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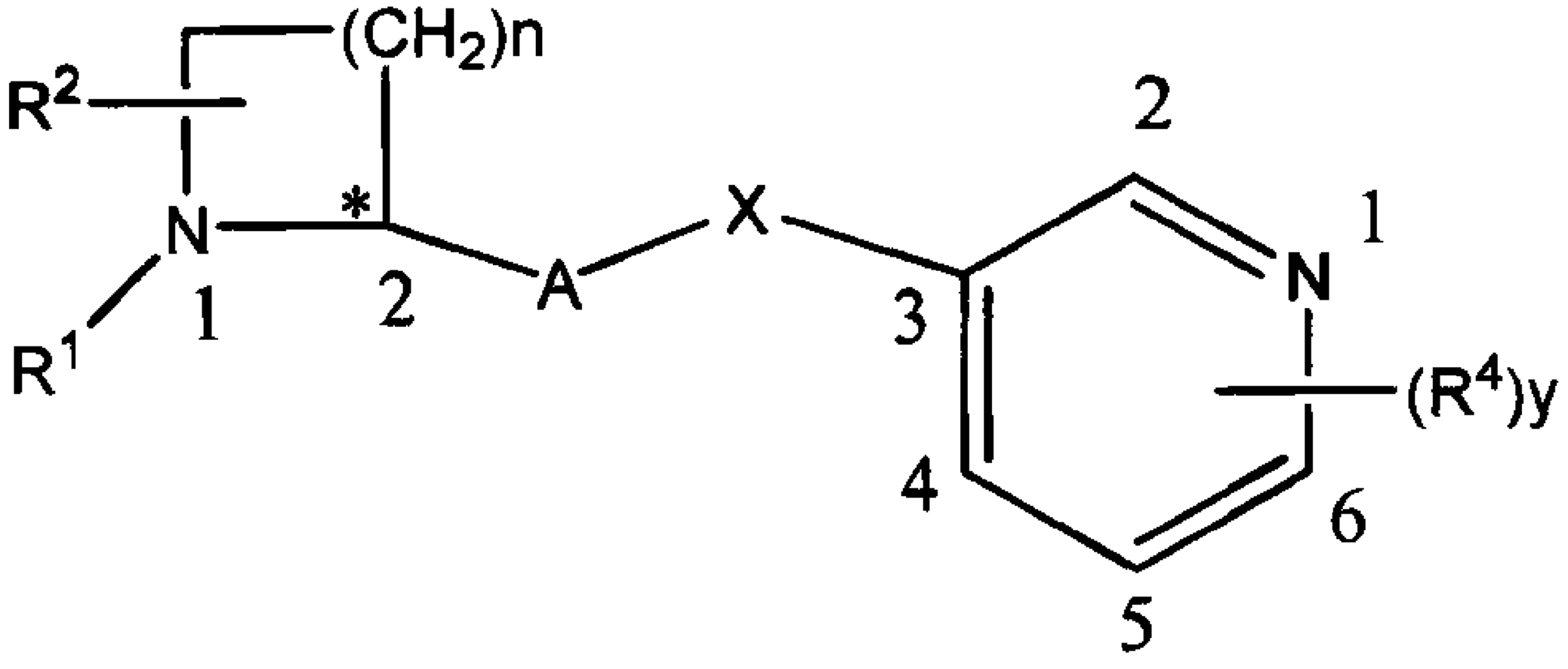
(54) Titre : COMPOSES D'ETHER HETEROCYCLIQUE DE 3-PYRIDYLOXYALKYLE UTILES POUR REGULER LA TRANSMISSION SYNAPTIQUE CHIMIQUE

(54) Title: 3-PYRIDYLOXYALKYL HETEROCYCLIC ETHER COMPOUNDS USEFUL IN CONTROLLING CHEMICAL SYNAPTIC TRANSMISSION



(57) Abrégé/Abstract:
Novel 3-pyridyloxymethyl heterocyclic ether compounds having formula (I), wherein * is a chiral center and n, X, R^1, R^2, A andB are specifically defined, which are useful in controlling chemical synaptic transmission; therapeutically-effective pharmaceutical compositions therof; and use of said compositions to selectively control synaptic transmission in mammals.

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(57) Abstract

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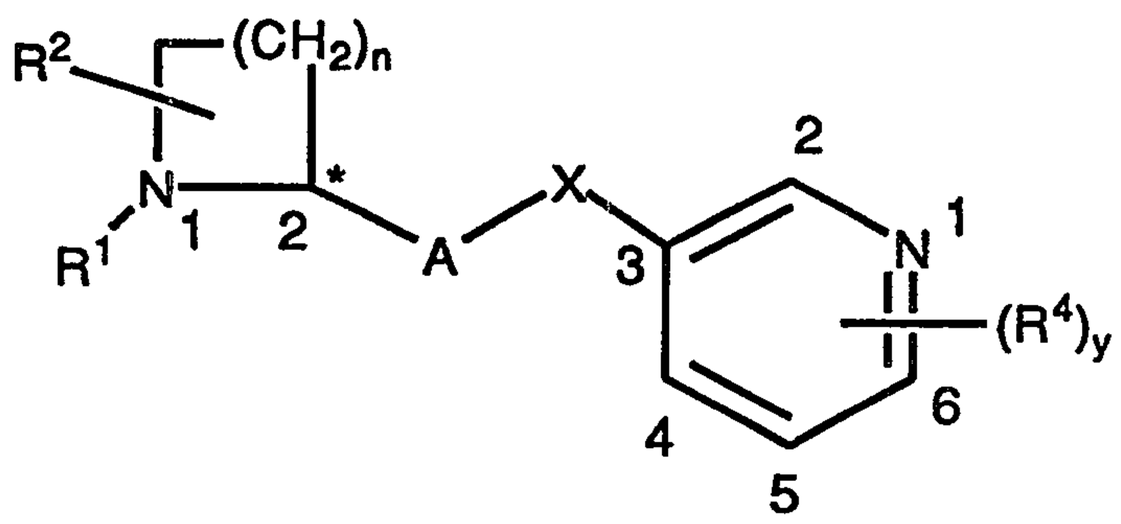


(I)

3-Pyridyloxyalkyl Heterocyclic Ether Compounds Useful in Controlling Chemical Synaptic Transmission

Technical Field

This invention relates to 3-pyridyloxymethyl heterocyclic ether compounds which control chemical synaptic transmission; to therapeutically-effective pharmaceutical compositions of these compounds; and to the use of said compositions to selectively control synaptic transmission.

Background of the Invention

Compounds that selectively control chemical synaptic transmission offer therapeutic utility in treating disorders that are associated with dysfunctions in synaptic transmission. This utility may arise from controlling either pre-synaptic or post-synaptic chemical transmission. The control of synaptic chemical transmission is, in turn, a direct result of a modulation of the excitability of the synaptic membrane. Presynaptic control of membrane excitability results from the direct effect an active compound has upon the organelles and enzymes present in the nerve terminal for synthesizing, storing, and releasing the neurotransmitter, as well as the process for active re-uptake. Postsynaptic control of membrane excitability results from the influence an active compound has upon the cytoplasmic organelles that respond to neurotransmitter action.

An explanation of the processes involved in chemical synaptic transmission will help to illustrate more fully the potential applications of the invention. (For a fuller explanation of chemical synaptic transmission refer to Hoffman *et al.*, "Neurotransmission: The autonomic and somatic motor nervous systems." In: Goodman and Gilman's, The Pharmacological Basis of Therapeutics, 9th ed., J.G. Hardman, L.E. Limbird, P.B. Molinoff, R.W. Ruddon, and A. Goodman Gilman, eds., Pergamon Press, New York, **1996**, pp. 105-139).

Typically, chemical synaptic transmission begins with a stimulus that depolarizes the transmembrane potential of the synaptic junction above the threshold that elicits an all-or-none action potential in a nerve axon. The action potential propagates to the nerve terminal where *ion fluxes* activate a mobilization process leading to neurotransmitter secretion and "transmission" to the postsynaptic cell. Those cells which receive communication from the central and peripheral nervous systems in the form of neurotransmitters are referred to as "excitable cells." Excitable cells are cells such as nerves, smooth muscle cells, cardiac cells and glands. The effect of a neurotransmitter upon an excitable cell may be to cause either an excitatory or an inhibitory postsynaptic potential (EPSP or IPSP respectively) depending upon the nature of the postsynaptic receptor for

the particular neurotransmitter and the extent to which other neurotransmitters are present. Whether a particular neurotransmitter causes excitation or inhibition depends principally on the ionic channels that are opened in the postsynaptic membrane (i.e., in the excitable cell).

EPSPs typically result from a local depolarization of the membrane due to a generalized increased permeability to cations (notably Na^+ and K^+), whereas IPSPs are the result of stabilization or hyperpolarization of the membrane excitability due to a increase in permeability to primarily smaller ions (including K^+ and Cl^-). For example, the neurotransmitter acetylcholine excites at skeletal muscle junctions by opening permeability channels for Na^+ and K^+. At other synapses, such as cardiac cells, acetylcholine can be inhibitory , primarily resulting from an increase in K^+ conductance.

The biological effects of the compounds of the present invention result from modulation of a particular subtype of acetylcholine receptor. It is, therefore, important to understand the differences between two receptor subtypes. The two distinct subfamilies of acetylcholine receptors are defined as nicotinic acetylcholine receptors and muscarinic acetylcholine receptors. (See Goodman and Gilman's, The Pharmacological Basis of Therapeutics, *op. cit.*).

The responses of these receptor subtypes are mediated by two entirely different classes of second messenger systems. When the nicotinic acetylcholine receptor is activated, the response is an increased flux of specific extracellular ions (e.g. Na^+, K^+ and Ca^{++}) through the neuronal membrane. In contrast, muscarinic acetylcholine receptor activation leads to changes in intracellular systems that contain complex molecules such as G-proteins and inositol phosphates. Thus, the biological consequences of nicotinic acetylcholine receptor activation are distinct from those of muscarinic receptor activation. In an analogous manner, inhibition of nicotinic acetylcholine receptors results in still other biological effects, which are distinct and different from those arising from muscarinic receptor inhibition.

As indicated above, the two principal sites to which drug compounds that affect chemical synaptic transmission may be directed are the presynaptic nerve terminal and the postsynaptic membrane. Actions of drugs directed to the presynaptic site may be mediated through presynaptic receptors that respond to the neurotransmitter which the same secreting structure has released (i.e., through an autoreceptor), or through a presynaptic receptor that responds to another neurotransmitter (i.e., through a heteroreceptor). Actions of drugs directed to the postsynaptic membrane mimic the action of the endogenous neurotransmitter or inhibit the interaction of the endogenous neurotransmitter with a postsynaptic receptor.

Classic examples of drugs that modulate postsynaptic membrane excitability are the neuromuscular blocking agents which interact with nicotinic acetylcholine-gated channel receptors on skeletal muscle, for example, competitive (stabilizing) agents, such as curare, or depolarizing agents, such as succinylcholine.

In the central nervous system, postsynaptic cells can have many neurotransmitters impinging upon them. This makes it difficult to know the precise net balance of chemical synaptic transmission required to control a given cell. Nonetheless, by designing compounds that selectively affect only one pre- or postsynaptic receptor, it is possible to modulate the net balance of all the other inputs. Obviously, the more that is understood about chemical synaptic transmission in CNS disorders, the easier it would be to design drugs to treat such disorders.

Knowing how specific neurotransmitters act in the CNS allows one to speculate about the disorders that may be treatable with certain CNS-active drugs. For example, dopamine is widely recognized as an important neurotransmitter in the central nervous systems in humans and animals. Many aspects of the pharmacology of dopamine have been reviewed by Roth and Elsworth, "Biochemical Pharmacology of Midbrain Dopamine Neurons", In: Psychopharmacology: The Fourth Generation of Progress, F.E. Bloom and D.J. Kupfer, Eds., Raven Press, NY, 1995, pp 227-243). Patients with Parkinson's disease have a primary loss of dopamine containing neurons of the nigrostriatal pathway, which results in profound loss of motor control. Therapeutic strategies to replace the dopamine deficiency with dopamine mimetics, as well as administering pharmacologic agents that modify dopamine release and other neurotransmitters have been found to have therapeutic benefit ("Parkinson's Disease", In: Psychopharmacology: The Fourth Generation of Progress, *op. cit*, pp 1479-1484).

