyl)-homopiperazine;
1-[5-(2-Methyl-propoxy)-3-pyridyl]-homopiperazine;
1-[5-(2-Hydroxy-ethoxy)-3-pyridyl]-homopiperazine;
1-[5-(3-Methyl-butoxy)-3-pyridyl]-homopiperazine;
1-(5-Cyclopropylmethoxy-3-pyridyl)-homopiperazine;
1-(5-Propyloxy-3-pyridyl)-homopiperazine;
1-(5-Hexyloxy-3-pyridyl)-homopiperazine;
1-(5-Cyclohexylmethoxy-3-pyridyl)-homopiperazine;
1-(6-Thioethoxy-3-pyridyl)-homopiperazine;
1-[5-(2-Ethoxy-ethoxy)-3-pyridyl]-homopiperazine;
1-(5-Pentyloxy-3-pyridyl)-homopiperazine;
1-(5-Heptyloxy-3-pyridyl)-homopiperazine;
1-[5-(Propyl-1-en-oxy)-3-pyridyl]-homopiperazine;
1-(5-Thiobenzyl-3-pyridyl)-homopiperazine;
1-(5-Carboxylamido-3-pyridyl)-homopiperazine;
1-(5-Thiophenyl-3-pyridyl)-homopiperazine;
1-[(5-Methoxy-methoxy)-3-pyridyl]-homopiperazine;
1-[5-(3-Pyridyl)-3-pyridyl]-homopiperazine;
1-(5-(1-Pyrrolyl)-3-pyridyl)-homopiperazine;
1-(5-(1-Indolyl)-3-pyridyl)-homopiperazine;
1-(5.6-Dimethoxy-3-pyridyl)-homopiperazine;
1-(5-Ethenyloxy-3-pyridyl)homopiperazine;

1-(5-Cyclopentyloxy-3-pyridyl)homopiperazine;

1-[5-(Ethoxy-d5)-3-pyridyl]-homopiperazine;

1-(3-Chloro-5-pyridyl)homopiperazine;

1-(3-Bromo-5-pyridyl)homopiperazine;

1-(4- Isoquinolinyl)-homopiperazine;

1-(5-Hydroxy-3-pyridyl)-homopiperazine;

1-(5-Trifluoromethanesulfonyl-oxy-3-pyridyl)-homopiperazine;

1-(5-Ethynyl-3-pyridyl)-homopiperazine;

1-(3-Nitrophenyl)-homopiperazine;

1-(3-Aminophenyl)-homopiperazine;

1-(3-Methoxyphenyl)-homopiperazine;

1-(3-Hydroxyphenyl)-homopiperazine;

1-(6-Chloro-3-pyridazinyl)-homopiperazine;

1-(6-Phenyl-3-pyridazinyl)-homopiperazine;

1-(6-Chloro-2-pyrazinyl)-homopiperazine;

1-(3,6-Dimethyl-2-pyrazinyl)-homopiperazine;

1-(6-Methyl-3-pyridazinyl)-homopiperazine;

1-(5-Triflouromethyl-3-pyridyl)-homopiperazine;

1-(6-Bromo-3-pyridyl)-homopiperazine;

1-(6-Chloro-3-pyridyl)-homopiperazine;

1-(3-Pyridazinyl)-homopiperazine;

N-(5-Methoxy-3-pyridyl)-ethylenediamine;

1-(5-Methoxy-3-pyridyl)-imidazolidine;

1-(5-Methoxy-3-pyridyl)-1.3-diazacyclohexane;

1-(5-Benzyloxy-3-pyridyl)-piperazine;

1-(5-Benzyloxy-3-pyridyl)-homopiperazine;

4-Methyl-1-(5-benzyloxy-3-pyridyl)-piperazine;

4-Methyl-1-(5-benzyloxy-3-pyridyl)-homopiperazine;

1-(5-Thiobenzyloxy-3-pyridyl)-piperazine;

4-Methyl-1-(5-thiobenzyloxy-3-pyridyl)-piperazine;

1-(5-Phenoxy-3-pyridyl)-piperazine;

1-(5-Phenoxy-3-pyridyl)-homopiperazine;

4-Methyl-1-(5-phenoxy-3-pyridyl)-piperazine;

4-Methyl-1-(5-phenoxy-3-pyridyl)-homopiperazine;

1-(5-Thiophenoxy-3-pyridyl)-piperazine;

4-Methyl-1-(5-thiophenoxy-3-pyridyl)-piperazine;
4-Methyl-1-(5-thiophenoxy-3-pyridyl)-homopiperazine;
1-(5-(3-Pyridyloxy)-3-pyridyl)-piperazine;
1-(5-(3-Pyridyloxy)-3-pyridyl)-homopiperazine;
4-Methyl-1-(5-(3-pyridyloxy)-3-pyridyl)-piperazine;
4-Methyl-1-(5-(3-pyridyloxy)-3-pyridyl)-homopiperazine;
1-(5-(2-Thiopyridyloxy)-3-pyridyl)-piperazine;
1-(5-(2-Thiopyridyloxy)-3-pyridyl)-homopiperazine;
4-Methyl-1-(5-(2-thiopyridyloxy)-3-pyridyl)-piperazine;
4-Methyl-1-(5-(2-thiopyridyloxy)-3-pyridyl)-homopiperazine;
1-(5-(4-Thiopyridyloxy)-3-pyridyl)-piperazine;
1-(5-(4-Thiopyridyloxy)-3-pyridyl)-homopiperazine;
4-Methyl-1-(5-(4-thiopyridyloxy)-3-pyridyl)-piperazine;
4-Methyl-1-(5-(4-thiopyridyloxy)-3-pyridyl)-homopiperazine;
1-(5-(2-Pyridyl)-3-pyridyl)-piperazine;
1-(5-(3-Pyridyl)-3-pyridyl)-piperazine;
1-(5-(4-Pyridyl)-3-pyridyl)-piperazine;
1-(5-(2-Pyridyl)-3-pyridyl)-homopiperazine;
1-(5-(4-Pyridyl)-3-pyridyl)-homopiperazine;
4-Methyl-1-(5-(2-pyridyl)-3-pyridyl)-piperazine;
4-Methyl-1-(5-(3-pyridyl)-3-pyridyl)-piperazine;
4-Methyl -1-(5-(4-pyridyl)-3-pyridyl)-piperazine;
4-Methyl -1-(5-(2-pyridyl)-3-pyridyl)-homopiperazine;
4-Methyl -1-(5-(4-pyridyl)-3-pyridyl)-homopiperazine;
1-(5-(2-Furanyl)-3-pyridyl)piperazine;
4-Methyl-1-(5-(2-furanyl)-3-pyridyl)piperazine;
1-(5-(3-Furanyl)-3-pyridyl)piperazine;
4-Methyl-1-(5-(3-furanyl)-3-pyridyl)piperazine;
1-(5-(2-Thienyl)-3-pyridyl)piperazine;
1-(5-(2-Thienyl)-3-pyridyl)homopiperazine;
4-Methyl-1-(5-(2-thienyl)-3-pyridyl)piperazine;
4-Methyl-1-(5-(2-thienyl)-3-pyridyl)homopiperazine;
1-(5-(3-Thienyl)-3-pyridyl)piperazine;
1-(5-(3-Thienyl)-3-pyridyl)homopiperazine;
4-Methyl-1-(5-(3-thienyl)-3-pyridyl)piperazine;

4-Methyl-1-(5-(3-thienyl)-3-pyridyl)homopiperazine;
1-(5-(2-Thiazolyl)-3-pyridyl)piperazine;
1-(5-(2-Thiazolyl)-3-pyridyl)homopiperazine;
4-Methyl-1-(5-(2-thiazolyl)-3-pyridyl)piperazine;
4-Methyl-1-(5-(2-thiazolyl)-3-pyridyl)homopiperazine;
1-(5-(Methyl-ethylendioxy)-3-pyridyl)piperazine;
4-Methyl-1-(5-(methyl-ethylendioxy)-3-pyridyl)piperazine;
1-(5-(Ethyl-ethylendioxy)-3-pyridyl)piperazine;
4-Methyl-1-(5-(ethyl-ethylendioxy)-3-pyridyl)piperazine;
1-(5-(Butyl-ethylendioxy)-3-pyridyl)piperazine;
1-(5-(Butyl-ethylendioxy)-3-pyridyl)homopiperazine;
4-Methyl-1-(5-(butyl-ethylendioxy)-3-pyridyl)piperazine;
4-Methyl-1-(5-(butyl-ethylendioxy)-3-pyridyl)homopiperazine;
1-(5-(Propyl-ethylendioxy)-3-pyridyl)piperazine;
1-(5-(Propyl-ethylendioxy)-3-pyridyl)homopiperazine;
4-Methyl-1-(5-(propyl-ethylendioxy)-3-pyridyl)piperazine;
4-Methyl-1-(5-(propyl-ethylendioxy)-3-pyridyl)homopiperazine;
1-(5-(1,4,7-Trioxanonyl)-3-pyridyl)piperazine;
1-(5-(1,4,7-Trioxanonyl)-3-pyridyl)homopiperazine;
4-Methyl-1-(5-(1,4,7-trioxanonyl)-3-pyridyl)piperazine;
4-Methyl-1-(5-(1,4,7-trioxanonyl)-3-pyridyl)homopiperazine;
1-(5-(1,7-Dioxa-4-thia-octanyl)-3-pyridyl)piperazine;
1-(5-(1,7-Dioxa-4-thia-octanyl)-3-pyridyl)homopiperazine;
4-Methyl-1-(5-(1,7-dioxa-4-thia-octanyl)-3-pyridyl)piperazine;
4-Methyl-1-(5-(1,7-dioxa-4-thia-octanyl)-3-pyridyl)homopiperazine;
1-(5-(2-Methylthio-ethoxy)-3-pyridyl)piperazine;
1-(5-(2-Methylthio-ethoxy)-3-pyridyl)homopiperazine;
4-Methyl-1-(5-(2-methylthio-ethoxy)-3-pyridyl)piperazine;
4-Methyl-1-(5-(2-methylthio-ethoxy)-3-pyridyl)homopiperazine;
1-(5-(2-Ethylthio-ethoxy)-3-pyridyl)piperazine;
1-(5-(2-Ethylthio-ethoxy)-3-pyridyl)homopiperazine;
4-Methyl-1-(5-(2-ethylthio-ethoxy)-3-pyridyl)piperazine;
4-Methyl-1-(5-(2-ethylthio-ethoxy)-3-pyridyl)homopiperazine;
1-(5-(Cyclopropylmethoxy)-3-pyridyl)piperazine;
4-Methyl-1-(5-(cyclopropylmethoxy)-3-pyridyl)piperazine;

1-(5-(sec-Butoxy)-3-pyridyl)piperazine;
4-Methyl-1-(5-(sec-butoxy)-3-pyridyl)piperazine;
1-(5-(Isopentoxy)-3-pyridyl)piperazine;
4-Methyl-1-(5-(isopentoxy)-3-pyridyl)piperazine;
1-(5-(Isopropoxy)-3-pyridyl)piperazine;
1-(5-(Isopropoxy)-3-pyridyl)homopiperazine;
4-Methyl-1-(5-(isopropoxy)-3-pyridyl)piperazine;
4-Methyl-1-(3-pyridyl)-1,4-diazacyclooctane;
1-(3-Pyridyl)-1,4-diazacyclooctane;
1-(3-Pyridyl)-1,5-diazacyclooctane
4-Methyl-1-(3-pyridyl)-1,5-diazacyclooctane;

or a pharmaceutically acceptable addition salt thereof;

**Pharmaceutical acceptable addition salts**

The chemical compound of the invention may be provided in any form suitable for the intended administration. Suitable forms include pharmaceutically (i.e. physiologically) acceptable salts, and pre- or prodrug forms of the chemical compound of the invention.
Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the acetate derived from acetic acid, the aconate derived from aconitic acid, the ascorbate derived from ascorbic acid, the benzenesulfonate derived from benzensulfonic acid, the benzoate derived from benzoic acid, the cinnamate derived from cinnamic acid, the citrate derived from citric acid, the embonate derived from embonic acid, the enantate derived from enanthic acid, the formate derived from formic acid, the fumarate derived from fumaric acid, the glutamate derived from glutamic acid, the glycolate derived from glycolic acid, the hydrochloride derived from hydrochloric acid, the hydrobromide derived from hydrobromic acid, the lactate derived from lactic acid, the maleate derived from maleic acid, the malonate derived from malonic acid, the mandelate derived from mandelic acid, the methanesulfonate derived from methane sulphonic acid, the naphthalene-2-sulphonate derived from naphtalene-2-sulphonic acid, the nitrate derived from nitric acid, the perchlorate derived from perchloric acid, the phosphate derived from phosphoric acid, the phthalate derived from phthalic acid, the salicylate derived from salicylic acid, the sorbate derived from sorbic acid, the stearate derived from stearic acid, the succinate derived from succinic acid, the sulphate derived from sulphuric acid, the tartrate derived from tartaric acid,

the toluene-p-sulphonate derived from p-toluene sulfonic acid, and the like. Such salts may be formed by procedures well known and described in the art.
Other acids such as oxalic acid, which may not be considered pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining a chemical compound of the invention and its pharmaceutically acceptable acid addition salt.
Metal salts of a chemical compound of the invention includes alkali metal salts, such as the sodium salt of a chemical compound of the invention containing a carboxy group.
The chemical compound of the invention may be provided in solved or unsolved form together with a pharmaceutically acceptable solvents such as water, ethanol and the like. In general, solved forms are considered equivalent to dissolved forms for the purposes of this invention.