New and selective neurotransmitter controlling agents are still being sought, in the hope that one or more will be useful in important, but as yet poorly controlled, disease states or behavior models. For example, dementia, such as is seen with Alzheimer's disease or Parkinsonism, remains largely untreatable. Symptoms of chronic alcoholism and nicotine withdrawal involve aspects of the central nervous system, as does the behavioral disorder Attention-Deficit Disorder (ADD). Specific agents for treatment of these and related disorders are few in number or non-existent.

A more complete discussion of the possible utility as CNS-active agents of compounds with activity as cholinergic ligands selective for neuronal nicotinic receptors, (*i.e.*, for controlling chemical synaptic transmission) may be found in U.S. Patent 5,472,958, to Gunn et al., issued Dec. 5, 1995.

Existing acetylcholine agonists are therapeutically sub-optimal in treating the conditions discussed above. For example, such compounds have unfavorable pharmacokinetics (e.g., arecoline and nicotine), poor potency and lack of selectivity (e.g., nicotine), poor CNS penetration (e.g., carbachol) or poor oral bioavailability (e.g., nicotine). In addition, other agents have many unwanted central agonist actions, including hypothermia, hypolocomotion and tremor and peripheral side effects, including miosis, lachrymation, defecation and tachycardia (Benowitz *et al.*, in: Nicotine Psychopharmacology, S. Wonnacott, M.A.H. Russell, & I.P. Stolerman, eds., Oxford University Press, Oxford, **1990**, pp. 112-157; and M. Davidson, *et al.*, in Current Research in Alzheimer Therapy, E. Giacobini and R. Becker, ed.; Taylor & Francis: New York, **1988**; pp 333-336).

Various heterocyclic 2-pyrrolidinyloxy-substituted compounds with analgesic and hypotensive activities have been disclosed by Scheffler *et al.* (U.S. Patent 4,643,995) and Tomioka *et al.* (*Chem. Pharm. Bull*, 38:2133-5, **1990**).

Certain other 2-pyridyloxy-substituted compounds are disclosed *inter alia* by Engel *et al.* in U.S. Patent 4,946,836 as having analgesic activity.

Various other compounds having a pyrrolidine or azetidine moiety substituted at the 3-position with a heterocycloxy group have also been disclosed (*cf.* U.S.Patents 4,592,866 to A.D. Cale; 4,705,853 to A.D. Cale; 4,956,359 to Taylor *et al.*; and 5,037,841 to Schoehe *et al.* and European patent application EP296560A2, to Sugimoto *et al.*).

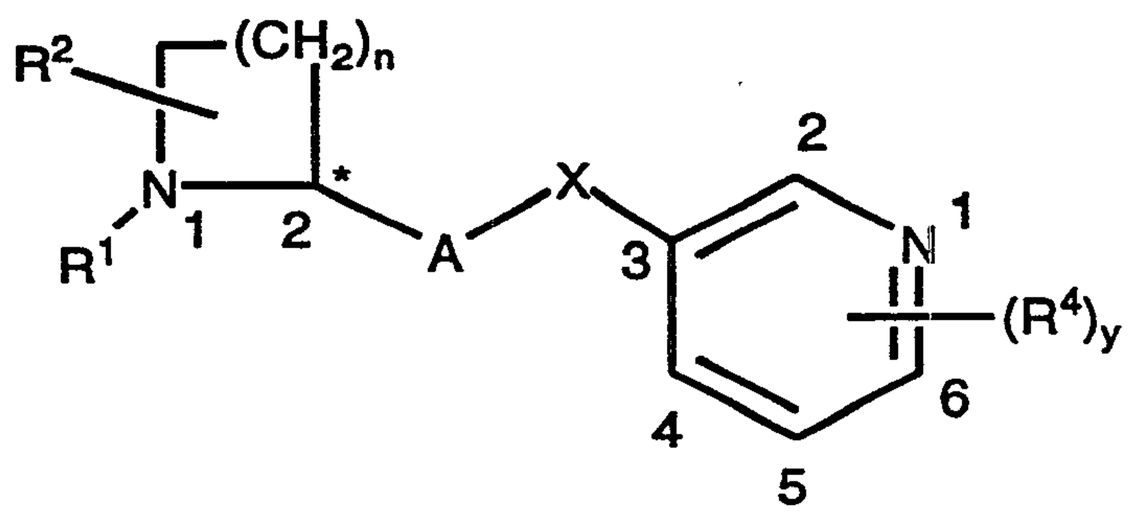
Certain nicotine-related compounds having utility in enhancing cognitive function have been reported by Lin in U.S. Patent 5,278,176, issued Jan. 11, 1994. Also, 2-(nitro)phenoxy compounds with similar function have been reported by Gunn *et al.*, U.S. Patent 5,472,958, issued Dec. 5, 1995.

In the PCT Patent Application WO94 08992 of Abreo *et al.*, published April 28, 1994, are disclosed, *inter alia,* various 3-pyridyloxy-heterocyclic compounds that are either unsubstituted or mono-substituted on the pyridine ring with groups such as Br, Cl, F, hydroxyl, C_1-C_3-alkyl or C_1-C_3-alkoxy, such compounds also described as having utility in enhancing cognitive function.

Summary of the Invention

It has been found, in accordance with the present invention, that a class of 3-pyridyloxyalkyl heterocyclic ether compounds are selective and potent neuronal nicotinic cholinergic compounds useful in controlling synaptic transmission.

In its principal aspect, the present invention provides a compound or a pharmaceutically acceptable salt or prodrug thereof having the formula **I**



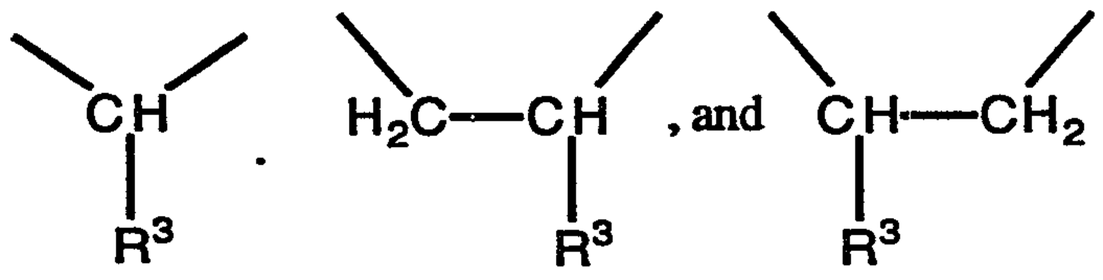
I

where the asterisk denotes a chiral center, and **n** is an integer selected from 1, 2, or 3.

X is oxygen or sulfur, and R^1 is selected from the group consisting of hydrogen, allyl, and C_1-C_6-alkyl.

The substituent R^2 is hydrogen or, when n=2, is a single substituent selected from the group consisting of -CH_2OH, -CH_2F, -CH_2CN, -CH_2OCH_3, -Br, -Cl, -F, -OH, -CN, -(C_1-C_3 alkoxyl), -$OCOCH_3$, and O-methanesulfonyl, with the proviso that when R^2 is substituted at the 3-position or the 5-position of the pyrrolidinyl ring, it is a C_1-C_3-alkyl group.

The group **A** is selected from the group consisting of



where R^3 is H or C_1-C_6-alkyl;

The integer **y** is selected from 1, 2 or 3, with the provisos that:

a) when y = 1, R^4 is selected from the group consisting of (i) a single substituent at the 2-position of the pyridine ring selected from chlorine and fluorine, and (ii) a single substituent substituted at the 5- or 6-position of the pyridine ring selected from the group consisting of -CN, -CF_3, -NO_2, -CH_2OH, -CH_2CN, -NH_2, -NH-CHO, -NHCO(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)-CO(C_1-C_3 alkyl), -NH-(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$,

-COOH, -COO(C_1-C_3 alkyl), -$CONH_2$, -CONH(C_1-C_3 alkyl), -CONHbenzyl, and -OCO(C_1-C_3-alkyl);

b) when y=2, R^4 is substituted at the 2,5-, 2,6- or 5,6- positions of the pyridine ring wherein the 2-position substituent is selected from the group consisting of -Br, -Cl, -F, -OH, -(C_1-C_4 alkyl) and -(C_1-C_3 alkoxy) and the substituents at the 5- or 6-positions of the pyridine ring are selected from the group consisting of -Br, -Cl, -F, -OH, -(C_1-C_4 alkyl), -CN, -CF_3, -NO_2, -CH_2OH, -CH_2CN, -(C_1-C_3 alkoxy), -NH_2, -NH-CHO, -NHCO(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)CO(C_1-C_3 alkyl), -NH-(C_1-C_3 alkyl), N(C_1-C_3 alkyl)$_2$, -COOH, -COO(C_1-C_3 alkyl), -$CONH_2$, -CONH-(C_1-C_3 alkyl), -CONHbenzyl, and -OCOC_1-C_3 alkyl); and

c) when y=3, R^4 is a substituent at the 2-position of the pyridine ring selected from the group consisting of -Br, -Cl, -F, -OH, -C_1-C_4 alkyl, and -C_1-C_3 alkoxy; and second and third substituents at the 5- and 6-position of the pyridine ring are independently selected from the group consisting of -Br, -Cl, -F, -OH, -C_1-C_4 alkyl, -CN, -CF_3,-NO_2, -CH_2OH, -CH_2CN, -(C_1-C_3 alkoxy), -NH_2, -NH-CHO, -NHCO(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)CO(C_1-C_3 alkyl), -NH-(C_1-C_3 alkyl), -N(C_1-C_3-alkyl)$_2$, -COOH, -COO(C_1-C_3-alkyl), -$CONH_2$, -CONH(C_1-C_3 alkyl), -CONHbenzyl, and -OCO(C_1-C_3 alkyl).

In another aspect, the present invention provides a pharmaceutical composition for selectively controlling synaptic transmission comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Formula (I) below.

In still another aspect, the present invention provides a method for selectively controlling synaptic transmission comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Formula (I) below.

Detailed Description of the Invention

In one preferred embodiment, compounds of the present invention comprise a class of substituted azetidine compounds of Formula (I) above wherein n=1.

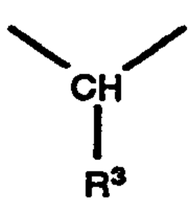
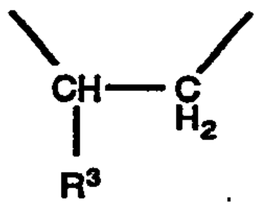
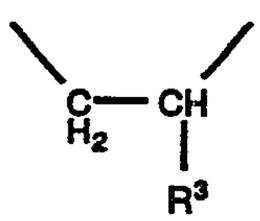
In another preferred embodiment, compounds of the present invention comprise a class of substituted pyrrolidine compounds of Formula (I) above wherein n=2.

In yet another preferred embodiment, compounds of the present invention comprise a class of substituted piperidine compounds of Formula (I) above wherein n=3.

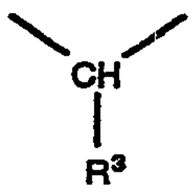
In a further preferred embodiment of the invention, the group X in compounds of Formula (I) above is oxygen.

In yet another preferred embodiment of the present invention, the group X in compounds of Formula (I) above is sulfur.

In still further preferred embodiments of the present invention, the group A in compounds of Formula I above is selected from the group consisting of


, 
, and 
and R^3 is as defined above.

In a particularly preferred embodiment of the present invention, n=0 or 1, X=oxygen,

A is 
and R^3 is H in compounds of Formula (I) above.

Representative substituted azetidine compounds falling within the scope of the present invention where n in the generic formula I is equal to one include:

5-bromo-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine;

5-bromo-6-chloro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;

2-chloro-3-(2-(S)-azetidinylmethoxy)pyridine;

2-chloro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;

5,6-dichloro-3-(2-(S)-azetidinylmethoxy)pyridine;

5,6-dichloro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;

5,6-dichloro-3-(2-(R)-azetidinylmethoxy)pyridine;

5,6-dichloro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;

3-(2-(S)-azetidinylmethoxy)-5-trifluoromethylpyridine;

2-fluoro-3-(2(S)-azetidinylmethoxy)pyridine;

2-fluoro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;

2-fluoro-3-(2(R)-azetidinylmethoxy)pyridine;

6-cyano-3-(2(S)-azetidinylmethoxy)pyridine;

5-cyano-3-(2-(S)-azetidinylmethoxy)pyridine;

5-ethyl-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine;

5-cyano-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine;

5-cyano-6-chloro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;

5-carbamoyl-6-chloro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;

5-bromo-6-methyl-3-(2-(S)-azetidinylmethoxy)pyridine;

5-nitro-3-(2-(S)-azetidinylmethoxy)pyridine;

5-nitro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;

6-fluoro-5-methyl-3-(2-(S)-azetidinylmethoxy)pyridine;

6-chloro-5-methyl-3-(2-(S)-azetidinylmethoxy)pyridine;
5-bromo-6-fluoro-3-(2-(S)-azetidinylmethoxy)pyridine;
5-methoxy-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine;
5-ethoxy-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine;
5-nitro-6-methyl-3-(2-(S)-azetidinylmethoxy)pyridine;
5,6-dimethyl-3-(2-(S)-azetidinylmethoxy)pyridine;
5-nitro-3-(2-(R)-azetidinylmethoxy)pyridine;
5-nitro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-nitro-6-methyl-3-(2-(R)-azetidinylmethoxy)pyridine;
5-nitro-6-methyl-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-nitro-6-methyl-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-amino-(2-(S)-azetidinylmethoxy)pyridine;
5-amino-3-(2-(R)-azetidinylmethoxy)pyridine;
5-amino-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-amino-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-amino-6-methyl-3-(2-(S)-azetidinylmethoxy)pyridine;
5-amino-6-methyl-3-(2-(R)-azetidinylmethoxy)pyridine;
5-amino-6-methyl-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-amino-6-methyl-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-bromo-6-methyl-3-(2-(S)-azetidinylmethoxy)pyridine;
5-bromo-6-methyl-3-(2-(R)-azetidinylmethoxy)pyridine;
5-bromo-6-methyl-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-bromo-6-fluoro-3-(2-(R)-azetidinylmethoxy)pyridine;
5-bromo-6-fluoro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-bromo-6-fluoro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-Bromo-6-chloro-3-(2-(R)-azetidinylmethoxy)pyridine;
5-Bromo-6-chloro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-cyano-3-(2-(S)-azetidinylmethoxy)pyridine;
5-cyano-3-(2-(R)-azetidinylmethoxy)pyridine;
5-cyano-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
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5-cyano-6-fluoro-3-(2-(R)-azetidinylmethoxy)pyridine;

5-cyano-6-fluoro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-cyano-6-fluoro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-cyano-6-chloro-3-(2-(R)-azetidinylmethoxy)pyridine;
5-cyano-6-chloro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-carbamoyl-3-(2-(S)-azetidinylmethoxy)pyridine;
5-carbamoyl-3-(2-(R)-azetidinylmethoxy)pyridine;
5-carbamoyl-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-carbamoyl-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
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5-carbamoyl-6-methyl-3-(2-(R)-azetidinylmethoxy)pyridine;
5-carbamoyl-6-methyl-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-carbamoyl-6-methyl-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-carbamoyl-6-fluoro-3-(2-(S)-azetidinylmethoxy)pyridine;
5-carbamoyl-6-fluoro-3-(2-(R)-azetidinylmethoxy)pyridine;
5-carbamoyl-6-fluoro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-carbamoyl-6-fluoro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-carbamoyl-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine;
5-carbamoyl-6-chloro-3-(2-(R)-azetidinylmethoxy)pyridine;
5-carbamoyl-6-chloro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-amino-6-fluoro-3-(2-(S)-azetidinylmethoxy)pyridine;
5-amino-6-fluoro-3-(2-(R)-azetidinylmethoxy)pyridine;
5-amino-6-fluoro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-amino-6-fluoro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-amino-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine;
5-amino-6-chloro-3-(2-(R)-azetidinylmethoxy)pyridine;
5-amino-6-chloro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-amino-6-chloro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-formamido-3-(2-(S)-azetidinylmethoxy)pyridine;
5-formamido-3-(2-(R)-azetidinylmethoxy)pyridine;
5-formamido-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-formamido-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-formamido-6-methyl-3-(2-(S)-azetidinylmethoxy)pyridine;
5-formamido-6-methyl-3-(2-(R)-azetidinylmethoxy)pyridine;
5-formamido-6-methyl-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-formamido-6-methyl-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-acetamido-6-fluoro-3-(2-(S)-azetidinylmethoxy)pyridine;
5-acetamido-6-fluoro-3-(2-(R)-azetidinylmethoxy)pyridine;

5-acetamido-6-fluoro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-acetamido-6-fluoro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-acetamido-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine;
5-acetamido-6-chloro-3-(2-(R)-azetidinylmethoxy)pyridine;
5-acetamido-6-chloro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-acetamido-6-chloro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-methylamino-3-(2-(S)-azetidinylmethoxy)pyridine;
5-methylamino-3-(2-(R)-azetidinylmethoxy)pyridine;
5-methylamino-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-methylamino-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-methylamino-6-methyl-3-(2-(S)-azetidinylmethoxy)pyridine;
5-methylamino-6-methyl-3-(2-(R)-azetidinylmethoxy)pyridine;
5-methylamino-6-methyl-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-methylamino-6-methyl-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-ethylamino-6-fluoro-3-(2-(S)-azetidinylmethoxy)pyridine;
5-ethylamino-6-fluoro-3-(2-(R)-azetidinylmethoxy)pyridine;
5-ethylamino-6-fluoro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-ethylamino-6-fluoro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-ethylamino-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine;
5-ethylamino-6-chloro-3-(2-(R)-azetidinylmethoxy)pyridine;
5-ethylamino-6-chloro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-ethylamino-6-chloro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-ethyl-6-methyl-3-(2-(S)-azetidinylmethoxy)pyridine;
5-ethyl-6-methyl-3-(2-(R)-azetidinylmethoxy)pyridine;
5-ethyl-6-methyl-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-ethyl-6-methyl-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-ethyl-6-fluoro-3-(2-(S)-azetidinylmethoxy)pyridine;
5-ethyl-6-fluoro-3-(2-(R)-azetidinylmethoxy)pyridine;
5-ethyl-6-fluoro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-ethyl-6-fluoro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-propyl-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine;
5-propyl-6-chloro-3-(2-(R)-azetidinylmethoxy)pyridine;
5-propyl-6-chloro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-propyl-6-chloro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-methyl-6-fluoro-3-(2-(R)-azetidinylmethoxy)pyridine;
5-methyl-6-fluoro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-methyl-6-fluoro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;

5-methyl-6-chloro-3-(2-(R)-azetidinylmethoxy)pyridine;
5-methyl-6-chloro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-methyl-6-chloro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5,6-dimethyl-3-(2-(R)-azetidinylmethoxy)pyridine;
5,6-dimethyl-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5,6-dimethyl-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
6-fluoro-5-methoxy-3-(2-(S)-azetidinylmethoxy)pyridine;
6-fluoro-5-methoxy-3-(2-(R)-azetidinylmethoxy)pyridine;
6-fluoro-5-methoxy-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
6-fluoro-5-methoxy-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
6-fluoro-5-ethoxy-3-(2-(S)-azetidinylmethoxy)pyridine;
6-fluoro-5-ethoxy-3-(2-(R)-azetidinylmethoxy)pyridine;
6-fluoro-5-ethoxy-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine; and
6-fluoro-5-ethoxy-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine; or a pharmaceutically acceptable salt or pro-drug thereof.

Preferred substituted azetididine compounds of the present invention include:
5-bromo-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine;
5-bromo-6-chloro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
2-chloro-3-(2-(S)-azetidinylmethoxy)pyridine;
2-chloro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5,6-dichloro-3-(2-(S)-azetidinylmethoxy)pyridine;
5,6-dichloro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5,6-dichloro-3-(2-(R)-azetidinylmethoxy)pyridine;
5,6-dichloro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
3-(2-(S)-azetidinylmethoxy)-5-trifluoromethylpyridine;
5,6-Dichloro-3-(2-(S)-azetidinylmethoxy)pyridine; and
5,6-Dichloro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
2-fluoro-3-(2(S)-azetidinylmethoxy)pyridine;
2-fluoro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
2-fluoro-3-(2(R)-azetidinylmethoxy)pyridine;
6-cyano-3-(2(S)-azetidinylmethoxy)pyridine;
5-cyano-3-(2-(S)-azetidinylmethoxy)pyridine;
5-ethyl-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine;
5-cyano-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine;
5-cyano-6-chloro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-carbamoyl-6-chloro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-bromo-6-methyl-3-(2-(S)-azetidinylmethoxy)pyridine;

5-nitro-3-(2-(S)-azetidinylmethoxy)pyridine; and
6-fluoro-5-methyl-3-(2-(S)-azetidinylmethoxy)pyridine; or a pharmaceutically acceptable salt or pro-drug thereof.

Representative substituted pyrrolidine compounds falling within the scope of the present invention where n in the generic formula I above is equal to two include:
5-ethylamino-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-bromo-6-chloro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-bromo-6-chloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-nitro-3-(1-Methyl-2-(S)-pyrrolidinylmethoxy)-pyridine;
5-bromo-6-chloro-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-bromo-6-chloro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5,6-dichloro-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5,6-dichloro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5,6-dichloro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5,6-dichloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
3-((*cis*-1,5-dimethyl-2-(S)-pyrrolidinyl)methoxy)pyridine;
3-(1-methyl-2-(S)-pyrrolidinylmethoxy)-5-trifluoromethylpyridine;
3-((*trans*-4-cyanomethyl-1-methyl-2-(S)-pyrrolidinyl)methoxy)pyridine;
3-((1-methyl-2-(R)-pyrrolidinyl)methoxy)-5-trifluoromethylpyridine;
3-((*cis*-3-propyl-2-pyrrolidinyl)methoxy)pyridine;
3-(2-(S)-pyrrolidinylmethoxy)-5-trifluoromethylpyridine;
3-(2-(R)-pyrrolidinylmethoxy)-5-trifluoromethylpyridine;
3-((*trans*-4-methanesulfonyloxy-1-methyl-2(S)-pyrrolidinyl)methoxy)pyridine;
6-hydroxymethyl-3-((1-methyl-2-(S)-pyrrolidinyl)methoxy)pyridine;
3-((*trans*-1,5-dimethyl-2-(S)-pyrrolidinyl)methoxy)pyridine;
3-((*cis*-4-cyano-1-methyl-2-(S)-pyrrolidinyl)methoxy)pyridine;
3-((cis-4-fluoromethyl-1-methyl-2-(S)-pyrrolidinyl)methoxy)pyridine;
5-amino-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
3-(2-(2-(S)-pyrrolidinyl)ethoxy)pyridine;
3-(2-(1-methyl-2-(S)-pyrrolidinyl)ethoxy)pyridine;
3-(2-(2-(S)-pyrrolidinyl)ethoxy)-6-chloropyridine;
3-(2-(1-methyl-2-(S)-pyrrolidinyl)ethoxy)-6-chloropyridine;
3-(2-(S)-pyrrolidinylmethylthioxy)pyridine;
3-(1-methyl-2-(S)-pyrrolidinylmethylthioxy)pyridine;
*5-nitro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-ethyl-6-chloro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-ethyl-6-chloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;