**Steric isomers**

The chemical compounds of the present invention may exist in (+) and (-) forms as well as in racemic forms. The racemates of these isomers and the individual isomers themselves are within the scope of the present invention.
Racemic forms can be resolved into the optical antipodes by known methods and techniques. One way of separating the diastereomeric salts is by use of an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optical active matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallisation of d- or l- (tartrates, mandelates, or camphorsulphonate) salts for example.
The chemical compounds of the present invention may also be resolved by the formation of diastereomeric amides by reaction of the chemical compounds of the present invention with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid or by the formation of diastereomeric carbamates by reaction of the chemical compound of the present invention with an optically active chloroformate or the like.
Additional methods for the resolving the optical isomers are known in the art. Such methods include those described by *Jaques J, Collet A, & Wilen S* in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).
Moreover, some of the chemical compounds of the invention contains double bonds and may thus exist in two forms, cis- and trans-forms (Z- and E-form), depending on the arrangement

of the substituents around the -C=C- double bond. A chemical compound of the present invention may thus be the cis- or trans-form (Z- and E-form), or it may be a mixture hereof.

**Definition of substituents**

Halogen is fluorine, chlorine, bromine or iodine.

Alkyl means a straight chain or branched chain of one to eight carbon atoms, including but not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, and hexyl;

Cycloalkyl means cyclic alkyl of three to seven carbon atoms, including but not limited to cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl;

Alkenyl means a group of from two to six carbon atoms, including at least one double bond, for example, but not limited to ethenyl, 1,2- or 2,3-propenyl, 1,2-, 2,3-, or 3,4-butenyl.

Alkynyl means a group of from two to six carbon atoms, including at least one triple bond, for example, but not limited to ethynyl, 1,2- or 2,3-propynyl, 1,2- or 2,3- or 3,4-butynyl.

Cycloalkylalkyl means cycloalkyl as above and alkyl as above, meaning for example, cyclopropylmethyl.

Alkoxy is O-alkyl, wherein alkyl is as defined above.

Cycloalkoxy is O-cycloalkyl, wherein cycloalkyl is as defined above.

Alkenoxy is O-alkenyl wherein alkenyl is as defined above.

Alkynoxy is O-alkynyl, wherein alkynyl is as defined above;

Thioalkoxy is S-alkyl, wherein alkyl is as defined above.

Amino is $NH_2$ or NH-alkyl or N-$(alkyl)_2$, wherein alkyl is as defined above.

A monocyclic 5- to 6-membered heterocyclic group includes, for example, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, isothiazol-3-yl, isothiazol-4-yl, isothiazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 1,2,5-oxadiazol-3-yl, 1,2,5-oxadiazol-4-yl, 1,2,5-thiadiazol-3-yl, 1,2,5-thiadiazol-4-yl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrazinyl and 3-pyrazinyl and 1-pyrazolyl, 3-pyrazolyl, and 4-pyrazolyl.

A bicyclic heterocyclic group composed of a 5 to 6 membered monocyclic heterocyclic group and a fused benzene ring means a monocyclic 5 to 6 membered heterocyclic group as above which is fused to a benzene ring including, for example,
2-, 3-, 4-, 5-, 6-, 7-benzofuranyl, 1-, 2-, 4-, 5- benzimidazolyl, 2-, 3-, 4-, 5-, 6-, 7-indolyl, 2-,3-,4-,5-,6-,7-,8-quinolinyl and 1-,3-,4-,5-,6-,7-,8-isoquinolinyl.

Aryl is an aromatic hydrocarbon, such as phenyl and naphthyl.

Aralkyl means alkyl as above and aryl as above, meaning for example benzyl, phenethyl.

Isotopes means one or more atom in the compound is substituted with an isotope of the naturally occuring atoms and includes though not limited to deuterium, tritium, $^{13}C$, $^{14}C$, $^{131}I$, $^{125}I$, $^{123}I$, $^{18}F$;

Further, the compounds of this invention may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

It will be appreciated by those skilled in the art that the compounds of the present invention may contain several chiral centers and that such compounds exist in the form of isomers (i.e. enantiomers). The invention includes all such isomers and any mixtures thereof including racemic mixtures.

Racemic forms can be resolved into the optical antipodes by known methods, for example, by separation of diastereomeric salts thereof with an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving

racemates into the optical antipodes is based upon chromatography on an optically active matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallization of d- or l- (tartrates, mandelates, or camphorsulphonate) salts for example. The compounds of the present invention may also be resolved by the formation of diastereomeric amides by reaction of the compounds of the present invention with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid or by the formation of diastereomeric carbamates by reaction of the compounds of the present invention with an optically active chloroformate or the like.

Additional methods for the resolvation of optical isomers, known to those skilled in the art may be used, and will be apparent to the average worker skilled in the art. Such methods include those discussed by J. Jaques, A. Collet, and S. Wilen in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Optical active compounds can also be prepared from optical active starting materials.

The compounds of the invention may be prepared by any conventional method useful for the preparation of analogous compounds and as described in the examples below.

Starting materials for the processes described in the present patent application are known or can be prepared by known processes from commercially available materials

A compound of the invention can be converted to another compound of the invention using conventional methods.

The products of the reactions described herein are isolated by conventional means such as extraction, crystallization, distillation, chromatography, and the like.

**Biology**

Nicotinic ACh receptors in the brain are pentameric structures composed of subunits distinct from those found in skeletal muscles. The existence of seven α-subunits (α2-α7, α9) and three β-subunits (β2 -β4) in the mammalian brain has been described.

The predominant subtype with high affinity for nicotine is comprised of $\alpha_4$ and $\beta_2$ subunits.

The affinity of compounds of the invention for nicotinic ACh receptors have been investigated in three test for *in vitro* inhibition of $^3$H-epibatidin binding, $^3$H-α-bungarotoxin binding and $^3$H-cytisine binding as described below:

**_In vitro_ inhibition of $^3$H-cytisine binding**

The predominant subtype with high affinity for nicotine is comprised of $\alpha_4$ and $\beta_2$ subunits. nAChRs of the latter type can selectively be labelled by the nicotine agonist $^3$H-cytisine.

Tissue Preparation: Preparations are performed at 0-4°C unless otherwise indicated. Cerebral corticies from male Wistar rats (150-250 g) are homogenized for 20 sec in 15 ml Tris, HCl (50 mM, pH 7.4) containing 120 mM NaCl, 5 mM KCl, 1 mM $MgCl_2$ and 2.5 mM $CaCl_2$ using an Ultra-Turrax homogenizer. The homogenate is centrifuged at 27,000 x g for 10 min. The supernatant is discarded and the pellet is resuspended in fresh buffer and centrifuged a second time. The final pellet is resuspended in fresh buffer (35 ml per g of original tissue) and used for binding assays.

Assay: Aliquots of 500 µl homogenate are added to 25 µl of test solution and 25 µl of $^3$H-cytisine (1 nM, final concentration), mixed and incubated for 90 min at 2°C. Non-specific binding is determined using (-)-nicotine (100 µM, final concentration). After incubation the samples are added 5 ml of ice-cold buffer and poured directly onto Whatman GF/C glass fibre filters under suction and immediately washed with 2 x 5 ml ice-cold buffer. The amount of radioactivity on the filters is determined by conventional liquid scintillation counting. Specific binding is total binding minus non-specific binding.

**_In vitro_ inhibition of $^3$H-α-bungarotoxin binding Rat brain**

α-Bungarotoxin is a peptide isolated from the venom of the Elapidae snake *Bungarus multicinctus* (Mebs et al., Biochem. Biophys. Res. Commun., 44(3), 711 (1971)) and has high affinity for neuronal and neuromuscular nicotinic receptors, where it acts as a potent antagonist. $^3$H-α-Bungarotoxin binds to a single site in rat brain with an unique distribution pattern in rat brain (Clarke et al., J. Neurosci. 5, 1307-1315 (1985)).

$^3$H-α-Bungarotoxin labels nAChR formed by the $\alpha_7$ subunit isoform found in brain and the $\alpha_1$ isoform in the neuromuscular junction (Changeaux, Fidia Res. Found. Neurosci. Found. Lect. 4, 21-168 (1990). Functionally, the $\alpha_7$ homo-oligomer expressed in oocytes has a calcium permeability greater than neuromuscular receptors and, in some instances greater than NMDA channels (Seguela et al., J. Neurosci. 13, 596-604 (1993).

Tissue preparation: Preparations are performed at 0-4°C unless otherwise indicated. Cerebral cortices from male Wistar rats (150-250 g) are homogenized for 10 sec in 15 ml 20 mM Hepes buffer containing 118 mM NaCl, 4.8 mM KCl, 1.2 mM $MgSO_4$ and 2.5 mM $CaCl_2$ (pH 7.5) using an Ultra-Turrax homogenizer. The tissue suspension is centrifuged at 27,000 x g for 10 min. The supernatant is discarded and the pellet is washed twice by centrifugation at 27,000 x g for 10 min in 20 ml fresh buffer, and the final pellet is resuspended in fresh buffer containing 0.01% BSA (35 ml per g of original tissue) and used for binding assays.

Assay: Aliquots of 500 µl homogenate are added to 25 µl of test solution and 25 µl of $^3$H-α-bungarotoxin (2 nM, final concentration), mixed and incubated for 2 h at 37°C. Non-specific binding is determined using (-)-nicotine (1 mM, final concentration). After incubation the samples are added 5 ml of ice-cold Hepes buffer containing 0.05% PEI and poured directly onto Whatman GF/C glass fibre filters (presoaked in 0.1% PEI for at least 6 h) under suction and immediately washed with 2 x 5 ml ice-cold buffer. The amount of radioactivity on the filters is determined by conventional liquid scintillation counting. Specific binding is total binding minus non-specific binding.

***In vitro* inhibition of $^3$H-epibatidin binding**

Epibatidin is an alkaloid that was first isolated from the skin of the Ecuadoran frog *Epipedobates tricolor* and was found to have very high affinity for neuronal nicotinic receptors, where it acts as a potent agonist. $^3$H-epibatidin binds to two sites in rat brain, both of which have pharmacological profiles consistent with neuronal nicotinic receptors and a similar brain regional distribution (Hougling et al., Mol. Pharmacol. 48, 280-287 (1995)).

The high affinity binding site for $^3$H-epibatidin is most certainly binding to the $\alpha_4\beta_2$ subtype of nicotinic receptors. The identity of the low affinity site is still unknown; does it represent a second nicotinic receptor or a second site in the same receptor. The inability of α-bungarotoxin

to compete for $^3$H-epibatidin binding sites indicates that neither site measured represents the nicotinic receptor composed of $\alpha_7$ subunits.