5-ethyl-6-chloro-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-nitro-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-nitro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-nitro-6-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-nitro-6-methyl-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-nitro-6-methyl-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-nitro-6-methyl-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-amino-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-amino-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-amino-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-amino-6-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-amino-6-methyl-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-amino-6-methyl-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-amino-6-methyl-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-bromo-6-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-bromo-6-methyl-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-bromo-6-methyl-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-bromo-6-methyl-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-bromo-6-fluoro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-bromo-6-fluoro-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-bromo-6-fluoro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-bromo-6-fluoro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-cyano-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-cyano-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-cyano-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-cyano-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-cyano-6-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-cyano-6-methyl-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-cyano-6-methyl-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-cyano-6-methyl-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-cyano-6-fluoro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-cyano-6-fluoro-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-cyano-6-fluoro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-cyano-6-fluoro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-cyano-6-chloro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-cyano-6-chloro-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-cyano-6-chloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;

5-cyano-6-chloro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-carbamoyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-carbamoyl-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-carbamoyl-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-carbamoyl-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-carbamoyl-6-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-carbamoyl-6-methyl-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-carbamoyl-6-methyl-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-carbamoyl-6-methyl-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-carbamoyl-6-fluoro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-carbamoyl-6-fluoro-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-carbamoyl-6-fluoro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-carbamoyl-6-fluoro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-carbamoyl-6-chloro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-carbamoyl-6-chloro-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-carbamoyl-6-chloro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-carbamoyl-6-chloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-carbamoyl-6-chloro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-amino-6-fluoro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-amino-6-fluoro-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-amino-6-fluoro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-amino-6-fluoro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-amino-6-chloro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-amino-6-chloro-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-amino-6-chloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-amino-6-chloro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-formamido-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-formamido-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-formamido-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-formamido-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-formamido-6-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-formamido-6-methyl-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-formamido-6-methyl-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-formamido-6-methyl-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-acetamido-6-fluoro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-acetamido-6-fluoro-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-acetamido-6-fluoro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;

5-acetamido-6-fluoro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-acetamido-6-chloro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-acetamido-6-chloro-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-acetamido-6-chloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-acetamido-6-chloro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-methylamino-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-methylamino-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-methylamino-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-methylamino-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-methylamino-6-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-methylamino-6-methyl-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-methylamino-6-methyl-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-methylamino-6-methyl-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-ethylamino-6-fluoro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-ethylamino-6-fluoro-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-ethylamino-6-fluoro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-ethylamino-6-fluoro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-ethylamino-6-chloro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-ethylamino-6-chloro-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-ethylamino-6-chloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-ethylamino-6-chloro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-ethyl-6-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-ethyl-6-methyl-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-ethyl-6-methyl-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-ethyl-6-methyl-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-ethyl-6-fluoro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-ethyl-6-fluoro-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-ethyl-6-fluoro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-ethyl-6-fluoro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-propyl-6-chloro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-propyl-6-chloro-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-propyl-6-chloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-propyl-6-chloro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-methyl-6-fluoro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-methyl-6-fluoro-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-methyl-6-fluoro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-methyl-6-fluoro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;

5-methyl-6-chloro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-methyl-6-chloro-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-methyl-6-chloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-methyl-6-chloro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5,6-dimethyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5,6-dimethyl-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5,6-dimethyl-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5,6-dimethyl-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
6-fluoro-5-methoxy-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
6-fluoro-5-methoxy-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
6-fluoro-5-methoxy-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
6-fluoro-5-methoxy-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
6-fluoro-5-ethoxy-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
6-fluoro-5-ethoxy-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
6-fluoro-5-ethoxy-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine; and
6-fluoro-5-ethoxy-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine; or a pharmaceutically acceptable salt thereof.

Preferred substituted pyrrolidinyl compounds of the present invention include:
5-ethylamino-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-bromo-6-chloro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-bromo-6-chloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-nitro-3-(1-Methyl-2-(S)-pyrrolidinylmethoxy)-pyridine;
5-bromo-6-chloro-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-bromo-6-chloro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5,6-dichloro-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5,6-dichloro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5,6-dichloro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5,6-dichloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
3-((*cis*-1,5-dimethyl-2-(S)-pyrrolidinyl)methoxy)pyridine;
3-(1-methyl-2-(S)-pyrrolidinylmethoxy)-5-trifluoromethylpyridine;
3-((*trans*-4-cyanomethyl-1-methyl-2-(S)-pyrrolidinyl)methoxy)pyridine;
3-((1-methyl-2-(R)-pyrrolidinyl)methoxy)-5-trifluoromethylpyridine;
3-((*cis*-3-propyl-2-pyrrolidinyl)methoxy)pyridine;
3-(2-(S)-pyrrolidinylmethoxy)-5-trifluoromethylpyridine;
3-(2-(R)-pyrrolidinylmethoxy)-5-trifluoromethylpyridine;
3-((*trans*-4-methanesulfonyloxy-1-methyl-2(S)-yridine;
6-hydroxymethyl-3-((1-methyl-2-(S)-pyrrolidinyl)methoxy)pyridine;

3-((*trans*-1,5-dimethyl-2-(S)-pyrrolidinyl)methoxy)pyridine;

3-((*cis*-4-cyano-1-methyl-2(S)-pyrrolidinyl)methoxy)pyridine;

3-((cis-4-fluoromethyl-1-methyl-2-(S)-pyrrolidinyl)methoxy)pyridine;

5-amino-3-(1-methyl-2(S)-pyrrolidinylmethoxy)pyridine;

3-(2-(2-(S)-pyrrolidinyl)ethoxy)pyridine;

3-(2-(1-methyl-2-(S)-pyrrolidinyl)ethoxy)pyridine;

3-(2-(2-(S)-pyrrolidinyl)ethoxy)-6-chloropyridine;

3-(2-(1-methyl-2-(S)-pyrrolidinyl)ethoxy)-6-chloropyridine;

3-(2-(S)-pyrrolidinylmethylthioxy)pyridine;

5-nitro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;

5-ethyl-6-chloro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;

5-ethyl-6-chloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine; and

5-ethyl-6-chloro-3-(2-(R)-pyrrolidinylmethoxy)pyridine; or a pharmaceutically acceptable salt thereof.

Definitions

The terms "C_1-C_3-alkyl," "C_1-C_4-alkyl,"or "C_1-C_6-alkyl" as used herein refer to saturated, straight- or branched-chain hydrocarbon radicals containing between one and three or one and six carbon atoms, respectively. Examples of C_1-C_4-alkyl radicals include, but are not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl and*t*-butyl. Examples of C_1-C_3 alkyl radicals include methyl, ethyl, propyl and isopropyl, examples of C_1-C_6-alkyl radicals include, but are not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *t*-butyl, neopentyl, n-hexyl.

The term "C_1-C_3-alkoxy" as used herein refers to an C_1-C_3-alkyl group, as previously defined, attached to the parent molecular moiety through an oxygen atom. Examples of C_1-C_3-alkoxy, but are not limited to, methoxy, ethoxy, propoxy and isopropoxy.

One or more asymmetric centers may exist in the compounds of the present invention. Except where otherwise noted, the present invention contemplates the various stereoisomers and mixtures thereof.

As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, *et al.* describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 66: 1-19 (1977).

The salts can be prepared *in situ* during the final

isolation and purification of the compounds of the invention, or separately by reacting the free base function with a suitable organic acid. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, *p*-toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

The term "prodrug" refers to compounds that are rapidly transformed *in vivo* to yield the parent compounds of Formula (I), as for example, by hydrolysis in blood. T. Higuchi and V. Stella provide a thorough discussion of the prodrug concept in Prodrugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, American Chemical Society (1975). Examples of esters useful as prodrugs for compounds containing carboxyl groups may be found on pages 14-21 of Bioreversible Carriers in Drug Design: Theory and Application, edited by E.B. Roche, Pergamon Press (1987).

The term "prodrug ester group" refers to any of several ester-forming groups that are hydrolyzed under physiological conditions. Examples of prodrug ester groups include pivoyloxymethyl, acetoxymethyl, phthalidyl, indanyl and methoxymethyl, as well as other such groups known in the art.

As used herein, the term "pharmaceutically acceptable ester" refers to esters which hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety

advantageously has not more than 6 carbon atoms. Examples of particular esters includes formates, acetates, propionates, butryates, acrylates and ethylsuccinates.

Abbreviations

Abbreviations which have been used in the descriptions of the scheme and the examples that follow are: BOC for t-butyloxycarbonyl; Et_2O for diethyl ether; EtOAc for ethyl acetate; DEAD for diethylazodicarboxylate; DMAP for 4-dimethylaminopyridine; DMF for dimethyl formamide; DPPA for diphenylphosphoryl azide; EDC for 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide HCl; EtOAc for ethyl acetate; MeOH for methanol; $NaN(TMS)_2$ for sodium bis(trimethylsilyl)amide; NMMO for N-methylmorpholine N-oxide; Ph for phenyl; TEA for triethylamine; TFA for trifluoroacetic acid; THF for tetrahydrofuran; TPP for triphenylphosphine.

Pharmaceutical Compositions

The pharmaceutical compositions of the present invention comprise a therapeutically effective amount of a compound of the present invention formulated together with one or more pharmaceutically acceptable carriers. As used herein, the term "pharmaceutically acceptable carrier" means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents; sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator. The pharmaceutical compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), bucally, or as an oral or nasal spray.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in

the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides) Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is

normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to the compounds of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

According to the methods of treatment of the present invention, disorders in synaptic transmission are treated or prevented in a patient such as a human or lower mammal by administering to the patient a therapeutically effective amount of a compound of the invention, in such amounts and for such time as is necessary to achieve the desired result. By a "therapeutically effective amount" of a compound of the invention is meant a sufficient amount of the compound to treat disorders in synaptic transmission, at a reasonable benefit/risk ratio applicable to any medical treatment. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical

judgment. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts.

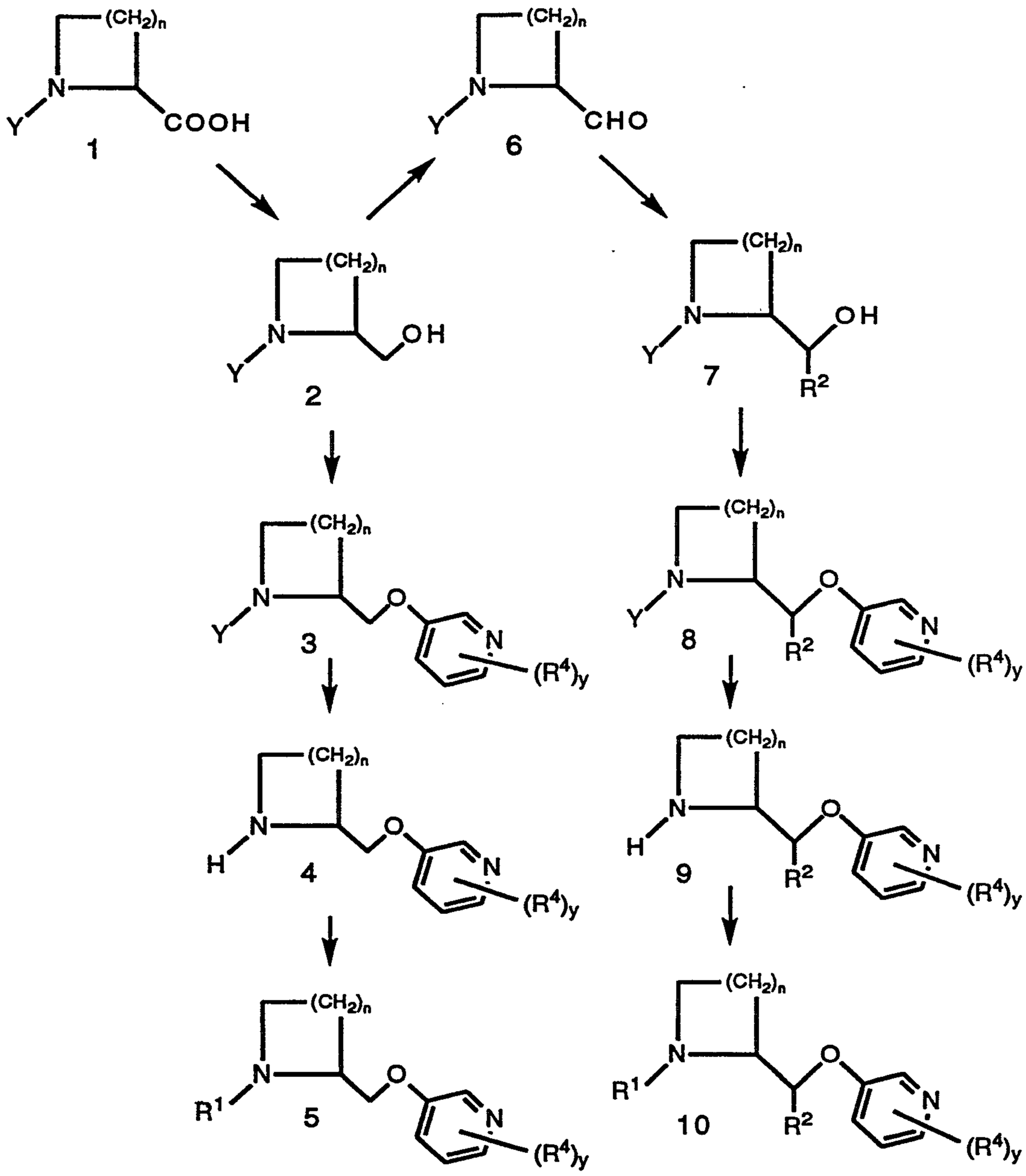
Therapeutic Administration

The total daily dose of the compounds of this invention administered to a human or other mammal in single or in divided doses can be in amounts, for example, from 0.001 to 50 mg/kg body weight or more usually from 0.01 to 25 mg/kg body weight. Single dose compositions may contain such amounts or submultiples thereof to make up the daily dose. In general, treatment regimens according to the present invention comprise administration to a patient in need of such treatment from about 1 mg to about 1000 mg of the compound(s) of this invention per day in single or multiple doses.