Tissue preparation: Preparations are performed at 0-4°C unless otherwise indicated. The forebrain (÷cerebellum) from a male Wistar rat (150-250 g) is homogenized for 10- 20 sec in 20 ml Tris, HCl (50 mM, pH 7.4) using an Ultra-Turrax homogenizer. The tissue suspension is centrifuged at 27,000 x g for 10 min. The supernatant is discarded and the pellet is washed three times by centrifugation at 27,000 x g for 10 min in 20 ml fresh buffer, and the final pellet is resuspended in fresh buffer (400 ml per g of original tissue) and used for binding assays. Assay: Aliquots of 2.0 ml homogenate are added to 0.100 ml of test solution and 0.100 ml of $^3$H-epibatidin (0.3 nM, final concentration), mixed and incubated for 60 min at room temperature. Non-specific binding is determined using (-)-nicotine (30 µM, final concentration). After incubation the samples are poured directly onto Whatman GF/C glass fibre filters (presoaked in 0.1% PEI for at least 20 min) under suction and immediately washed with 2 x 5 ml ice-cold buffer. The amount of radioactivity on the filters is determined by conventional liquid scintillation counting. Specific binding is total binding minus non-specific binding.

| Compound | $^3$H-cytisine $IC_{50}$(µM) | $^3$H-epibatidin $IC_{50}$(µM) | $^3$H-α-bungarotoxin $IC_{50}$(µM) |
|---|---|---|---|
| **4-Methyl-1-(3-pyridyl)-piperazine fumaric acid salt (1A)** | 0.06 | 0.38 | 6.80 |
| **4-Methyl-1-(5-methoxy-3-pyridyl)-piperazine (3A)** | 0.068 | 0.38 | 32.50 |
| **1-(5-Chloro-3-pyridyl)-4-Methyl-piperazine fumaric acid salt (5A)** | 0.08 | 0.65 | 73.40 |
| **4-Methyl-1-(5-phenyl-3-pyridyl)-piperazine fumaric acid salt (6A)** | 0.08 | 1.10 | >30 |
| **1-(5-Ethoxy-3-pyridyl)-4-methyl-piperazine fumaric acid salt (7A)** | 0.006 | 0.09 | >30 |
| **1-(5-Methoxy-3-pyridyl)-4-methyl-1,5-diazacyclooctane fumaric acid salt (11A)** | 0.04 | 1.2 | >30 |
| **1-(3-Pyridyl)-piperazine fumaric acid salt** | 0.13 | 0.63 | >30 |

| | | | |
|---|---|---|---|
| (1B) | | | |
| 1-(5-Methoxy-3-pyridyl)-piperazine fumaric acid salt (3B) | 0.80 | 4.50 | >30 |
| 1-(5-Chloro-3-pyridyl)-piperazine fumaric acid salt (4B) | 0.31 | 3.00 | >30 |
| 1-(5-Methoxy-3-pyridyl)-1,5-diazacyclooctane fumaric acid salt (6B) | 0.001 | 0.0032 | 2.5 |
| 1-(6-Chloro-3-pyridazinyl)-1,5-diazacyclooctane fumaric acid salt (7B) | 0.03 | 0.15 | 0.46 |
| 1-(6-Chloro-3-pyridazinyl)-1,4-diazacyclooctane fumaric acid salt (8B) | 0.55 | 0.92 | 5.50 |
| 1-(5-Ethoxy-3-pyridyl)piperazine fumaric acid salt (1D) | 0.50 | 1.00 | >30 |
| 1-(5-Butoxy-3-pyridyl)piperazine fumaric acid salt (2D) | 0.18 | 1.40 | >30 |
| 1-(5-Ethoxy-3-pyridyl)-4-ethyl-piperazine fumaric acid salt (9D) | 0.07 | 0.21 | >30 |
| 4-Methyl-1-(3-pyridyl)-homopiperazine (1E) | 0.15 | 0.4 | 4.6 |
| 4-Methyl-1-(3-quinolinyl)-homopiperazine fumaric acid salt (2E) | 0.34 | 4.90 | 1.80 |
| 1-(5-Methoxy-3-pyridyl)-4-methyl-homopiperazine fumaric acid salt (3E) | 0.094 | 0.75 | 26.00 |
| 1-(5-Ethoxy-3-pyridyl)-4-methyl-homopiperazine fumaric acid salt (4E) | 0.05 | 0.30 | >30 |
| 4-Methyl-1-(5-phenyl-3-pyridyl)-homopiperazine fumaric acid salt (5E) | 0.20 | 1.50 | 16.0 |
| 1-(5-Butoxy-3-pyridyl)-4-methyl-homopiperazine fumaric acid salt (6E) | 0.045 | 0.24 | >30 |
| 1-(5-Methoxyethoxy-3-pyridyl)-4-methyl-homopiperazine (7E) | 0.07 | 0.55 | >30 |
| 4-Methyl-1-[5-(2-methyl-propyloxy)-3-pyridyl]-homopiperazine fumaric acid salt (8E) | 0.07 | 0.45 | >30 |

| | | | |
|---|---|---|---|
| 1-(5-Cyclopropylmethoxy-3-pyridyl)-4-methyl-homopiperazine fumaric acid salt (9E) | 0.078 | 4.80 | >30 |
| 4-Methyl-1-(5-propyloxy-3-pyridyl)-homopiperazine fumaric acid salt (10E) | 0.06 | 0.29 | >30 |
| 1-(5-Hexyloxy-3-pyridyl)-4-methyl-homopiperazine fumaric acid salt (11E) | 0.80 | 0.25 | >30 |
| 4-Methyl-1-[5-(3-methyl-butoxy)-3-pyridyl]-homopiperazine fumaric acid salt (12E) | 0.055 | 0.27 | >30 |
| 1-(5-Cyclohexylmethoxy-3-pyridyl)-4-methyl-homopiperazine fumaric acid salt (14E) | 0.20 | 0.48 | >30 |
| 4-Methyl-1-(5-pentyloxy-3-pyridyl)-homopiperazine fumaric acid salt (15E) | 0.03 | 0.21 | >30 |
| 1-(5-Heptyloxy-3-pyridyl)-4-methyl-homopiperazine fumaric acid salt (16E) | 0.28 | 0.70 | >30 |
| *trans*-4-Methyl-1-(5-propyl-1-en-oxy-3-pyridyl)-homopiperazine fumaric acid salt (17E) | 0.02 | 0.09 | >30 |
| 4-Methyl-1-(5-thiobenzyl-3-pyridyl)-homopiperazine fumaric acid salt (18E) | 0.60 | 0.80 | 15.0 |
| 4-Methyl-1-[5-(3-pyridyl)-3-pyridyl]-homopiperazine fumaric acid salt (19E) | 0.17 | 1.80 | >30 |
| 1-(5-Cyclopentyloxy-3-pyridyl)-4-methyl-homopiperazine fumaric acid salt (25E) | 0.08 | 0.61 | >30 |
| 1-(3-Pyridyl)-homopiperazine fumaric acid salt (1F) | 0.002 | 0.005 | 0.19 |
| 1-(3-Quinolinyl)-homopiperazine fumaric acid salt (2F) | 0.006 | 0.084 | 5.90 |
| 1-(6-Chloro-5-methoxy-3-pyridyl)-homopiperazine fumaric acid salt (5F) | 0.0007 | 0.005 | 0.90 |
| 1-(5-Methoxy-3-pyridyl)-homopiperazine fumaric acid salt (1H) | 0.002 | 0.02 | 3.00 |

| | | | |
|---|---|---|---|
| 1-(5-Phenyl-3-pyridyl)-homopiperazine fumaric acid salt (2H) | 0.003 | 0.02 | 37.00 |
| 1-(5-Ethoxy-3-pyridyl)-homopiperazine fumaric acid salt (3H) | 0.002 | 0.01 | 20.00 |
| 1-(5-Methoxyethoxy-3-pyridyl)-homopiperazine fumaric acid salt (5H) | 0.002 | 0.02 | 19.00 |
| 1-[5-(2-Methyl-propoxy)-3-pyridyl]-homopiperazine fumaric acid salt (6H) | 0.002 | 0.01 | >30 |
| 1-(5-Cyclopropylmethoxy-3-pyridyl)-homopiperazine fumaric acid salt (9H) | 0.001 | 0.006 | >30 |
| 1-(5-Propyloxy-3-pyridyl)-homopiperazine fumaric acid salt (10H) | 0.0009 | 0.0054 | >30 |
| 1-(6-Chloro-3-pyridazinyl)-homopiperazine fumaric acid salt (1K) | 0.01 | 0.06 | 1.40 |
| 1-(6-Chloro-2-pyrazinyl)-homopiperazine fumaric acid salt (3K) | 0.02 | 0.16 | 5.60 |
| 1-(6-Methyl-3-pyridazinyl)-homopiperazine fumaric acid salt (5K) | 0.16 | 0.74 | 4.80 |
| 1-(5-Triflouromethyl-3-pyridyl)-homopiperazine fumaric acid salt(6K) | 0.009 | 0.04 | 6.40 |
| 1-(6-Bromo-3-pyridyl)-homopiperazine fumaric acid salt (8K) | 0.001 | 0.01 | 0.62 |
| 1-(3-Pyridazinyl)-homopiperazine (1L) | 0.03 | 0.25 | 1.60 |
| 1-(2-Quinoxalinyl)-homopiperazine fumaric acid salt (2L) | 0.26 | 2.00 | 27.00 |
| 1-(5-Methoxy-3-pyridyl)-3-methyl-imidazolidine fumaric acid salt (1M) | 0.59 | 8.80 | >30.0 |
| 1-(5-Methoxy-3-pyridyl)-3-methyl-1.3-diazacyclohexane fumaric acid salt (2M) | 0.09 | 2.70 | >30 |

**Pharmaceutical Compositions**

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceutical formulation.

The invention thus further provides pharmaceutical formulations comprising a compound of the invention or a pharmaceutically acceptable salt or derivative thereof together with one or more pharmaceutically acceptable carriers therefor and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation.

The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. Formulations containing ten (10) milligrams of active ingredient or, more broadly, 0.1 to one hundred (100) milligrams, per tablet, are accordingly suitable representative unit dosage forms.

The compounds of the present invention can be administrated in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise, as the active component, either a compound of the invention or a pharmaceutically acceptable salt of a compound of the invention.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents,

solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as admixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated as solutions in aqueous polyethylene glycol solution.

The compounds according to the present invention may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as

suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavours, stabilizing and thickening agents, as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavours, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

For topical administration to the epidermis the compounds according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

Formulations suitable for topical administration in the mouth include lozenges comprising active agent in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in single or multidose form. In the latter case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this may be achieved for example by means of a metering atomising spray pump.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurised pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide, or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

Alternatively the active ingredients may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

In formulations intended for administration to the respiratory tract, including intranasal formulations, the compound will generally have a small particle size for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization.

When desired, formulations adapted to give sustained release of the active ingredient may be employed.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Tablets or capsules for oral administration and liquids for intravenous administration are preferred compositions.

**Method of Treating**

The compounds of the present invention are valuable nicotinic ACh receptor modulators and therefore useful for the treatment of a range of ailments involving cholinergic dysfunction as well as a range of disorders responsive to the activity of nicotinic ACh receptor modulators. The compounds may be used in the treatment, prevention, profylaxis or alleviation of a disease, disorder or condition of the central or peripheral system as for example: neurodegenerative disorders, cognitive or memory dysfunction, Alzheimer's disease, Parkinson's disease, Huntington's disease, Amyotrophic Lateral Sclerosis, Gilles de la Tourettes syndrome, attention deficit hyperactivity disorder, anxiety, depression, mania, manic depression, schizophrenia, obsessive compulsive disorders, eating disorders like anorexia nervosa, bulimia and obesity, narcolepsy, nociception, memory loss, memory dysfunction, AIDS-dementia, senile dementia, peripherial neuropathy, learning deficit, cognition deficit, attention deficit, autism, dyslexia, tardive dyskinesia, hyperkinesia, epilepsy, bulimia, post-traumatic syndrome, social phobia, chronic fatigue syndrome, disorders of sleep, pseudodementia, Ganser's syndrome, prementraul syndrome, late luteal phase syndrome, chronic fatigue syndrome, premature ejaculation, erectile difficulty, mutism and trichotillomania.

The compounds of this invention may also be used in the treatment of inflammatory conditions as for example: inflammatory skin conditions like acne and rosacea, Chron's disease, inflammatory bowel disease, ulcerative collitis, irritable colon, diarrhoea.

Also the compounds of the invention may be used in the treatment of diseases associated with smooth muscle contractions as for example: convulsive disorders, angina pectoris, premature labor, convulsions, diarrhoea, asthma, epilepsy, tardive dyskinesia, hyperkinesia.

The compounds of this invention may also be used in the treatment of pain as for example chronic, acute and recurrent pain, postoperative pain, migraine pain or phantom limb pain; The compounds of the present invention may also be used for the assistance in cessation of abuse of chemical substances as for example smoking cessation as well as cessation of use of other nicotine containing products, cessation of use of opiods like heroin, cocaine and morphine and cessation of use of benzodiazepines or alcohol. In the context of the present invention "treatment" means as well treatment as prevention, profylaxis and alleviation of withdrawal symptoms and abstinence as well as treatment resulting in a voluntary diminished intake of the addictive substance.

Suitable dosage range are 0.1-500 milligrams daily, and especially 10-70 milligrams daily, administered once or twice a day, dependent as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

I.p. means intraperetoneally, which is a well known route of administration.
P.o. means peroral, which is a well known route of administration.

The invention then comprises the following alone or in combination:

The use as above wherein the disease to be treated is pain, a disease in the central or peripheral system, a disease caused by smooth muscle contraction, neurodegeneration, inflammation, chemical substance abuse or withdrawal symptoms caused by the cessation of intake of the chemical substance, such as assistance in the cessation of smoking;

The use as above wherein a disease in the central or peripheral system is Alzheimer's disease, Parkinson's disease, memory dysfunction or attention deficit hyperactivity disorder.

The method as above wherein pain, a disease in the central or peripheral system, a disease caused by smooth muscle contraction, neurodegeneration, inflammation, chemical substance abuse or withdrawal symptoms caused by the cessation of intake of chemical substances, such as smoking cessation, is treated.
The method as above wherein chemical substance abuse or withdrawal symptoms caused by the cessation of intake of the chemical substance, said chemical substance abuse being smoking or use of other nicotine containing products and withdrawal symptoms caused by cessation of use of nicotine containing products, is treated;
A method as above wherein a disease in the central or peripheral system, said disease being Alzheimer's disease, Parkinson's disease, memory dysfunction or attention deficit hyperactivity disorder, is treated.