Synthetic Methods

The compounds and processes of the present invention will be better understood in connection with the following synthetic schemes which illustrate the methods by which the compounds of the invention may be prepared. The groups n, y, R^1, R^2, R^3 and R^4 are as defined above unless otherwise noted.

Scheme 1

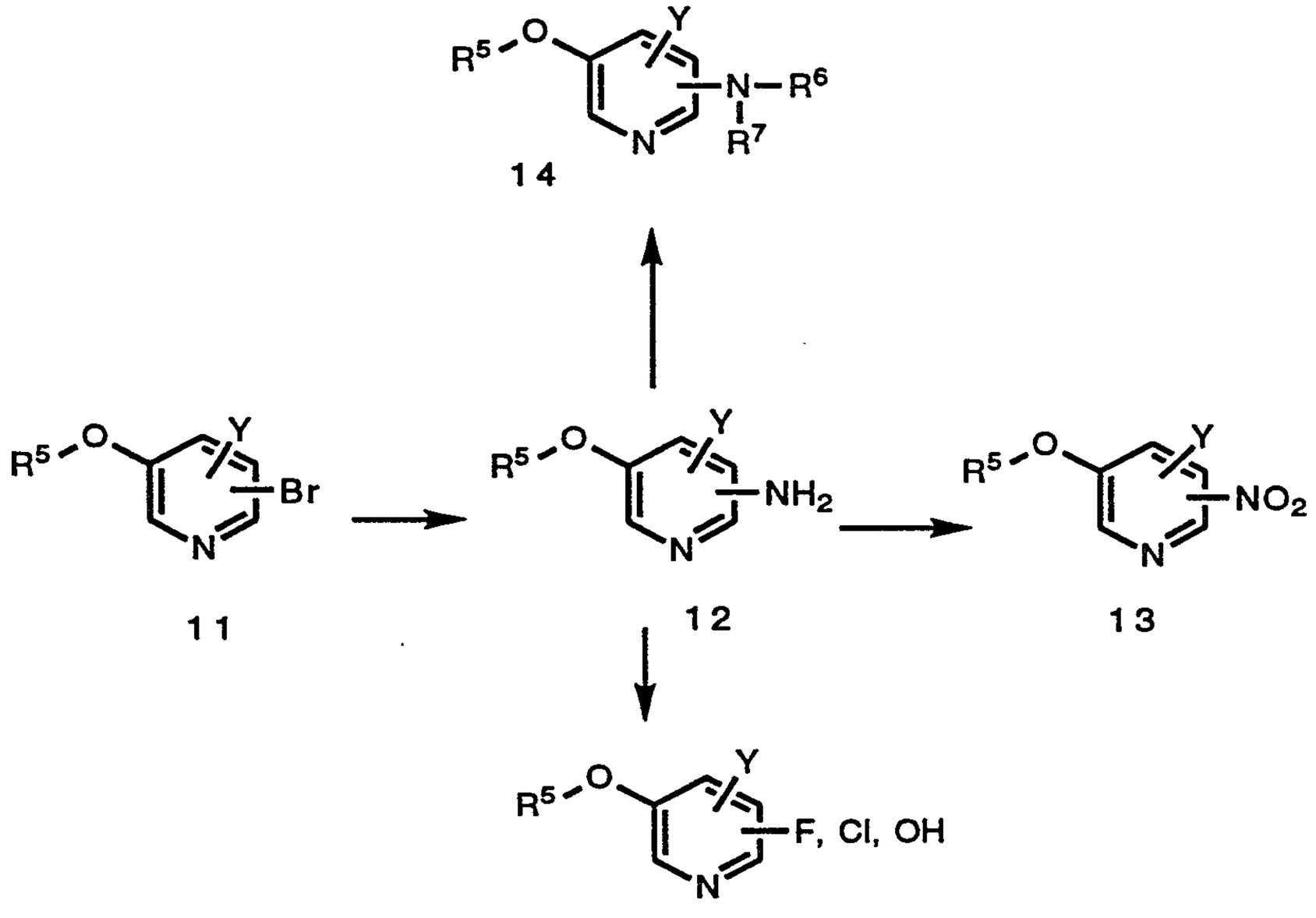


In accordance with reaction Scheme 1, compounds of Formula (I) are prepared by reacting a 2-carboxyl-substituted azacycloalkyl compound (1), wherein n is as described above, R^3 is H and Y is a C_1-C_3-alkyl or a suitable protecting group, such as BOC or CBZ, for example, which may subsequently be removed and replaced with H, allyl, or C_1-C_3-alkyl, is converted to the hydroxymethyl compound of formula (2) with a suitable

reducing agent, such as Red-Al®, borane/THF, borane/methyl sulfide or $LiAlH_4$, for example. Compound (2) is reacted with an appropriately substituted 3-hydroxypyridine compound, wherein R^4 is as described above or is an appropriately protected R^4 group (wherein the protecting group may be removed after the coupling reaction), in the presence of triphenylphosphine and DEAD as described by O. Mitsunobu (*Synthesis*, **1981**: 1) to form the pyridine compound of formula (3). This compound is then treated with a reagent suitable for removing the N-protecting group, such as trifluoroacetic acid for BOC removal, HCl in ethanol for CBZ removal, HBr in acetic acid, or hydrogenolysis with hydrogen in the presence of a noble metal catalyst, to form the unprotected compound (4), which is a compound of Formula (I) above. The ring nitrogen may then be alkylated, for example, by treatment with alkyl halide in the presence of a base, formaldehyde in formic acid, or with an aldehyde and sodium cyanoborohydride in an alcohol solvent, such as methanol, ethanol or isopropanol, or by reaction with the appropriate alkylating reagent, such as, for example, allyl bromide, to give the desired compound (5), wherein R^1 is as described above.

Alternately, compound (2) may be oxidized using a suitable mild oxidizing agent such as DMSO/pyridine•SO_3, pyridinium chlorochromate or DMSO/oxalyl chloride, for example, to afford the aldehyde (6). The aldehyde is then reacted with a suitable organometallic nucleophile, for example, a Grignard reagent, to afford the alcohol (7), wherein R^2 is as described above. The alcohol is then reacted as described above with a 3-hydroxypyridine and carried through the same series of reactions as described above, starting with compound (2) and leading to compounds (3), (4) and (5), to give the compounds (8), (9) and (10), wherein R^1 is as described above.

Scheme 2

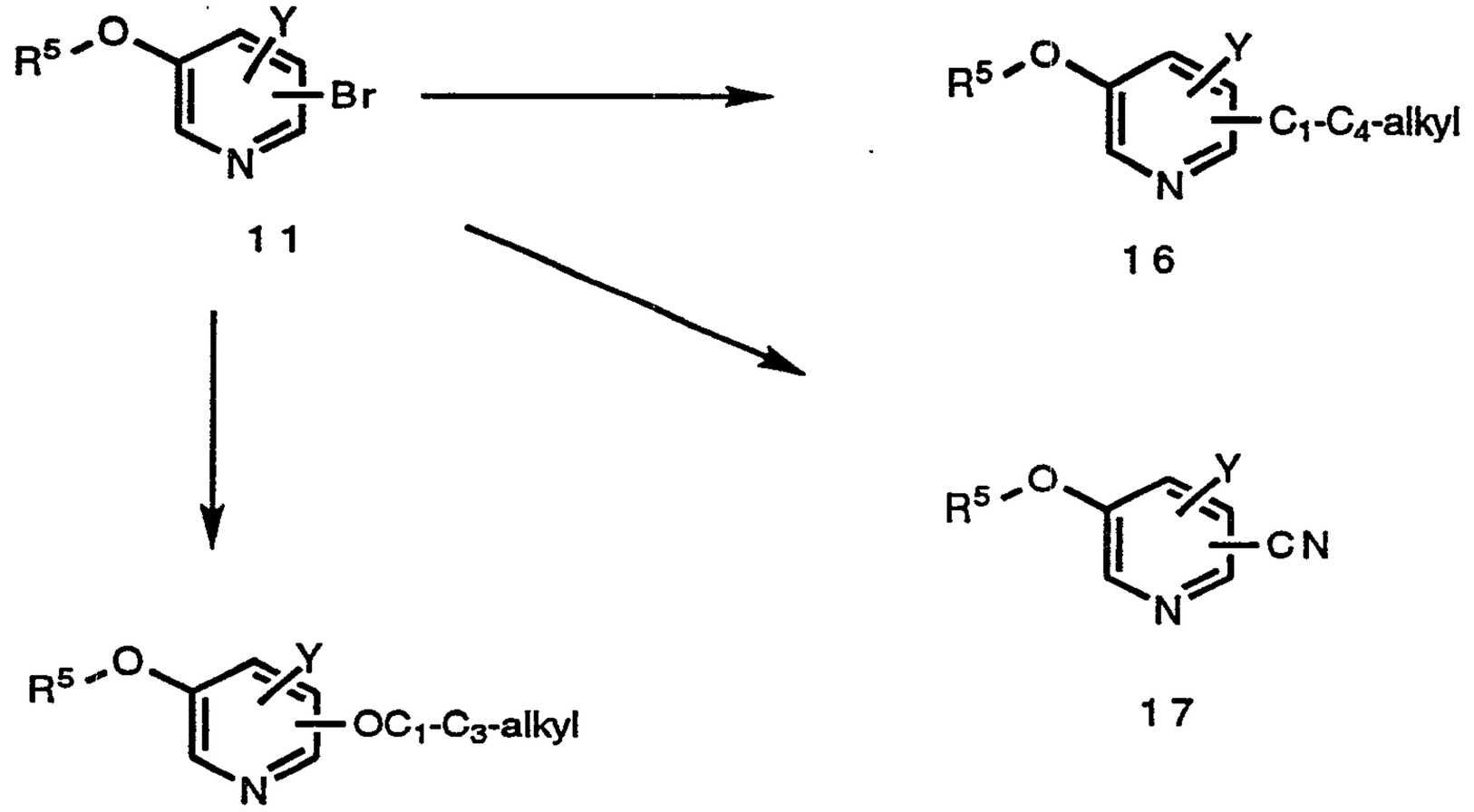


In accordance with Scheme 2, compounds (11), which may be either protected pyridine compounds wherein R^5 is a protecting group or the conjugated compounds of formulas (5) or (10) above, and Y may be hydrogen or a suitable group selected by one skilled in the art, may be utilized as starting materials to prepare various compounds of Formula (I) wherein R^4 represents different chemical moieties. For example, compound (11) may be reacted with NH_3 by heating in an alcoholic solvent, such as methanol, ethanol, propanol, i-propanol, t-butanol or the like, preferably in the presence of Cu^{2+} as a catalyst to give the compound (12).