The following examples will illustrate the invention further, however, they are not to be construed as limiting.

**Examples**

**General:** All reactions involving air sensitive reagents or intermediates were performed under nitrogen and in anhydrous solvents. Magnesium sulfate is used as drying agent in the workup-procedures and solvents were evaporated under reduced pressure.

**Method A**

**4-Methyl-1-(3-pyridyl)-piperazine fumaric acid salt (1A)**

A solution of 1-(3-pyridyl)-piperazine (0.35 g, 2.1 mmol), formic acid (1.0 g, 21.7 mmol), formaldehyde (0.64 g, 37 %) and water (2 ml) was stirred at reflux for 15 h. The mixture was evaporated and sodium hydroxide (30 ml, 1 M) was added and the product was extracted three times with ethyl acetate (15 ml). The corre
sponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Yield 0.21 g, 34 %. Mp 144.5 - 145.9 °C.

**4-Methyl-1-(3-quinolinyl)-piperazine (2A)**

Was prepared according to method A. Isolated as free base. Mp 116.5 - 117.0 °C. This compound is previously known in the literature (B. Schonen and F. Zymalkowski, Arch Pharm. (Weinheim) 314, 464 - 470 (1981)).

**4-Methyl-1-(5-methoxy-3-pyridyl)-piperazine (3A)**

Was prepared according to method A. Isolated as free base. Mp 67.5 - 68.0 °C.

**3,5-Bis-[4,4´-methyl-1,1´-piperazinyl]pyridine (4A)**

Was prepared according to method A. Mp 132 - 133 °C.

**1-(5-Chloro-3-pyridyl)-4-Methyl-piperazine fumaric acid salt (5A)**

Was prepared according to method A. Mp 162 - 163 °C.

**4-Methyl-1-(5-phenyl-3-pyridyl)-piperazine fumaric acid salt (6A)**

Was prepared according to method A. Mp 179 - 180 °C.

**1-(5-Ethoxy-3-pyridyl)-4-methyl-piperazine fumaric acid salt (7A)**

Was prepared according to method A. Mp 162.2 - 163.7 °C.

**1-(5-Butoxy-3-pyridyl)-4-methyl-piperazine fumaric acid salt (8A)**

Was prepared according to method A. Mp 136.9 - 139.2 °C.

***trans*-4-Methyl-1-[5-(Propyl-1-en-oxy)-3-pyridyl]-piperazine fumaric acid salt (9A)**

Was prepared according to method A. Mp 145.1 - 145.7 °C.

**1-(5-Ethenyloxy-3-pyridyl)-4-methyl-piperazine fumaric acid salt (10A)**

Was prepared according to method A. Mp 136.4 - 138.2 °C.

**1-(5-Methoxy-3-pyridyl)-4-methyl-1,5-diazacyclooctane fumaric acid salt (11A)**

Was prepared according to method A. Mp 137 - 139 °C.

**1-(6-Chloro-3-pyridazinyl)-4-methyl-1,5-diazacyclooctane fumaric acid salt (12A)**

Was prepared according to method A. Mp 166 - 168 °C.

**Method B**

**1-(3-Pyridyl)-piperazine fumaric acid salt (1B)**

A solution of 1-(3-pyridyl)-4-*tert*-butoxycarbonylpiperazine (1.3 g, 4.9 mmol), trifluoroacetic acid (11.3 g, 99 mmol) and dichloromethane (50 ml) was stirred for 15 h. The mixture was evaporated. Sodium hydroxide (4 M) was added. The product was extracted three times with dichloromethane (50 ml) and isolated as an oil. Yield 0.72 g, 90 %. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1), saturated with fumaric acid. Mp 161.7 - 164.8 °C.

**1-(3-Quinolinyl)-piperazine (2B)**

Was prepared according to method B. The reactant was obtained according to method C from 3-bromoquinoline. Mp 87.7 - 88.5 °C.

**1-(5-Methoxy-3-pyridyl)-piperazine fumaric acid salt (3B)**

Was prepared according to method B. The reactant was obtained according to method C from 3-bromo-5-methoxypyridine. Mp 168.5 - 170.5 °C.

**1-(5-Chloro-3-pyridyl)-piperazine fumaric acid salt (4B)**

Was prepared according to method B. The reactant was obtained according to method C from 3,5-dichloropyridine. Mp 195 - 196 °C.

**1-(5-Phenyl-3-pyridyl)-piperazine fumaric acid salt (5B)**

Was prepared according to method B. The reactant was obtained according to method C from 3-bromo-5-phenylpyridine. Mp 167.5 - 168.5 °C.

**1-(5-Methoxy-3-pyridyl)-1,5-diazacyclooctane fumaric acid salt (6B)**

Was prepared according to method B. The reactants were obtained according to method C from 3-bromo-5-methoxypyridine and 1-*tert*-butoxycarbonyl-(1,5-diazacyclooctane). Mp 158 - 160 °C.

**1-(6-Chloro-3-pyridazinyl)-1,5-diazacyclooctane fumaric acid salt (7B)**

A mixture of 1.5-diazacyclooctane (2.07 g, 18.1 mmol), 3,6-dichloropyridazine (2.70 g, 18.1 mmol) and toluene (50 ml) was stirred at reflux overnight. Aqueous sodium hydroxide (50 ml, 1 M) was added followed by extraction seven times with ethyl acetate (50 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound. Yield 1.72 g, 42 %. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9 : 1) saturated with fumaric acid. Mp 176 - 178 °C.

**1-(6-Chloro-3-pyridazinyl)-1,4-diazacyclooctane fumaric acid salt (8B)**

A mixture of 1.4-diazacyclooctane (2.07 g, 18.1 mmol), (this starting material was prepared according to J. Hernandez-Mora and Nadia Cordero-Antunano, Carib. J. Sci., 14, 77, 1974) 3,6-dichloropyridazine (2.70, 18.1 mmol) and toluene (50 ml) was stirred at reflux overnight. Aqueous sodium hydroxide (50 ml, 1 M) was added followed by extraction seven times with ethyl acetate (40 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound. Yield 1.2 g, 29 %. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9 : 1) saturated with fumaric acid. Mp 177 - 179 °C.

**Method C**

**1-(3-Pyridyl)-4- *tert*-butoxycarbonyl-piperazine**

A mixture of 3-bromopyridine (7.8 g, 49.4 mmol), 1-*tert*-butoxycarbonylpiperazine (9.2 g, 49.4 mmol), tetrakis(triphenylphosphine)palladium(0) (286 mg, 0.247 mmol), potassium *tert*-butoxide (11.1 g, 98.8 mmol) and anhydrous toluene (100 ml) was stirred at 80 °C for 0.5 h. Water (100 ml) was added and the mixture was extracted three times with ethyl acetate (75 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound as an oil. Yield 1.34 g, 10 %.

**Method D**

**1-(5-Ethoxy-3-pyridyl)piperazine fumaric acid salt (1D)**

A mixture of 3-chloro-5-ethoxypyridine (6.5 g, 45.8 mmol), piperazine (19.7 g, 229 mmol), potassium *tert*-butoxide (11.2 g, 91.6 mmol) and 1,2-dimethoxyethane (150 ml) was stirred at reflux for 1 h. Aqueous sodium hydroxide (1 M, 100 ml) was added and the mixture was extracted two times with ethyl acetate (150 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound. Yield 4.6 g, 48 %. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Mp 160.0 - 161.2 °C.

**1-(5-Butoxy-3-pyridyl)piperazine fumaric acid salt (2D)**

Was prepared according to method D. Mp 149.4 - 151.7 °C.

***trans*-1-[5-(Propyl-1-en-oxy)-3-pyridyl]-piperazine fumaric acid salt (3D)**

Was prepared according to method D, from 3-chloro-5-(propyl-2-en-oxy)-pyridine involving isomerization of the double bond. Mp 145.1 - 145.7 °C.

**1-(5-Ethenyloxy-3-pyridyl)piperazine fumaric acid salt (4D)**

Was prepared according to method D. Mp 136.4 - 138.2 °C.

**1-(5-Ethoxy-3-pyridyl)-1,5-diazacyclooctane fumaric acid salt (5D)**

Was prepared according to method D from 1.5-diazacyclooctane (prepared according to J. Hernandez-Mora "Derivatives of 1.5-diazacyclooctane " Ph.D. Dissertation, University of Michigan (1959)) at room temperature over night. Mp 162.5 - 164.5 °C.

**1-(5-Propyloxy-3-pyridinyl)-1,5-diazacyclooctane fumaric acid salt (6D)**

Was prepared according to method D from 1.5-diazacyclooctane at 70 °C over night in the presence of tetrakis(triphenylphosphine)palladium(0) (3 %). Mp 150 - 152 °C.

***trans*-1-[5-(Propyl-1-en-oxy)-3-pyridyl]-1,5-diazacyclooctane fumaric acid salt (7D)**

Was prepared according to method D, from 3-chloro-5-(propyl-2-en-oxy)-pyridine involving isomerization of the double bond. Mp 135 - 137 °C.

**1-(5-Ethenyloxy-3-pyridyl) 1,5-diazacyclooctane fumaric acid salt (8D)**

Was prepared according to method D. Mp 142 - 144 °C.

**1-(5-Ethoxy-3-pyridyl)-4-ethyl-piperazine fumaric acid salt (9D)**

A mixture of 1-(5-ethoxy-3-pyridyl)-piperazine (1.4 g, 6.8 mmol), triethylamine (0.69 g, 6.8 mmol), bromoethane (0.88 g, 8.1 mmol) and dimethylformamide (25 ml). Aqueous sodium hydroxide (1 M, 50 ml) was added and the mixture was extracted two times with ethyl acetate (50 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound. Yield 0.75 g, 47 %. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1), saturated with fumaric acid. Mp 144.8 - 145.9 °C.

**General procedure for 3-bromo and 3-chloro-5-arylpyridines:**

**3-Bromo-5-phenylpyridine**

A mixture of 3,5-dibromopyridine (10.0 g, 42.2 mmol), phenylboronic acid (4.6 g, 38.0 mmol), tetrakis(triphenylphosphine)palladium(0) (1.45 g, 1.25 mmol), potassium carbonate (17.5 g, 127 mmol), water (63 ml) and 1,2-dimethoxyethane (126 ml) was stirred at reflux overnight. Aqueous sodium hydroxide (1 M, 60 ml) was added followed by extraction twice with diethyl ether (100 ml). Chromatography on silica gel with dichloromethane as solvent gave the title compound. Yield 6.1 g, 68 %, Mp 42 - 44 °C.

**3-Bromo-6-thioethoxypyridine**

A mixture of sodium thioethoxide (7.81 g, 92.9 mmol), 2.5-dibromopyridine (20.0 g, 84.4 mmol) and dimethyl sulfoxide (100 ml). The mixture was stirred at 20 °C overnight. Sodium hydroxide (300 ml, 1 M) was added and the mixture was extracted twice with diethyl ether (200 ml). Chromatography on silica gel with dichloromethane : petroleum ether, 1:2 as eluent, gave the title compound as an oil. Yield 16.8 g, 85 %.

**Method E**

**4-Methyl-1-(3-pyridyl)-homopiperazine (1E)**

A solution of 1-(3-pyridyl)-homopiperazine (0.42 g, 2.4 mmol), formic acid (3.3 g, 71.7 mmol), formaldehyde (2.1 g, 37 %) and water (10 ml) was stirred at reflux for 15 h. The mixture was evaporated and sodium hydroxide (15 ml, 4 M) was added and the product was extracted two times with ethyl acetate (15 ml). The product was obtained as an oil. Yield 0.46 g, 100 %.

**4-Methyl-1-(3-quinolinyl)-homopiperazine fumaric acid salt (2E)**

Was prepared according to method E. Mp 170 - 171 °C.

**1-(5-Methoxy-3-pyridyl)-4-methyl-homopiperazine fumaric acid salt (3E)**
Was prepared according to method E. Mp 145 - 147 °C.

**1-(5-Ethoxy-3-pyridyl)-4-methyl-homopiperazine fumaric acid salt (4E)**
Was prepared according to method E. Mp 150 - 152 °C.

**4-Methyl-1-(5-phenyl-3-pyridyl)-homopiperazine fumaric acid salt (5E)**
Was prepared according to method E. Mp 161 - 162 °C.

**1-(5-Butoxy-3-pyridyl)-4-methyl-homopiperazine fumaric acid salt (6E)**
Was prepared according to method E. Mp 127 - 129 °C.

**1-(5-Methoxyethoxy-3-pyridyl)-4-methyl-homopiperazine (7E)**
Was prepared according to method E. Isolated as an oil.

**4-Methyl-1-[5-(2-methyl-propyloxy)-3-pyridyl]-homopiperazine fumaric acid salt (8E)**
Was prepared according to method E. Mp 145.7 - 146.9 °C.

**1-(5-Cyclopropylmethoxy-3-pyridyl)-4-methyl-homopiperazine fumaric acid salt (9E)**
Was prepared according to method E. Mp 160.4 - 161.9 °C.

**4-Methyl-1-(5-propyloxy-3-pyridyl)-homopiperazine fumaric acid salt (10E)**
Was prepared according to method E. Mp 148.8 - 153.5 °C.

**1-(5-Hexyloxy-3-pyridyl)-4-methyl-homopiperazine fumaric acid salt (11E)**
Was prepared according to method E. Mp 128.7 - 130.8 °C.

**4-Methyl-1-[5-(3-methyl-butoxy)-3-pyridyl]-homopiperazine fumaric acid salt (12E)**
Was prepared according to method E. Mp 130.4 - 131.9 °C.

**4-Methyl-1-(6-thioethoxy-3-pyridyl)-homopiperazine fumaric acid salt (13E)**
Was prepared according to method E. Mp 119 - 121 °C.

**1-(5-Cyclohexylmethoxy-3-pyridyl)-4-methyl-homopiperazine fumaric acid salt (14E)**
Was prepared according to method E. Mp 160.4 - 162.0 °C.

**4-Methyl-1-(5-pentyloxy-3-pyridyl)-homopiperazine fumaric acid salt (15E)**
Was prepared according to method E. Mp 129.0 - 130.8 °C.

**1-(5-Heptyloxy-3-pyridyl)-4-methyl-homopiperazine fumaric acid salt (16E)**
Was prepared according to method E. Mp 120.2 -121.8 °C.

***trans*-4-Methyl-1-(5-propyl-1-en-oxy-3-pyridyl)-homopiperazine fumaric acid salt (17E)**
Was prepared according to method E. Mp 126 - 128 °C.

**4-Methyl-1-(5-thiobenzyl-3-pyridyl)-homopiperazine fumaric acid salt (18E)**
Was prepared according to method E. Mp 131 - 133 °C.

**4-Methyl-1-[5-(3-pyridyl)-3-pyridyl]-homopiperazine fumaric acid salt (19E)**
Was prepared according to method E. Mp 165.5 - 167.5 °C.

**4-Methyl-1-(3-nitrophenyl)-homopiperazine (20E)**
Was prepared according to method E. Mp 163.1 - 164.4 °C.

**4-Methyl-1-(6-chloro-3-pyridazinyl)-homopiperazine fumaric acid salt (21E)**
Was prepared according to method E. Mp 171 - 172 °C.

**4-Methyl-1-(6-phenyl-3-pyridazinyl)-homopiperazine fumaric acid salt (22E)**
Was prepared according to method E. Mp 185 - 186 °C.

**4-Methyl-1-(3-pyridazinyl)-homopiperazine fumaric acid salt (23E)**
Was prepared according to method E. Mp 137.8 - 139.3 °C.

**4-Methyl-1-(6-methyl-3-pyridazinyl)-homopiperazine fumaric acid salt (24E)**
Was prepared according to method E. Mp 152 - 153 °C.

**1-(5-Cyclopentyloxy-3-pyridyl)-4-methyl-homopiperazine fumaric acid salt (25E)**
Was prepared according to method E. Mp 123 -125 °C.

**4-Benzyl-1-(3-Pyridyl)-homopiperazine fumaric acid salt (26E)**

1-(3-Pyridyl)-homopiperazine (0.54 g, 3.0 mmol), potassium carbonate (0.42 g, 3.0 mmol), benzylbromide (0.56 g, 3.3 mmol) in dimethylformamide (40 ml) was stirred at 80 °C for one hour. Water (100 ml) was added and the mixture was extracted twice with ethyl acetate (25 ml). Yield 0.39 g, 49 %. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1), saturated with fumaric acid. Mp 148.4 - 149.0 °C.

**4-Ethyl-1-(3-pyridyl)-homopiperazine fumaric acid salt (27E)**

Was prepared according to 4-benzyl-1-(3-pyridyl)-homopiperazine from 1-(3-pyridyl)homopiperazine. Mp 145.3 - 147.5 °C.

**Method F**

**1-(3-Pyridyl)-homopiperazine fumaric acid salt (1F)**

A solution of 1-(3-pyridyl)-4-*tert*-butoxycarbonylhomopiperazine (0.91 g, 3.3 mmol), trifluoroacetic acid (7.5 g, 66 mmol) and dichloromethane (30 ml) was stirred for 15 h. The mixture was evaporated. Sodium hydroxide (30 ml, 4 M) was added. The product was extracted two times with dichloromethane (30 ml) and isolated as an oil. Yield 0.50 g, 85 %. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Mp 172.1 - 172.9 °C.

**1-(3-Quinolinyl)-homopiperazine fumaric acid salt (2F)**

Was prepared according to method F. Mp 181 - 182 °C.

**1-(6-Methoxy-3-pyridyl)-homopiperazine fumaric acid salt (3F)**

Was prepared according to method F. Mp 127 - 128 °C.

**1-(2-Chloro-5-methoxy-3-pyridyl)-homopiperazine fumaric acid salt (4F)**

Was prepared according to method F. Mp 117 - 118 °C.

**1-(6-Chloro-5-methoxy-3-pyridyl)-homopiperazine fumaric acid salt (5F)**

Was prepared according to method F. Mp 196 - 197 °C.

**1-(6-Bromo-5-ethoxy-3-pyridyl)-homopiperazine fumaric acid salt (6F)**

Was prepared according to method F. Mp 181.7 - 183.2 °C.

**1-[6-(N-Pyrrolidinyl)-3-pyridyl]-homopiperazine fumaric acid salt (7F)**
Was prepared according to method F. Mp 148.6 - 150.5 °C.

**1-(6-Phenyl-3-pyridyl)-4-homopiperazine fumaric acid salt (8F)**
Was prepared according to method F. Mp 180 - 182 °C.

**1-[5-(3-Nitrophenyl)-3-pyridyl]-4-homopiperazine fumaric acid salt (9F)**
Was prepared according to method F. Mp 186 - 188 °C.

**Method G**

**1-(3-Pyridyl)-4-*tert*-butoxycarbonylhomopiperazine**
A mixture of 3-bromopyridine (3.95 g, 25.0 mmol), 1-*tert*-butoxycarbonylhomopiperazine (5.0 g, 25.0 mmol), tetrakis(triphenylphosphine)palladium(0) (145 mg, 0.125 mmol), potassium *tert*-butoxide (6.1 g, 50.0 mmol) and anhydrous toluene (75 ml) was stirred at 80 °C for 4 h. Water (100 ml) was added and the mixture was extracted three times with ethyl acetate (50 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound as an oil. Yield 0.92 g, 13 %.

**1-(6-Methoxy-3-pyridyl)-4-*tert*-butoxycarbonylhomopiperazine**Was prepared according to Method G. Isolated as an oil.

**1-(3-Quinolinyl)-4-*tert*-butoxycarbonylhomopiperazine**
Was prepared according to Method G. Isolated as an oil.

**Method H**

**1-(5-Methoxy-3-pyridyl)-homopiperazine fumaric acid salt (1H)**
A mixture of 3-bromo-5-methoxypyridine (5.6 g, 30.0 mmol), homopiperazine (15.0 g, 150 mmol), tetrakis(triphenylphosphine)palladium(0) (173 mg, 0.15 mmol), potassium-*tert*-butoxide (6.7 g, 60 mmol) and anhydrous toluene (150 ml) was stirred at 80 °C for 4 h. Water (100 ml) was added and the mixture was extracted seven times with ethyl acetate (150 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound. Yield 3.5 g, 56 %. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Mp 161 - 162 °C.

**1-(5-Phenyl-3-pyridyl)-homopiperazine fumaric acid salt (2H)**
Was prepared according to method H. Mp 185 - 186 °C.

**1-(5-Ethoxy-3-pyridyl)-homopiperazine fumaric acid salt (3H)**
Was prepared according to method H. Mp 157.5 - 159 °C.

**1-(5-Butoxy-3-pyridyl)-homopiperazine fumaric acid salt (4H)**
Was prepared according to method H. Mp 150 - 151 °C.

**1-(5-Methoxyethoxy-3-pyridyl)-homopiperazine fumaric acid salt (5H)**
Was prepared according to method H. Mp 126 - 127 °C.

**1-[5-(2-Methyl-propoxy)-3-pyridyl]-homopiperazine fumaric acid salt (6H)**
Was prepared according to method H. Mp 121.9 - 123.3 °C.

**1-[5-(2-Hydroxy-ethoxy)-3-pyridyl]-homopiperazine (7H)**
Was prepared according to method H. Was isolated as an oil.

**1-[5-(3-Methyl-butoxy)-3-pyridyl]-homopiperazine fumaric acid salt (8H)**
Was prepared according to method H. Mp 139.9 - 142.0 °C.

**1-(5-Cyclopropylmethoxy-3-pyridyl)-homopiperazine fumaric acid salt (9H)**
Was prepared according to method H. Mp 154 - 156 °C.

**1-(5-Propyloxy-3-pyridyl)-homopiperazine fumaric acid salt (10H)**
Was prepared according to method H. Mp 156.2 - 157.8 °C.

**1-(5-Hexyloxy-3-pyridyl)-homopiperazine fumaric acid salt (11H)**
Was prepared according to method H. Mp 149.5 - 151.8 °C.

**1-(5-Cyclohexylmethoxy-3-pyridyl)-homopiperazine fumaric acid salt (12H)**
Was prepared according to method H. Mp 163.3 - 164.5 °C.

**1-(6-Thioethoxy-3-pyridyl)-homopiperazine fumaric acid salt (13H)**
Was prepared according to method H. Mp 115 - 119 °C.

**1-[5-(2-Ethoxy-ethoxy)-3-pyridyl]-homopiperazine fumaric acid salt (14H)**
Was prepared according to method H. Mp 139.3 - 140.4 °C.

**1-(5-Pentyloxy-3-pyridyl)-homopiperazine fumaric acid salt (15H)**
Was prepared according to method H. Mp 155.5 - 156.7 °C.

**1-(5-Heptyloxy-3-pyridyl)-homopiperazine fumaric acid salt (16H)**
Was prepared according to method H. Mp 132.8 - 136.6 °C.

***trans*-1-[5-(Propyl-1-en-oxy)-3-pyridyl]-homopiperazine fumaric acid salt (17H)**
Was prepared according to method H, from 3-chloro-5-(propyl-2-en-oxy)-pyridine involving isomerization of the double bond. Mp 124 -126 °C.

**1-(5-Thiobenzyl-3-pyridyl)-homopiperazine fumaric acid salt (18H)**
Was prepared according to method H. Mp 148 - 150 °C.

**1-(5-Carboxylamido-3-pyridyl)-homopiperazine fumaric acid salt (19H)**
Was prepared according to method H. Mp 149 - 151 °C.

**1-(5-Thiophenyl-3-pyridyl)-homopiperazine fumaric acid salt (20H)**
Was prepared according to method H. Mp 177 - 179 °C.

**Method I**

**1-[(5-Methoxy-methoxy)-3-pyridyl]-homopiperazine fumaric acid salt (1I)**
A mixture of 3-chloro-5-methoxymethoxypyridine (10.0 g, 57.6 mmol), homopiperazine (28.8 g, 288 mmol), 1.3-bis(diphenylphosphino)propanepalladiumdichloride (170 mg, 0.29 mmol), potassium *tert*-butoxide (12.9 g, 115 mmol) and 1,2-dimethoxyethane (100 ml) was stirred at reflux for 3 h. Sodium hydroxide (1 M, 100 ml) was added and the mixture was extracted two times with ethyl acetate (150 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound as free base. Yield 9.7 g, 71 %. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Mp 129.5 - 131 °C.

**1-[5-(3-Pyridyl)-3-pyridyl]-homopiperazine fumaric acid salt (2I)**

Was prepared according to method I. Mp 160 - 162 °C.

**Method J**

**1-(5-(1-Pyrrolyl)-3-pyridyl)-homopiperazine fumaric acid salt (1J)**

A mixture of 3-chloro-5-(1-pyrrolyl)-pyridine (6.3 g, 35.3 mmol), homopiperazine (7.06 g, 70.5 mmol), potassium *tert*-butoxide (7.91 g, 70.5 mmol) and 1,2-dimethoxyethane (100 ml) was stirred at reflux for 3 h. Sodium hydroxide (1 M, 120 ml) was added and the mixture was extracted three times with ethyl acetate (100 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound. Yield 3.45 g, 40 %. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Mp 174 - 175 °C.

**1-(5-(1-Indolyl)-3-pyridyl)-homopiperazine fumaric acid salt (2J)**

Was prepared according to method J from 3-chloro-5-(1-indolyl)-pyridine. Mp 193 - 195 °C.