In turn, compound (12) may be used to generated additional functionally substituted compounds. For example, compound (12) may be treated with potassium persulfate and sulfuric acid to oxidize the amino group to a nitro group and prepare compound (13). Or, compound (12) may be treated with R^6-X or R^7-X, wherein R^6 and R^7 are independently -C_1-C_3-alkyl or -CO-C_1-C_3-alkyl and X is Cl, to give the appropriately derivatized compounds (14). Alternately, compound (12) may be treated with nitrous acid under diazotizing conditions, then the diazo compound may be reacted with an M-X compound, wherein M is sodium or copper, and X is F or Cl to give selected compounds (15). The

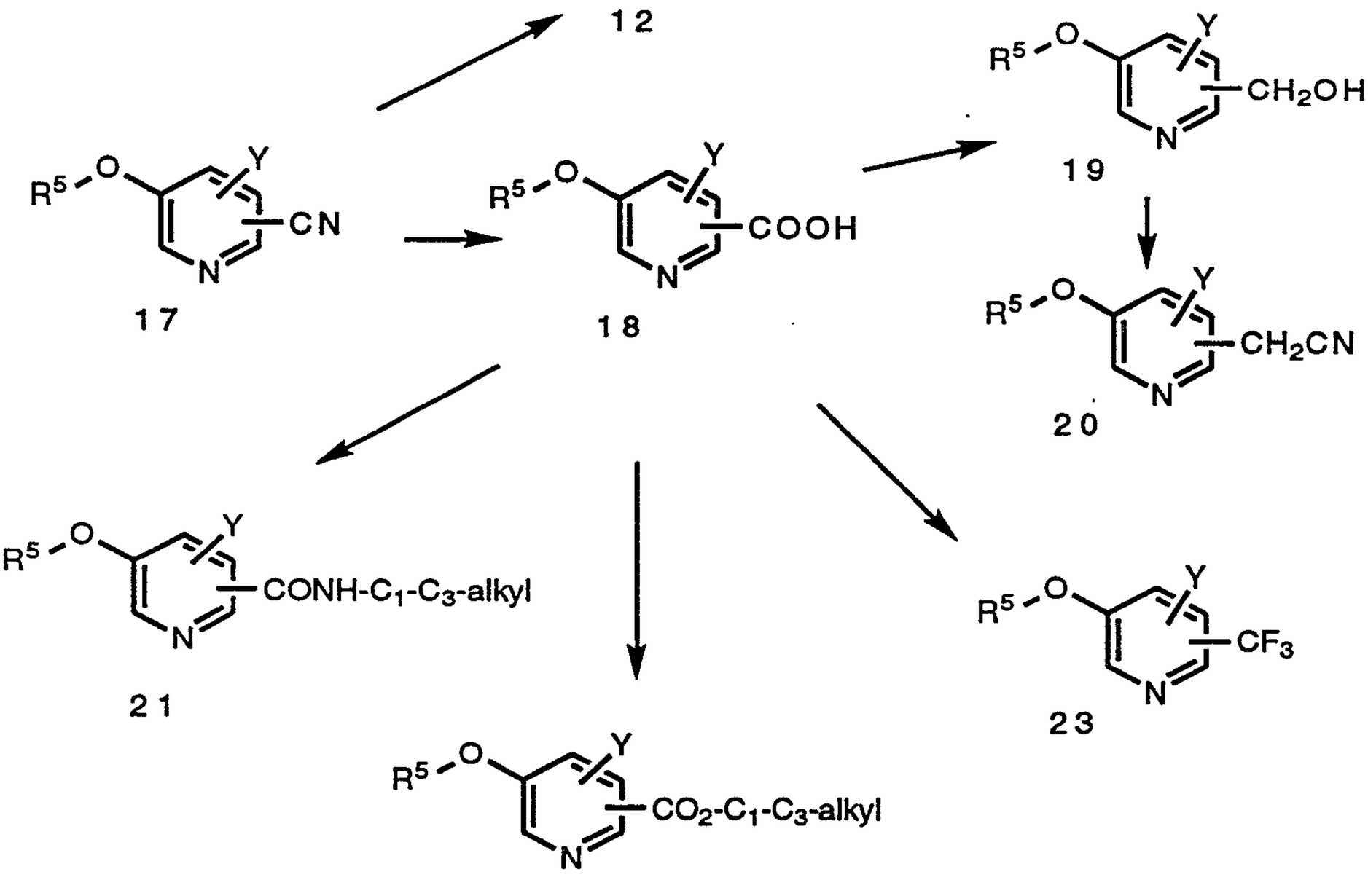
intermediate diazo compound may instead be treated with aqueous sulfuric acid to prepare a hydroxy-substituted compound (15). If R^5 is a protecting group, deprotection followed by conjugation as in Scheme 1 gives compounds of Formula (I).

Scheme 3



In accordance with Scheme 3 compounds (11), which may be either protected pyridine compounds wherein R^5 is a protecting group or the conjugated compounds of formulas (5) or (10) above, and Y may be hydrogen or a suitable group selected by one skilled in the art, may be utilized as starting materials to prepare various compounds of Formula (I) wherein R^4 is represented by additional chemical moieties. For example, compound (11) may be reacted with a C_1-C_3-alkyl-Cu-halide, or alternately, a C_1-C_3-alkyl-Mg-halide in the presence of a nickel or copper catalyst, or in certain cases, the anion of diethyl malonate followed by hydrolysis and decarboxylation, to give the alkyl-substituted compound (16). Compound (11) may be treated with $Zn(CN)_2$ in the presence of a Pd catalyst (according to the procedure given by D. M. Tschaen *et al., Synth. Commun.*, 24:887 (1994)) to afford the cyano compound (17). In the event that alkoxy substituent is desired, compound (11) may be reacted with C_1-C_3-alkyl-O^- M^+ salt in heated DMF or a similar dipolar aprotic solvent or in the corresponding C_1-C_3-alkanol solvent to give the compound (18).

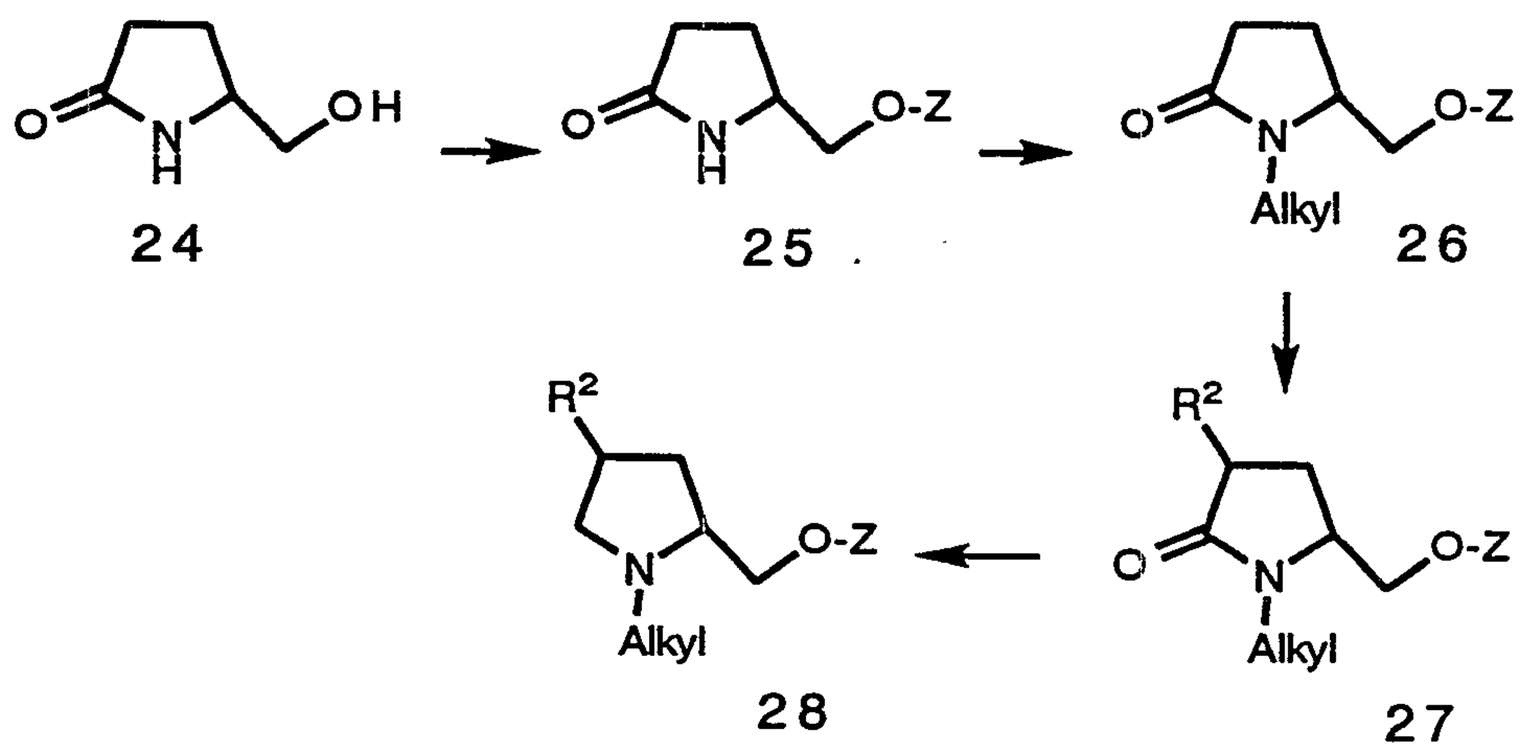
Scheme 4



In accordance with Scheme 4 the cyano compounds (17), which may be either protected pyridine compounds wherein R^5 is a protecting group or the conjugated compounds of formulas (5) or (10) above, and Y may be hydrogen or a suitable group selected by one skilled in the art, may be utilized as starting materials to prepare various compounds of Formula (I) wherein R^4 is represented by additional chemical moieties. For example, compound (17) may be reacted with H_3O^+ and the intermediate amide subjected to a Hofmann rearrangement to provide an alternate route to compounds (12). Also, compound (17) may be converted with H_3O^+ and heat or NaOH and H_2O_2 to the carboxylic acid compound (18). Reduction of compound (18) with BH_3 or Red-Al™, for example, gives compound (19). By treating compound (19) with a reagent to convert the OH to a leaving group, such as a halo or sulfonate group, then replacing the leaving group with CN in a standard nucleophilic reaction, the cyanomethyl compound (20) may be prepared. Alternately, treating the acid (18) with an C_1-C_3-alkylamine under dehydrating conditions allows for preparation of the amide compound (21). Or, reaction of the acid (18) with a suitable alcohol, acid catalyst and heat, the ester compound (22) may be prepared. Another reagent MoF_6 may be reacted with compound (18) by a process similar

to that described by Shustov *et al.*, *J. Gen. Chem. USSR* (Engl. Transl.) 53:85-86 (1983) to prepare compound (23).