**1-(5.6-Dimethoxy-3-pyridyl)-homopiperazine fumaric acid salt (3J)**

Was prepared according to method J from 3-chloro-5.6-dimethoxypyridine. Mp 150 - 152 °C.

**1-(5-Ethenyloxy-3-pyridyl)homopiperazine fumaric acid salt (4J)**

Was prepared according to method J from 3-Chloro-5-ethenyloxypyridine. Mp 143 -144 °C.

**1-(5-Cyclopentyloxy-3-pyridyl)homopiperazine fumaric acid salt (5J)**

Was prepared according to method J. Mp 148 -150 °C.

**1-[5-(Ethoxy-d5)-3-pyridyl]-homopiperazine fumaric acid salt (6J)**

Was prepared according to method J, using 3-chloro-5-(penta-deuterium-ethoxy)-pyridine as starting material. Mp 163 - 165 °C.

**1-(3-Chloro-5-pyridyl)homopiperazine fumaric acid salt (7J)**

Was prepared according to method J, using room temperature as reaction temperature. Mp 144.4 -146.6 °C.

**1-(3-Bromo-5-pyridyl)homopiperazine fumaric acid salt (8J)**

Was prepared according to method J, using room temperature as reaction temperature. Mp 180.7 -185.4 °C.

**1-(4- Isoquinolinyl)-homopiperazine fumaric acid salt (9J)**

A mixture of 4-bromoisoquinoline (0.80 g, 3.85 mmol) and homopiperazine (3.85 g, 38.5 mmol) was stirred at 170 °C overnight. Aqueous sodium hydroxide (20 ml, 1M) was added. The mixture was extracted three times with ethyl acetete (30 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound. Yield 0.40 g, 46 %. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Mp 160 - 162 °C.

**3-Chloro-5-(1-pyrrolyl)-pyridine**

A mixture of 3.5 dichloropyridine (10.0 g, 67.6 mmol), pyrrole (5.50 g, 81.1 mmol), sodium hydride 60 % (3.52 g, 87.9 mmol) and dimethyl sulfoxide (50 ml) was stirred at 70 °C for 2 h. Aqueous sodium hydroxide (200 ml, 1 M) was added and the mixture was extracted three times with diethyl ether (100 ml). The mixture was evaporated and, purified by chromatography on silica gel with dichloromethane and ethanol (4 %) as solvent. Yield 6.3 g, 52 %. Mp 70.5 - 72.0 °C.

**3-Chloro-5-(1-indolyl)-pyridine**

Was prepared according to 3-Chloro-5-(1-pyrrolyl)-pyridine. Yield 5.9 g, 38 %. Mp 56 - 57 °C.

**3-Chloro-5-ethenyloxypyridine**

Thionyl chloride (58.6 g, 492.6 mmol) was added to a mixture of 1[3-chloro-5-(2-hydroxyethoxy)]pyridine (14.5 g, 82.1 mmol) and tetrahydrofuran (100). The mixture was stirred for 1 h at 50 °C. The mixture was evaporated. Potassium hydroxide (9.0 g, 164 mmol) and *tert*-butanol (100 ml) was added and the mixture was stirred for 3 days at 100 °C. The solvent was evaporated. Water (150 ml) was added and extracted twice with diethyl ether (100 ml). Yield 6.77 g, 53 %.

**1-(5-Hydroxy-3-pyridyl)-homopiperazine hydrochloric acid salt (10J)**

1-(5-Methoxymethoxy-3-pyridyl)-homopiperazine (8.5 g, 35.9 mmol) was stirred in hydrochloric acid (4 M, 100 ml) at room temperature for 1 h. The excess of hydrochloric acid was evaporated. A crystaline compound was obtained by triturating with a mixture of 5% methanol and ether. Yield 9.56 g, 100 %. Mp 290 - 300 °C.

**1-(5-Trifluoromethanesulfonyl-oxy-3-pyridyl)-homopiperazine fumaric acid salt (11J)**

To a mixture of 1-(5-trifluoromethanesulfonyl-oxy-3-pyridyl)-4-*tert*-butoxycarbonyl-homopiperazine (0.82 g, 1.9 mmol) and dichloromethane (10 ml) was added trifluoro acetic acid (2.18 g, 19.2 mmol) at room temperature. The mixture was stirred at room temperature for 3 h. Aqueous sodium hydroxide (30 ml) was added and the mixture was extracted twice with dichloromethane (30 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Mp 154 - 156 °C. Yield 0.29 g, 35 %.

**1-(5-Trifluoromethanesulfonyl-oxy-3-pyridyl)-4-*tert*-butoxycarbonyl-homopiperazine**

To a mixture of 1-(5-hydroxy-3-pyridyl)-4-*tert*-butoxycarbonyl-homopiperazine (4.0 g, 13.6 mmol), pyridine (3.23 g, 40.8 mmol) and dichloromethane (40 ml) was added: triflouromethane sulfonic anhydride (3.85 g, 13.6 mmol) at 0 °C. The mixture was allowed to react at room temperature overnight. The organic phase was washed twice with aqeous sodium hydroxide (1 M, 30 ml). Chromatography on silica gel with ethyl acetate - toluene (2:1). Yield 2.26 g, 56 %.

**1-(5-Hydroxy-3-pyridyl)-4-*tert*-butoxycarbonyl-homopiperazine**

A mixture of 1-(5-hydroxy-3-pyridyl)-homopiperazine hydrochloric acid salt (15.5 g, 58.1 mmol) *tert*-butoxycarbonyl anhydride (12.7 g, 58.1 mmol), an aqueous solution of sodium hydrogen carbonate (1 M, 290 mmol) and dichloromethane (290 ml) was stirred overnight. The organic phase was separated and purified with chromatography on silica gel, using 6 % ethanol and dichloromethane as eluent. The product was isolated as an oil. Yield 8.17 g, 48 %.

**1-(5-Ethynyl-3-pyridyl)-homopiperazine fumaric acid salt (12J)**

A mixture of 1-(5-ethynyl-3-pyridyl)-4-*tert*-butoxycarbonyl-homopiperazine (0.13 g, 0.43 mmol), trifluoro acetic acid (0.98 g, 8.6 mmol) and dichloromethane (10 ml) was stirred for 5 h. Aqueous sodium hydroxide (1 M, 15 ml) was added the organic phase was separated and the aqueous phase was extracted twice with dichloromethane (15 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Yield 30 mg, 22 %. Mp 172.5 - 174.0 °C.

**1-(5-Ethynyl-3-pyridyl)-4-tert-butoxycarbonyl-homopiperazine**

A mixture of 1-[5-(3-methyl-3-hydroxy-butyn-1-yl)-3-pyridyl]-4-tert-butoxycarbonyl-homopiperazine (0.40 g, 1.1 mmol), sodium hydride 60 % (4.5 mg, 0.11 mmol) and toluene

(10 ml) was stirred at 110 °C for 3 h. The crude mixture was purified by chromatography on silica gel with ethyl acetate : toluene, (3 : 1) gave the title compound. Yield 0.13 g, 39 %.

**1-[5-(3-Methyl-3-hydroxy-butyn-1-yl)-3-pyridyl]-4-*tert*-butoxycarbonyl-homopiperazine**

A mixture of 1-(5-trifluoromethanesulfonyl-oxy-3-pyridyl)-4-*tert*-butoxycarbonyl-homopiperazine (8.15 g, 1.9 mmol), potassium carbonate (0.66 g, 4.8 mmol), copper (I)iodide (37 mg, 0.19 mmol), palladium on carbon (5 %, 10 mg), triphenylphosphine (50 mg, 0.19 mmol), lithium chloride (81 mg, 1.9 mmol) and 1,2-dimethoxyethane (15 ml) was stirred at room temperature for 30 min. 2-Methyl-3-butyn-2-ol (1.62 g, 3.8 mmol) solved in 1,2-dimethoxyethane (30 ml) was added to the mixture which was stirred at reflux overnight. The crude mixture was filtered through celite and hydrochloric acid (20 ml, 2 M) and toluene (30 ml) was added. The organic phase was discarded and the mixture was made alkaline with aqueous sodium hydroxide, followed by extraction with ethyl acetate (30 ml). The mixture was purified by chromatography on silica gel with ethyl acetate : toluene, (3:1) and gave the title compound. Yield 0.40 g, 58 %.

**1-(2-Chloro-5-methoxy-3-pyridyl)-4-*tert*-butoxycarbonylhomopiperazine and 1-(6-Chloro-5-methoxy-3-pyridyl)-4-*tert*-butoxycarbonylhomopiperazine**

An aqueous solution of sodium hypochlorite (16.3 ml, 8.14 mmol) was added to mixture of 1-(5-methoxy-3-pyridyl)-4-*tert*-butoxycarbonylhomopiperazine (2.5 g, 8.14 mmol) and dimethylformamide (185 ml) at room temperature and stirred for 0.5 h at room temperature. Water was added (300 ml) and the mixture was extracted twice with diethyl ether (200 ml). The mixture was separated by chromatography on silica gel with ethyl acetate : toluene (2:1). The title compounds eluated in the order indicated above in in 2.0 g and 0.5 g respectively, total yield 90 %.

**1-[5-(3-Nitrophenyl)-3-pyridyl]-4-*tert*-butoxycarbonylhomopiperazine (13J)**

A mixture of (5-trifluoromethanesulfonyl-oxy-3-pyridyl)-4-*tert*-butoxycarbonyl-homopiperazine (3.0 g, 7.1 mmol), 1.3-propandiol (2.68 g, 35.3 mmol), lithium chloride (0.90 g, 21.2 mmol), potassium carbonate (10.6 ml, 2 M), tetrakis(triphenylphosphine)palladium(0) (244 mg, 0.21 mmol), 3-nitrophenyl boronic acid (1.77 g, 10.6 mmol) and 1.2-dimethoxyethane was stirred at reflux for 2 h. Aqueous sodium hydroxide was added. The mixture was extracted twice with ethyl acetate (40 ml). The mixture was separated by chromatography on silica gel with petroleum : ethyl acetate, (2:1). The product was isolated in quantitative yield. Mp 129 - 130 °C.

**1-(3-Nitrophenyl)-homopiperazine fumaric acid salt (14J)**

A mixture of 1-fluoro-3-nitrobenzene (10.0 g, 71 mmol), and homopiperazine (21.3 g, 213 mmol) in dioxane (100 ml) was refluxed for 15 h. Water (100 ml) was added and the mixture was extracted twice with ethyl acetate (100 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound. Yield 0.69 g, 4 %. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Mp 163.1 - 164.4 °C.

**1-(3-Aminophenyl)-homopiperazine fumaric acid salt (15J)**

A mixture of 1-(3-nitrophenyl)-homopiperazine (2.4 g, 12.2 mmol), palladium on carbon (0.25 g, 5 %) and ethanol (75 ml) was stirred under hydrogen for 24 h. The crude mixture was filtered through celite. Aqueous sodium hydroxide (50 ml, 1 M) was added and the mixture was extracted twice with diethyl ether (50 ml). Yield 0.61 g, 26 %. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Mp 165.4 - 167.7 °C.

**1-(3-Methoxyphenyl)-homopiperazine fumaric acid salt (16J)**

A mixture of 3-bromoanisole (10.0 g, 53.4 mmol), homopiperazine (10.7 g, 106.9 mmol), potassium *tert*-butoxide (10.6 g, 106.9 mmol), tetrakis(triphenylphosphine)palladium(0) (62 mg, 0.53 mmol) and 1.2-dimethoxyethane (100 ml) was stirred at reflux for 1 h. tetrakis(triphenylphosphine)palladium(0) (286 mg, 0.247 mmol) Sodium hydroxide (1 M, 100 ml) was added and the mixture was extracted two times with ethyl acetate (150 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound as free base. Yield 0.79 g, 7 %. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Mp 164.1 - 165.7 °C.

**1-(3-Hydroxyphenyl)-homopiperazine fumaric acid salt (17J)**

Boron tribromide (11.1g, 44.4 mmol) was added to a mixture of 1-(3-Methoxyphenyl)-homopiperazine (0.54 g, 2.8 mmol) in dichloromethane (50 ml) at -70 °C. The reaction was allowed to reach room temperature overnight. The precipitated crystals were filtered and purified by chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound as free base. Yield 0.22 g, 41 %. The corresponding salt

was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Mp 165 °C, decomp.

**General procedure for 3-bromo and 3-chloro-5- or 6-alkoxypyridines:**

**3-Bromo-5-methoxypyridine**

Sodium (2.33 g, 101.3 mmol) was added to methanol (50 ml) and was allowed to react, the mixture was evaporated. 3.5-Dibromopyridine (20.0 g, 84.4 mmol) and dimethyl sulfoxide (100 ml) were added. The mixture was stirred at 90 °C for 2 h. Sodium hydroxide (400 ml, 1 M) was added and the mixture was extracted twice with diethyl ether (200 ml). Chromatography on silica gel with dichloromethane and 3% ethanol as solvent gave the title compound. Yield 10.6 g, 67 %. Mp 30-32 °C.