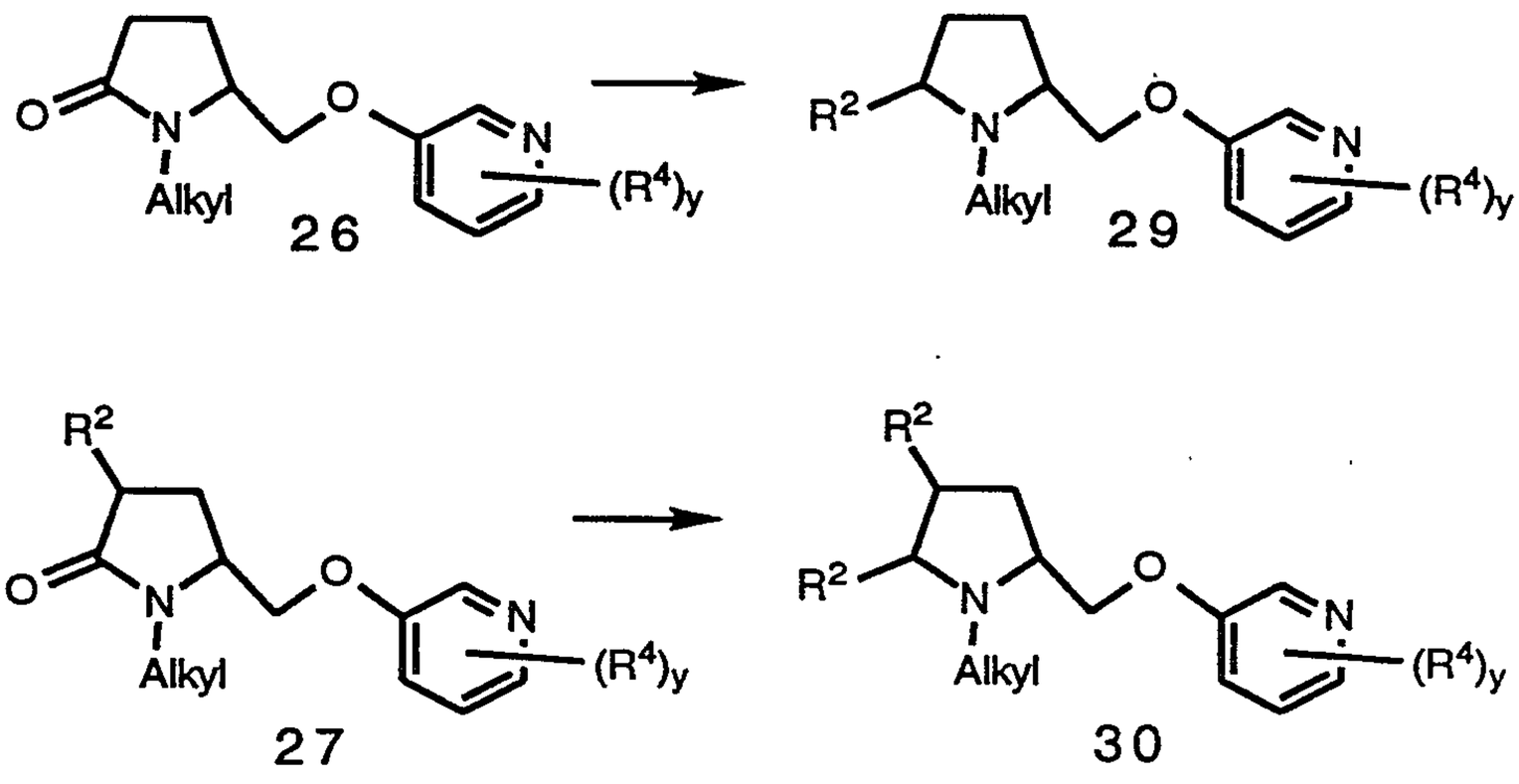
Scheme 5



24 25 26 27 28

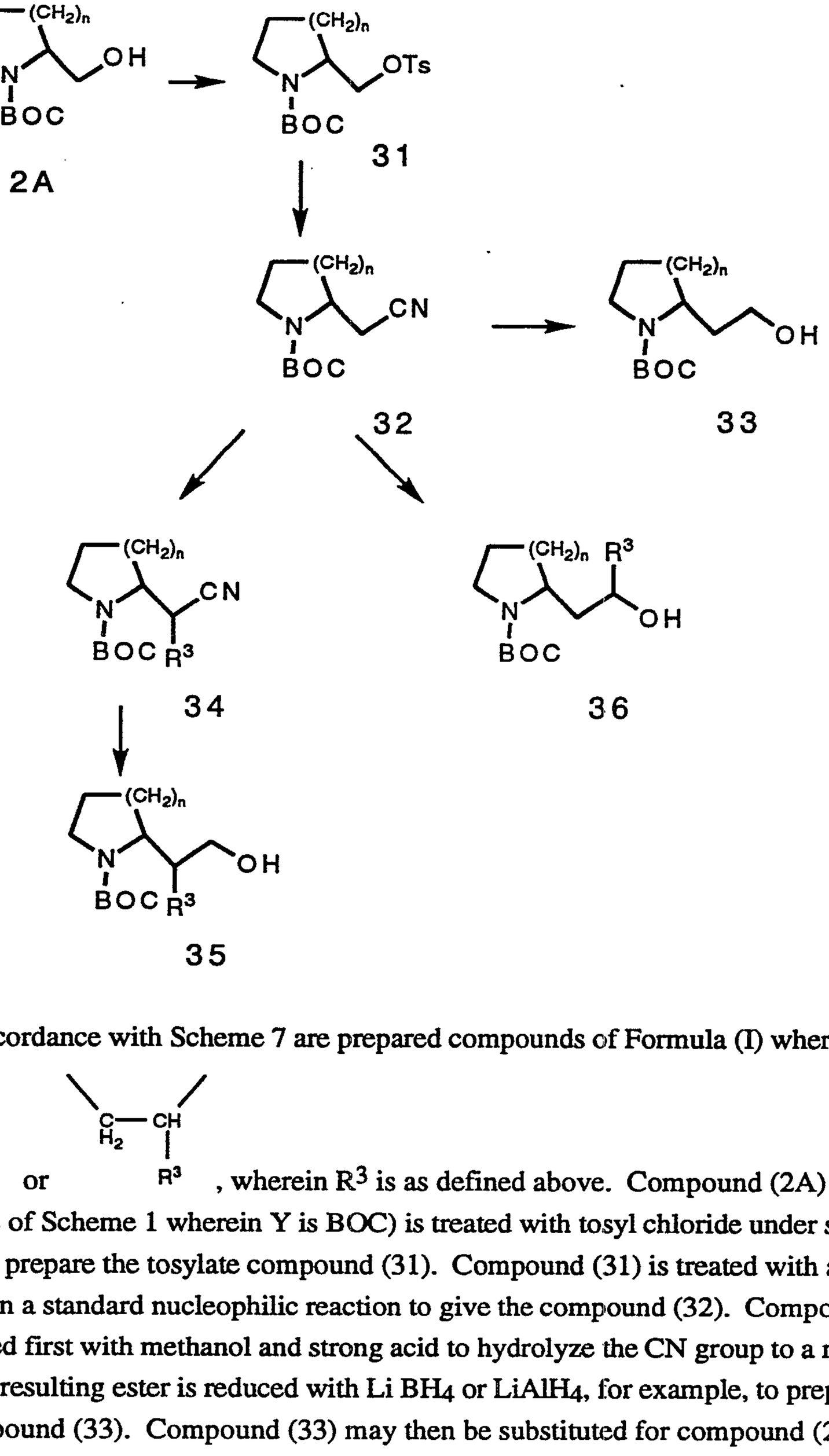
In accordance with Scheme 5, the compound (24) may be reacted according to the alternate reaction pathways shown for compounds (2) or (7) in Scheme 1 to give the desired compound (25). In compound (25) Z may represent the pyridine moiety shown in Schemes 1 or may represent a protecting group. Those skilled in the art will recognized that the protecting group may be removed and replaced by the "B" moiety at alternate positions in the synthetic scheme. Such variations in the process will be obvious to skilled practitioners, and exhaustive explanations of the synthetic options are not deemed necessary. The N-alkyl group, wherein the alkyl group is C_1-C_6-alkyl, is added to compound (25) by reaction with NaH and the appropriate alkyl iodide in anhydrous THF to give compound (26). Compound (26) is treated with LDA and an electrophile such as an alkyl halide, oxaziridine, formaldehyde, a halomethyl ether, N-halo-succinimide, or molecular halogen, for example, to give the substituted compound (27). In addition, compound (27) wherein R^2 is hydroxy or carboxy may be further reacted with an alkyl halide under standard Williamson ether conditions, acetic anhydride, or methanesulfonyl chloride to give additional precursors to compounds of Formula (I). The methanesulfonate from above (27, R=OMs or CH_2OMs may be further reacted with CN^- or F^- anions to produce additional precursors to compounds of Formula (I). B reducing the lactam moiety of (27) with BH_3 followed by treatment with CsF, the desired compound (28) is obtained. Conventional use of nitrogen or oxygen protecting groups for achieving selective reactions are included within the processes discussed herein.

Scheme 6



In accordance with Scheme 6 are synthesized the compounds of formula (I) wherein R^2 therein represents the appropriate 5-substituent group or the desired 4- and 5-substituent groups as described above, compound (26) is reacted with an C_1-C_3-alkyl Grignard reagent followed by $NaBH_3CN$ to give the compound (29). Compound (27), from Scheme 5 wherein Z is as shown above, or a suitably protected derivative, may be further reacted with the appropriate C_1-C_3-alkyl Grignard reagent to prepare the disubstituted compound (30).

Scheme 7



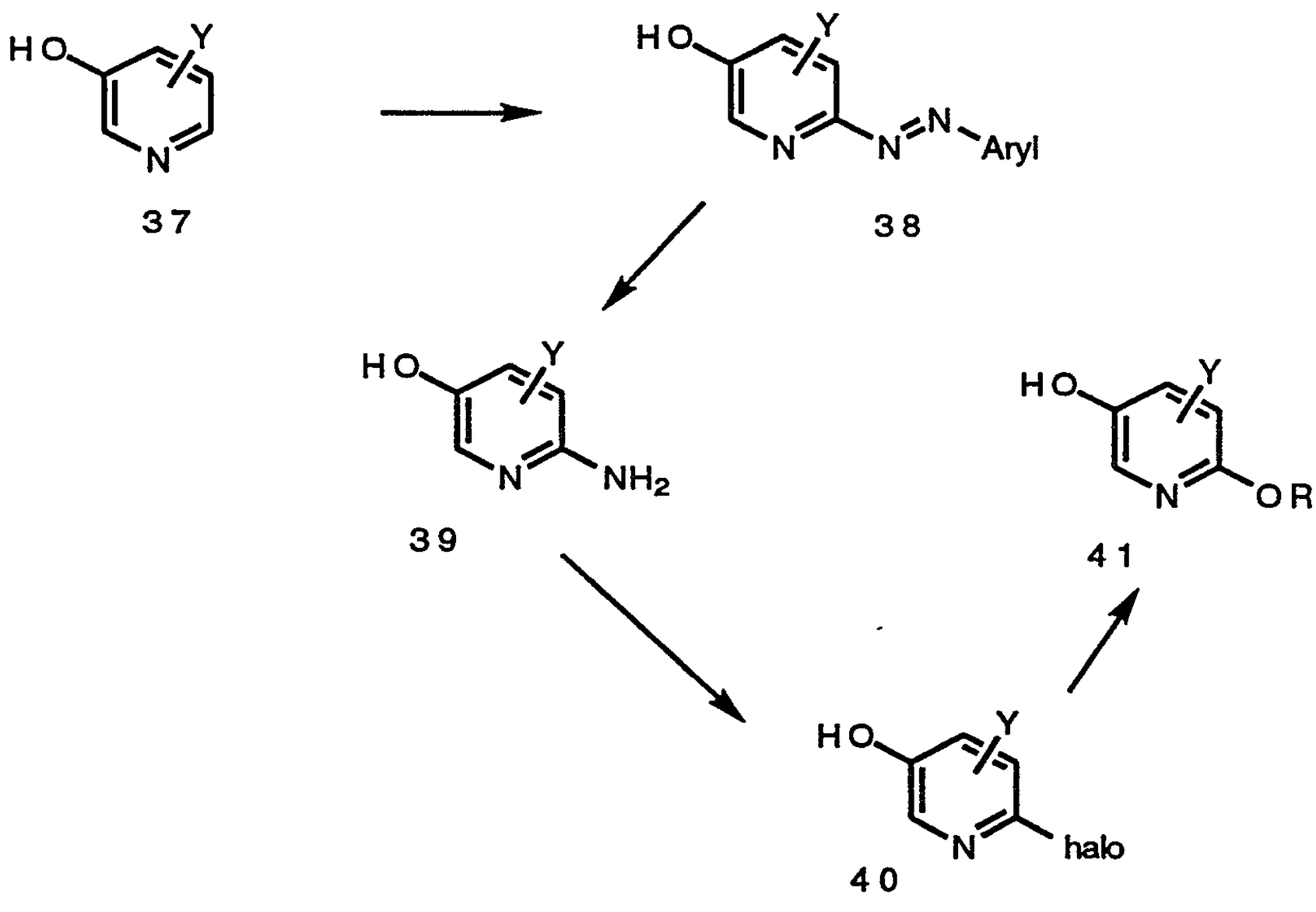
In accordance with Scheme 7 are prepared compounds of Formula (I) wherein A is