**General procedure for 3-bromo and 3-chloro-5-arylpyridines:**

**3-Bromo-5-phenylpyridine**

A mixture of 3,5-dibromopyridine (10.0 g, 42.2 mmol), phenylboronic acid (4.6 g, 38.0 mmol), tetrakis(triphenylphosphine)palladium(0) (1.45 g, 1.25 mmol), potassium carbonate (17.5 g, 127 mmol), water (63 ml) and 1,2-dimethoxyethane (126 ml) was stirred at reflux overnight. Aqueous sodium hydroxide (1 M, 60 ml) was added followed by extraction twice with diethyl ether (100 ml). Chromatography on silica gel with dichloromethane as solvent gave the title compound. Yield 6.1 g, 68 %, Mp 42 - 44 °C.

**3-Bromo-6-thioethoxypyridine**

A mixture of sodium thioethoxide (7.81 g, 92.9 mmol), 2.5-Dibromopyridine (20.0 g, 84.4 mmol) and dimethyl sulfoxide (100 ml). The mixture was stirred at 20 °C overnight. Sodium hydroxide (300 ml, 1 M) was added and the mixture was extracted twice with diethyl ether (200 ml). Chromatography on silica gel with dichloromethane : petroleum ether, (1:2) as eluent, gave the title compound as an oil. Yield 16.8 g, 85 %.

**3-Bromo-5-thioethoxypyridine**

Prepared according to 3-Bromo-6-thioethoxypyridine, using 40 °C as reaction temperature. The title compound was obtained as an oil

**Method K**

**1-(6-Chloro-3-pyridazinyl)-homopiperazine fumaric acid salt (1K)**

A mixture of 3,6-dichloropyridazine (5.0 g, 33.5 mmol), homopiperazine (3.36 g, 33.5 mmol) and 50 ml of toluene was stirred at reflux for 0.5 h. Sodium hydroxide (50 ml, 1 M) was added and the mixture was extracted three times with ethyl acetate (100 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound as free base. Yield 2.2 g, 31 %. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Mp 165 - 166 °C.

**1-(6-Phenyl-3-pyridazinyl)-homopiperazine fumaric acid salt (2K)**

Was prepared according to method K from 2-chloro-6-phenylpyridazine. Mp 187 - 189 °C.

**1-(6-Chloro-2-pyrazinyl)-homopiperazine fumaric acid salt (3K)**

Was prepared according to method K from 2,6-dichloropyrazine. Mp 180 - 181 °C.

**1-(3,6-Dimethyl-2-pyrazinyl)-homopiperazine fumaric acid salt (4K)**

Was prepared according to method K, in the absence of solvent from 2-chloro-3,6-dimethylpyrazine at 130 °C. Mp 149 - 151 °C.

**1-(6-Methyl-3-pyridazinyl)-homopiperazine fumaric acid salt (5K)**

Was prepared according to method K in the absence of solvent at 130 °C. from 3-chloro-6-methyl-pyridazine. Mp 102 - 105 °C.

**1-(5-Triflouromethyl-3-pyridyl)-homopiperazine fumaric acid salt (6K)**

Was prepared according to method K in the absence of solvent at 140 °C overnight from 3-chloro-5-trifluoromethylpyridine. Mp 164 - 166 °C.

**1-(3-Chloro-2-quinoxalinyl)-homopiperazine fumaric acid salt (7K)**

Was prepared according to method K in the absence of solvent at 130 °C for 4 h from 2.3-dichloroquinoxaline. Mp **136.2 - 139.9** °C.

**1-(6-Bromo-3-pyridyl)-homopiperazine fumaric acid salt (8K)**

1-(3-Pyridyl)-homopiperazine (0.885 g, 5.0 mmol) was solved in acetonitrile (50 ml). N-Bromosuccinimide (1.7 g, 10.0 mmol) was added, and the mixture was stirred for 15 min. The crude mixture was evaporated. Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound as free base. Yield 0.50 g, 39 %. The

corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Mp 164 -166 °C.

**1-(6-Bromo-3-pyridyl)-4- *tert*-butoxycarbonyl homopiperazine**

1-(3-Pyridyl)-4- *tert*-butoxycarbonyl homopiperazine (25.0 g, 90.1 mmol) was solved in acetonitrile (400 ml) and cooled to 0 °C. N-Bromosuccinimide (19.3 g, 108.2 mmol) was added during 10 min. Water (400 ml) was added and the mixture was extracted twice with diethyl ether (200 ml). Chromatography on silica gel with a mixture of petroleum: ethyl acetate (1 : 1) gave the title compound as free base. Yield 18.7 g, 58 %.

**1-(6-Chloro-3-pyridyl)-4- *tert*-butoxycarbonyl homopiperazine**

A stirred solution of 1-(6-Bromo-3-pyridyl)-4- *tert*-butoxycarbonyl homopiperazine (3.6 g, 10 mmol) in tetrahydrofuran (200 ml) was cooled to -78 °C. *Tert*-butyllithium (14.7 ml, 1.5 M) in pentane was added during 10 min, followed by stirring for 5 min at -78 °C. 1,3-Dichloro-5,5-dimethylhydantoin (1.97 g, 10 mmol) was added in small portions. The mixture was stirred for 0.5 min. Aqueous sodium hydroxide was added (100 ml, 4 M), and the reaction was allowed reach room temperature. The mixture was extracted twice with diethyl ether (100 ml) Chromatography on silica gel with a mixture of petroleum: ethyl acetate (1 : 1) gave the title compound as free base. Yield 1.7 g, 55 %.

**1-(6-Chloro-3-pyridyl)-homopiperazine (9K)**

A mixture of 1-(6-chloro-3-pyridyl)-4- *tert*-butoxycarbonyl homopiperazine (1.7 g, 5.5 mmol), trifluoro acetic acid (4.5 ml, 55 mmol) and dichloromethane at room temperature for 1 h. The mixture was evaporated. Chromatography on silica gel with a mixture of petroleum: ethyl acetate (1 : 1) gave the title compound as free base. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9 : 1) saturated with fumaric acid. Mp 165 - 167 °C. Yield 0.72 g, 40 %.

**1-[6-(N-Pyrrolidinyl)-3-pyridyl]-4- *tert*-butoxycarbonyl homopiperazine**

A stirred solution of 1-(6-Bromo-3-pyridyl)-4- *tert*-butoxycarbonyl homopiperazine (0.71 g, 2.0 mmol), pyrrolidine (2.0 g, 20 mmol), potassium *tert*-butoxide (0.45 g, 4.0 mmol), tetrakis(triphenylphosphine)palladium(0) (0.12 g, 0.10 mmol) and 1.2-dimethoxyethane was stirred at reflux overnight. Water (40 ml) was added and the mixture was extracted twice with ethyl acetate (20 ml) Chromatography on silica gel with a mixture of petroleum: ethyl acetate (1 : 1) gave the title compound as free base. Yield 0.21 g, 30 %.

**1-(6-phenyl-3-pyridyl)-4- *tert*-butoxycarbonyl homopiperazine (10K)**

1-(6-Bromo-3-pyridyl)-4- *tert*-butoxycarbonyl homopiperazine (0.89 g, 2.5 mmol), phenyl boronic acid (0.37 g, 3.0 mmol), tetrakis(triphenylphosphine)palladium(0) (0.15 g, 0.12 mmol), 1.2-dimethoxyethane (50 ml), potassium carbonate (1.0 g, 7.5 mmol) and water (7.5 ml) was stirred at reflux overnight. Water (50 ml) was added and the mixture was extracted twice with ethyl acetate (40 ml). Chromatography on silica gel with a mixture of petroleum: ethyl acetate (1 : 1) gave the title compoundas an oil. Yield 0.83 g. 94 %.

**1-(6-Bromo-5-ethoxy-3-pyridyl)-4- *tert*-butoxycarbonyl homopiperazine**

N-Bromosuccinimide (2.7g, 15.2 mmol) was added to 1-(5-Ethoxy-3-pyridyl)-4- *tert*-butoxycarbonyl homopiperazine (4.5 g, 14.0 mmol) at roomtemperature. The mixture was stirred for 2 min. The mixture was washed with saturated sodium sulfite (100 ml) was. Chromatography on silica gel with a mixture of petroleum: ethyl acetate (1 : 1) gave the title compound as an oil. Yield 3.3 g, 58 %.

**Method L**

**1-(3-Pyridazinyl)-homopiperazine (1L)**

A mixture of 1-(3-Chloro-6-pyridazinyl)-homopiperazine (5.56 g, 26.1 mmol), palladium on carbon (2.1 g, 10 %) and ethanol (150 ml) was stirred under hydrogen overnight. The crude product was filtered through celite and evaporated. Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound as free base. Yield 2.78 g, 60 %, 185.0 - 186.9 °C.

**1-(2-Quinoxalinyl)-homopiperazine fumaric acid salt (2L)**

Was prepared according to method L from 1-(3-Chloro-2-quinoxalinyl)-homopiperazine Mp 177- 180 °C.

**N-(5-Methoxy-3-pyridyl)-ethylenediamine (3L)**

Sodium (4.98 g, 216.7 mmol) was added to methanol (100 ml), and was allowed to react, the mixture was evaporated. 3.5-Dichloropyridine (25.0 g, 166.7 mmol) and dimethyl sulfoxide (250 ml) were added. The mixture was stirred at 70 °C overnight. Aqueous sodium hydroxide (500 ml, 1 M) was added, and the mixture was extracted twice with diethyl ether (500 ml). The crude mixture was stirred together with ethylenediamine (50.0 g, 833.5 mmol), potassium *tert*-butoxide (37.4 g, 333.4 mmol) and 1,2-dimethoxyethane (500 ml) at reflux for 4 h. Aqueous

sodium hydroxide (1 l, 1 M) was added, and the mixture was extracted five times with ethyl acetate (500 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound as free base. Yield 13.0 g, 47 %.

**Method M**

**1-(5-Methoxy-3-pyridyl)-3-methyl-imidazolidine fumaric acid salt (1M)**

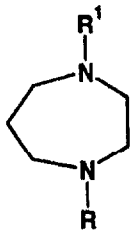
A mixture of N-(5-methoxy-3-pyridyl)-ethylenediamine (0.76 g, 4.5 mmol), formic acid (6.3 g, 136.4 mmol) and formaldehyde (4.1 g, 136.4 mmol) was stirred at reflux for 2 h at reflux. The crude mixture was evaporated. Sodium hydroxide (50 ml, 4 M) was added and the mixture was extracted with ethyl acetate. Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound as free base. Yield 9.7 g, 44 %. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Mp 139 - 142 °C.

**1-(5-Methoxy-3-pyridyl)-3-methyl-1.3-diazacyclohexane fumaric acid salt (2M)**

Was prepared according to method M from N-(5-methoxy-3-pyridyl)-1,3-propylene-diamine. Mp 149 - 151 °C.

**Claims:**

1. A homopiperazine derivative represented by Formula II



(II)

any of its enantiomers or any mixture of its enantiomers, isotopes thereof or a pharmaceutically acceptable salt thereof;

wherein

R represents hydrogen, alkyl or benzyl; and

$R^1$ represents **aminophenyl, nitrophenyl, hydroxyphenyl, or alkoxyphenyl; or a 3-pyridyl, a pyridazinyl or a pyrazinyl group,** which heterocyclic group may be substituted one or more times with substituents selected from

the group consisting of alkyl, cycloalkyl, alkenyl, ethynyl, alkoxy, hydroxyalkoxy, thioalkoxy, cycloalkoxy, cyclopropylmethoxy, cyclohexylmethoxy, alkenoxy, halogen, hydroxy, $-CONH_2$, and trifluoromethanesulfonyloxy;

phenyl, which is optionally substituted with alkyl, cycloalkyl, hydroxy, alkoxy, cycloalkoxy, halogen, $CF_3$, $OCF_3$, CN, amino and/or nitro;

-X-alkyl-Y-alkyl, wherein X and Y independently represents O or S;

$-X-(alkyl)_o$-aryl, wherein o is 0 or 1, and X represents O or S; and

a pyrrolyl, pyrrolidinyl or pyridyl group group, which monocyclic heterocyclic group is optionally substituted one or more times with alkyl, cycloalkyl, alkoxy, cycloalkoxy, halogen, $CF_3$, $OCF_3$, CN, amino and/or nitro; or

$R^1$ represents **an indolyl, a quinolinyl or an isoquinolinyl group,** which bicyclic heterocyclic group may be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, alkoxy, cycloalkoxy, halogen, $CF_3$, $OCF_3$, CN, amino or nitro.

2. The homopiperazine derivative of claim 1, wherein $R^1$ represents 3-nitrophenyl,

3-aminophenyl,
3-methoxyphenyl, or
3-hydroxyphenyl.

3. The homopiperazine derivative according to claim 2, which is
4-Methyl-1-(3-nitrophenyl)-homopiperazine;
1-(3-Nitrophenyl)-homopiperazine;
1-(3-Aminophenyl)-homopiperazine;
1-(3-Methoxyphenyl)-homopiperazine; or
1-(3-Hydroxyphenyl)-homopiperazine;
an enantiomer thereof or a mixture of enantiomers, isotopes thereof, or a pharmaceutically acceptable salt thereof.

4. The homopiperazine derivative according to claim 1, wherein $R^1$ represents
3-pyridyl,
5-methoxy-3-pyridyl,
5-chloro-3-pyridyl,
5-ethoxy-3-pyridyl,
6-methoxy-3-pyridyl,
5-propyloxy-3-pyridinyl,
5-phenyl-3-pyridyl,
5-(2-methyl-propyloxy)-3-pyridyl,
5-propyl-1-en-oxy-3-pyridyl,
2-chloro-5-methoxy-3-pyridyl,
6-chloro-5-methoxy-3-pyridyl,
6-bromo-5-ethoxy-3-pyridyl,
6-(N-pyrrolidinyl)-3-pyridyl,
6-phenyl-3-pyridyl,
5-(3-nitrophenyl)-3-pyridyl,
5-butoxy-3-pyridyl,
5-methoxyethoxy-3-pyridyl,
5-(2-methyl-propoxy)-3-pyridyl,
5-(2-hydroxy-ethoxy)-3-pyridyl,
5-(3-methyl-butoxy)-3-pyridyl,
5-cyclopropylmethoxy-3-pyridyl,
5-propyloxy-3-pyridyl,
5-hexyloxy-3-pyridyl,

5-cyclohexylmethoxy-3-pyridyl,
6-thioethoxy-3-pyridyl,
5-(2-ethoxy-ethoxy)-3-pyridyl,
5-pentyloxy-3-pyridyl,
5-heptyloxy-3-pyridyl,
5-(propyl-1-en-oxy)-3-pyridyl,
5-thiobenzyl-3-pyridyl,
5-carboxylamido-3-pyridyl,
5-thiophenyl-3-pyridyl,
5-methoxy-3-pyridyl,
5-(3-pyridyl)-3-pyridyl,
5-(1-pyrrolyl)-3-pyridyl,
5-(1-indolyl)-3-pyridyl,
5,6-dimethoxy-3-pyridyl,
5-ethenyloxy-3-pyridyl,
5-cyclopentyloxy-3-pyridyl,
5-(ethoxy-d5)-3-pyridyl,
3-chloro-5-pyridyl,
3-bromo-5-pyridyl,
5-hydroxy-3-pyridyl,
5-trifluoromethanesulfonyl-oxy-3-pyridyl,
5-ethynyl-3-pyridyl,
5-triflouromethyl-3-pyridyl,
6-bromo-3-pyridyl, or
6-chloro-3-pyridyl.

5. The homopiperazine derivative according to claim 4, which is
4-Methyl-1-(3-pyridyl)-homopiperazine;
1-(5-Methoxy-3-pyridyl)-4-methyl-homopiperazine;
1-(5-Ethoxy-3-pyridyl)-4-methyl-homopiperazine;
4-Methyl-1-(5-phenyl-3-pyridyl)-homopiperazine;
1-(5-Butoxy-3-pyridyl)-4-methyl-homopiperazine;
1-(5-Methoxyethoxy-3-pyridyl)-4-methyl-homopiperazine;
4-Methyl-1-[5-(2-methyl-propyloxy)-3-pyridyl]-homopiperazine;
1-(5-Cyclopropylmethoxy-3-pyridyl)-4-methyl-homopiperazine;
4-Methyl-1-(5-propyloxy-3-pyridyl)-homopiperazine;
1-(5-Hexyloxy-3-pyridyl)-4-methyl-homopiperazine;

4-Methyl-1-[5-(3-methyl-butoxy)-3-pyridyl]-homopiperazine;
4-Methyl-1-(6-thioethoxy-3-pyridyl)-homopiperazine;
1-(5-Cyclohexylmethoxy-3-pyridyl)-4-methyl-homopiperazine;
4-Methyl-1-(5-pentyloxy-3-pyridyl)-homopiperazine;
1-(5-Heptyloxy-3-pyridyl)-4-methyl-homopiperazine;
4-Methyl-1-(5-propyl-1-en-oxy-3-pyridyl)-homopiperazine;
4-Methyl-1-(5-thiobenzyl-3-pyridyl)-homopiperazine;
4-Methyl-1-[5-(3-pyridyl)-3-pyridyl]-homopiperazine;
1-(5-Cyclopentyloxy-3-pyridyl)-4-methyl-homopiperazine;
4-Benzyl-1-(3-pyridyl)-homopiperazine;
4-Ethyl-1-(3-pyridyl)-homopiperazine;
1-(3-Pyridyl)-homopiperazine;
1-(6-Methoxy-3-pyridyl)-homopiperazine;
1-(2-Chloro-5-methoxy-3-pyridyl)-homopiperazine;
1-(6-Chloro-5-methoxy-3-pyridyl)-homopiperazine;
1-(6-Bromo-5-ethoxy-3-pyridyl)-homopiperazine;
1-[6-(N-Pyrrolidinyl)-3-pyridyl]-homopiperazine;
1-(6-Phenyl-3-pyridyl)-4-homopiperazine;
1-[5-(3-Nitrophenyl)-3-pyridyl]-4-homopiperazine;
1-(5-Methoxy-3-pyridyl)-homopiperazine;
1-(5-Phenyl-3-pyridyl)-homopiperazine;
1-(5-Ethoxy-3-pyridyl)-homopiperazine;
1-(5-Butoxy-3-pyridyl)-homopiperazine;
1-(5-Methoxyethoxy-3-pyridyl)-homopiperazine;
1-[5-(2-Methyl-propoxy)-3-pyridyl]-homopiperazine;
1-[5-(2-Hydroxy-ethoxy)-3-pyridyl]-homopiperazine;
1-[5-(3-Methyl-butoxy)-3-pyridyl]-homopiperazine;
1-(5-Cyclopropylmethoxy-3-pyridyl)-homopiperazine;
1-(5-Propyloxy-3-pyridyl)-homopiperazine;
1-(5-Hexyloxy-3-pyridyl)-homopiperazine;
1-(5-Cyclohexylmethoxy-3-pyridyl)-homopiperazine;
1-(6-Thioethoxy-3-pyridyl)-homopiperazine;
1-[5-(2-Ethoxy-ethoxy)-3-pyridyl]-homopiperazine;
1-(5-Pentyloxy-3-pyridyl)-homopiperazine;
1-(5-Heptyloxy-3-pyridyl)-homopiperazine;
1-[5-(Propyl-1-en-oxy)-3-pyridyl]-homopiperazine;
1-(5-Thiobenzyl-3-pyridyl)-homopiperazine;

1-(5-Carboxylamido-3-pyridyl)-homopiperazine;
1-(5-Thiophenyl-3-pyridyl)-homopiperazine;
1-[(5-Methoxy-methoxy)-3-pyridyl]-homopiperazine;
1-[5-(3-Pyridyl)-3-pyridyl]-homopiperazine;
1-(5-(1-Pyrrolyl)-3-pyridyl)-homopiperazine;
1-(5-(1-Indolyl)-3-pyridyl)-homopiperazine;
1-(5.6-Dimethoxy-3-pyridyl)-homopiperazine;
1-(5-Ethenyloxy-3-pyridyl)homopiperazine;
1-(5-Cyclopentyloxy-3-pyridyl)homopiperazine;
1-[5-(Ethoxy-d5)-3-pyridyl]-homopiperazine;
1-(3-Chloro-5-pyridyl)homopiperazine;
1-(3-Bromo-5-pyridyl)homopiperazine;
1-(5-Hydroxy-3-pyridyl)-homopiperazine;
1-(5-Trifluoromethanesulfonyl-oxy-3-pyridyl)-homopiperazine;
1-(5-Ethynyl-3-pyridyl)-homopiperazine;
1-(5-Triflouromethyl-3-pyridyl)-homopiperazine;
1-(6-Bromo-3-pyridyl)-homopiperazine; or
1-(6-Chloro-3-pyridyl)-homopiperazine;
an enantiomer thereof or a mixture of enantiomers, isotopes thereof, or a pharmaceutically acceptable salt thereof.

6. The homopiperazine derivative according to claim 1, wherein $R^1$ represents
6-chloro-3-pyridazinyl,
6-phenyl-3-pyridazinyl,
6-methyl-3-pyridazinyl, or
3-pyridazinyl.

7. The homopiperazine derivative according to claim 6, which is
4-Methyl-1-(6-chloro-3-pyridazinyl)-homopiperazine;
4-Methyl-1-(6-phenyl-3-pyridazinyl)-homopiperazine;
4-Methyl-1-(3-pyridazinyl)-homopiperazine;
4-Methyl-1-(6-methyl-3-pyridazinyl)-homopiperazine;
1-(6-Chloro-3-pyridazinyl)-homopiperazine;
1-(6-Phenyl-3-pyridazinyl)-homopiperazine;
1-(6-Methyl-3-pyridazinyl)-homopiperazine;
1-(3-Pyridazinyl)-homopiperazine;

an enantiomer thereof or a mixture of enantiomers, isotopes thereof, or a pharmaceutically acceptable salt thereof.

8. The homopiperazine derivative according to claim 1, wherein $R^1$ represents
6-chloro-2-pyrazinyl, or
3,6-dimethyl-2-pyrazinyl.

9. The homopiperazine derivative according to claim 8, which is
1-(6-Chloro-2-pyrazinyl)-homopiperazine; or
1-(3,6-Dimethyl-2-pyrazinyl)-homopiperazine;
an enantiomer thereof or a mixture of enantiomers, isotopes thereof, or a pharmaceutically acceptable salt thereof.

10. The homopiperazine derivative according to claim 1, wherein $R^1$ represents
3-quinolinyl, or
4-isoquinolinyl.

11. The homopiperazine derivative according to claim 10, which is
1-(4-Isoquinolinyl)-homopiperazine;
an enantiomer thereof or a mixture of enantiomers, isotopes thereof, or a pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition, comprising a therapeutically effective amount of a compound of any of the claims 1 to 11, or a pharmaceutically acceptable addition salt thereof, together with at least one pharmaceutically acceptable carrier or diluent.

13. The pharmaceutical composition according to claim 12, formulated for topical administration to the epidermis as ointments, creams or lotions, or as a transdermal patch.

14. A homopiperazine derivative of any of the claims 1-11 for use as a medicament for treatment of a disease of a living animal body, including a human, which disease is responsive to the activity of nicotinic acetylcholine receptors modulators.

15. Use of a homopiperazine derivative according to any of the claims 1 to 11 for the manufacture of a medicament for the treatment of a disease of a living animal body, including a human, which disease is responsive to the activity of nicotinic acetylcholine receptor modulators.

16. The use according to claim 15 wherein the disease to be treated is pain, a disease in the central or peripheral system, a disease caused by smooth muscle contraction, neurodegeneration, inflammation, chemical substance abuse or withdrawal symptoms caused by the cessation of intake of the chemical substance, such as assistance in the cessation of smoking.

17. The use according to claim 16, wherein pain is chronic, acute and recurrent pain, post-operative pain, migraine pain or phantom limb pain.

18. The use according to claim 16 wherein a disease in the central or peripheral system isa neurodegenerative disorder, a cognitive or memory dysfunction, Alzheimer's disease, Parkinson's disease, Huntington's disease, Amyotrophic Lateral Sclerosis, Gilles de la Tourettes syndrome, attention deficit hyperactivity disorder, anxiety, depression, mania, manic depression, schizophrenia, obsessive compulsive disorders, eating disorders, anorexia nervosa, bulimia and obesity, narcolepsy, nociception, memory loss, memory dysfunction, AIDS-dementia, senile dementia, peripherial neuropathy, learning deficit, cognition deficit, attention deficit, autism, dyslexia, tardive dyskinesia, hyperkinesia, epilepsy, bulimia, post-traumatic syndrome, social phobia, chronic fatigue syndrome, disorders of sleep, pseudodementia, Ganser's syndrome, prementraul syndrome, late luteal phase syndrome, chronic fatigue syndrome, premature ejaculation, erectile difficulty, mutism and trichotillomania.

19. The use according to claim 16, wherein the disease associated with smooth muscle contractions is a convulsive disorder, angina pectoris, premature labor, convulsions, diarrhoea, asthma, epilepsy, tardive dyskinesia or hyperkinesia.

20. The use according to claim 16, wherein the inflammatory disease is an inflammatory skin condition, acne and rosacea, Chron's disease, inflammatory bowel disease, ulcerative collitis, irritable colon or diarrhoea.

21. The use according to claim 16, wherein the chemical substance abuse or withdrawal symptoms is caused by the cessation of intake of the chemical substance, and this chemical substance being nicotine, a benzodiazepine or alcohol, or an opiod, heroin, cocaine or morphine.