or

, wherein R^3 is as defined above. Compound (2A) (compound 2 of Scheme 1 wherein Y is BOC) is treated with tosyl chloride under standard conditions to prepare the tosylate compound (31). Compound (31) is treated with a cyanide salt in a standard nucleophilic reaction to give the compound (32). Compound (32) may be treated first with methanol and strong acid to hydrolyze the CN group to a methyl ester and the resulting ester is reduced with Li BH_4 or $LiAlH_4$, for example, to prepare the alcohol compound (33). Compound (33) may then be substituted for compound (2) or (7)

of Scheme 1 and carried forward as desired. Alternately, compound (32) may be treated with LDA and R^3-X, wherein X is a halogen or other suitable leaving group, to prepare compound (34). Compound (34) may be treated first with methanol and strong acid to convert the CN group to a methyl ester and the resulting ester is reduced with $LiBH_4$ or $LiAlH_4$, for example, to prepare the alcohol compound (35). In yet another alternate process, compound (32) may be treated with Dibal-H™, H_3O^+, and R^3-Mg-X in sequence to prepare the desired alcohol compound (36). Compounds (35) or (36) may then be substituted for compound (2) or (7) of Scheme 1 and carried forward as desired. Compounds (33), (35) and (36) present opportunities for substitution, in accord with the appropriate Schemes above, thus allowing one skilled in the art to prepare other selected compounds of the invention.

Scheme 8



In accordance with Scheme 8 are prepared compounds that may be utilized as starting materials to provide for additional substituted pyridine moieties in selected compounds of the invention. Appropriate substituted compounds (37), wherein Y is a pre-existing group selected from C_1-C_3 alkyl, C_1-C_3 alkoxy, halo, -CN, -CF_3, -NO_2, -CH_2OH, -CH_2CN, -NH-CHO, -NHCO(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)-CO(C_1-C_3 alkyl), -COOH, -COO(C_1-C_3 alkyl), -$CONH_2$, -CONH-(C_1-C_3 alkyl), -CONHbenzyl,

and -$OCOC_1$-C_3 alkyl), may be treated with an aryldiazonium compound in the presence of aqueous base to give the diazo compounds (38). Compounds (38) may be reduced by treatment with H_2 and a noble metal catalyst or $SnCl_2$ to prepare the amino compounds (39). Alternately, treatment of compound (39) with a nucleophilic halide, in the presence of Cu^+ when necessary, allows the preparation of compounds (40). Treatment of compound (40) with a nucleophilic alcohol ROH, allows the preparation of compounds (41).

In vitro Determination of Neuronal Nicotinic Receptor Binding Potencies, Selectivity and Functionality

For the purpose of identifying compounds as cholinergic agents which are capable of interacting with cholinergic channel receptors in the brain, a ligand-receptor binding assay was carried out as the initial screen. Compounds of the present invention were effective at interacting with neuronal nicotinic cholinergic receptors as assayed *in vitro* for their ability to displace radioligand from neuronal nicotinic cholinergic channel receptors labeled with [^{3}H]-cytisine ([^{3}H]-CYT) (Protocol A below).

For the purpose of directly evaluating the ability of test compounds to functionally activate or inhibit certain subtypes of neuronal nicotinic cholinergic channels, an assay to determine $^{86}Rb^+$ efflux in IMR-32 cells was employed (Protocol B below).

A. Protocol For Determination of Nicotinic Cholinergic Channel Receptor Binding Potencies of Ligands .

Binding of [^{3}H]-cytisine ([^{3}H]-CYT) to nicotinic receptors was accomplished using crude synaptic membrane preparations from whole rat brain (Pabreza *et al.*, *Molecular Pharmacol.* , **1990**, 39:9). Washed membranes were stored at -80°C prior to use. Frozen aliquots were slowly thawed and resuspended in 20 volumes of buffer (containing: 120 *mM* NaCl, 5 *mM* KCl, 2 *mM* $MgCl_2$, 2 *mM* $CaCl_2$ and 50 *mM* Tris-Cl, pH 7.4 @4°C). After centrifuging at 20,000x g for 15 minutes, the pellets were resuspended in 30 volumes of buffer. Homogenate (containing 125-150 µg protein) was added to triplicate tubes containing concentrations of test compound and [^{3}H]-CYT (1.25 *nM*) in a final volume of 500 µL. Samples were incubated for 60 minutes at 4°C, then rapidly filtered through Whatman* GF/B filters presoaked in 0.5% polyethyleneimine using 3 x 4 mL of ice-cold buffer. The filters are counted in 4 mL of Ecolume® (ICN). Nonspecific binding was determined in the presence of 10 µM (-)-nicotine and values were expressed as a percentage of total binding. IC_{50} values were determined with the RS-1 (BBN) nonlinear least squares curve-fitting program and IC_{50} values were converted to Ki values using the Cheng and Prusoff correction ($Ki=IC_{50}/(1+[ligand]/Kd\ of\ ligand)$. Alternately, data were

* trade-mark

expressed as a percentage of the total specific binding. The binding data (shown in Table 1) suggest that the compounds of the present invention have high affinity for the neuronal nicotinic cholinergic channel receptor.

B. Protocols for the Determination of Functional Effects of Cholinergic Channel Receptor Ligands on Synaptic Transmission

Cells of the IMR-32 human neuroblastoma clonal cell line (ATCC, Rockville, MD) were maintained in a log phase of growth according to established procedures (Lukas, 1993). Experimental cells were seeded at a density of 500,000 cells/mL into a 24-well tissue culture dish. Plated cells were allowed to proliferate for at least 48 hours before loading with 2 μCi/mL of $^{86}Rb^+$ (35 Ci/mmol) overnight at 37°C. The $^{86}Rb^+$ efflux assays were performed according to previously published protocols (Lukas, R.J., *J. Pharmacol. Exp. Ther.*, 265: 294-302, **1993**) except serum-free Dulbecco's Modified Eagle's Medium was used during the $^{86}Rb^+$ loading, rinsing, and agonist-induced efflux steps.

EC_{50} data and maximal responses (reported as percent relative to the response elicited by 100 μM (S)-nicotine) are shown for selected compounds of the invention. The inhibition data (given for other selected compounds) reflect inhibition of the efflux elicited by 100 μM (S)-nicotine for either a single dose (% inhibition at 1 or 10 μM) or over a range of doses (IC_{50} of inhibition). The results (also shown in Table 1) suggest that selected compounds of the present invention either activate or inhibit the initial ion flux aspects of synaptic transmission mediated by neuronal nicotinic acetylcholine receptors. This finding is in agreement with the results of others who have linked dopamine release, which is dependent upon the ion flux in synaptic transmission, to binding at nicotinic receptors (cf., for example, Lippiello and Caldwell, U.S.Patent 5,242,935, issued Sept. 7, 1993; Caldwell and Lippiello, U.S.Patent 5,248,690, issued Sept. 28, 1993; and Wonnacott *et al.*, Prog. Brain Res., 79: 157-163 (**1989**)).

Table 1
Binding to Neuronal Nicotinic Receptors
and Activation or Inhibition of Neuronal Nicotinic
Cholinergic Channels in IMR-32 Cells

Ex. No	Binding (nM)	IMR-32 EC_{50} (μM)	IMR-32 maximal response	% Inhibition @ 1 μM	% Inhibition @ 10 μM	Inhibition IC_{50} (μM)
1	2	>10,000	0			
2	0.02	0.1	120			
3	0.38			55		

4	0.06	0.78	102			
5	0.35	>10,000	12	12	22	
6	5	>10,000	4.5	14	7	
7	0.099	4.9	70			
8	13	>10,000	10.6	28	60	
9	0.03	1.6	67			
10	20	>10,000	3.3	18	90	
11	0.029	0.6	93			
12	0.11	>10,000	16	5	8	
13	2.5					
14	206					
15	0.024	0.3	152			
16	0.7	0.5	37	35		
17	0.06	0.2	108			
18	2.4	>10,000	22.5	0	18	
19	29					
20	1.8			12	26	
21	7.1					
22	72	>10,000	0	15	10	
23	1.3	>10,000	15.5			
24	.44	16	50			
25	2.1	25	69			
26	1.0	8	150			
27	11	>10,000	18	0	11	
28	91					
29	18.4					
30	1.5	50	69	>30		
31	5.2	61	36			
32	0.63	6	37	17	58	
33	32	>10,000	0			160
34	18	>10,000	0			75
35	22	>10,000	0			6
36	33					
37	320					
38	297	>10,000	0			
39	0.15	3.4	72			
40	4	>10,000	6.5	39	46	
41	2.46	>10,000	19	12	30	
42	0.44	20.2	83			
43	2.14	9.1	67			
44	0.03	7.4	89			
45	0.04	0.4	137			
46	0.6	>10,000	11			
47	0.065	22	152			
48	0.027	56	129			
49	0.097	0.29	158			
50	0.88	10	35			
51	0.19	16	64			
52		1.6	124			

Examples

The present invention will be better understood by reference to the following examples, which are intended as an illustration of, and not a limitation upon, the scope of the invention as it is defined by the appended claims

Preparations of Starting Materials

Several starting materials are used repeatedly throughout the examples that follow. 1-Methyl-2-(S)-pyrrolidinemethanol was obtained from Aldrich Chemical Co. 1-Methyl-2-(R)-pyrrolidinemethanol was obtained from Fluka.

In the PCT Patent Application WO94 08992 of Abreo *et al.*, published April 28, 1994, and in Abreo, *et al. J. Med Chem.*, 3:, 817-825 (**1996**), are disclosed methods for preparing, *inter alia*, the (R) and (S) 1-BOC-2-(S)-pyrrolidinemethanol compounds, the (R) and (S) 1-BOC-2-(S)-azetidinemethanol compounds, and 1-Cbz-2-(R)-azetidinemethanol. 1-Cbz-2-(S)-azetidinemethanol is prepared from 2-(S)-azetidinecarboxylic acid using analogous procedures.

Example 1

5-Ethylamino-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine hydrochloride

Step 1a. 5-bromo-3-((1-methyl-2-(S)-pyrrolidinyl)methoxy)pyridine

(S)-1-Methyl-2-pyrrolidinemethanol (Aldrich Chemical Co., 4.96 g, 40.0 mmol) was carefully added to a suspension of sodium hydride (1.32 g, 80% yield, 44.0 mmol) in anhydrous DMF (100 mL). After stirring at room temperature for 0.5 hour, 3,5-dibromopyridine (4.83 g, 20.0 mmol) was added, and the reacting mixture was stirred at 50°C for 4 hours. After cooling, 5.0 mL of water was added, and the solvents were removed under reduced pressure. Additional water (5.0 mL) was added, and the slurry was washed extensively with EtOAc (4X40 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography on silica gel eluting with $CHCl_3$/MeOH (10:1) to provide 4.50 g (83% yield) of the title compound. TLC R_f 0.33 (10:1 $CHCl_3$/MeOH). MS (DCI/NH_3) m/z 271, 273 $(M+H)^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.37 (d, J = 1.8 Hz, 1H), 8.26 (d, J = 2.7 Hz, 1H), 7.39 (dd, J = 1.8, 2.7 Hz, 1H), 4.01 (dd, J = 3.3, 11.1 Hz, 1H), 3.93 (dd, J = 6.9, 11.1 Hz, 1H), 3.15 (m, 1H), 2.69 (m, 1H), 2.49 (s, 3H), 2.34 (m, 1H), 2.44-2.00 (m, 4H).

Step 1b. 5-Amino-3-(1-methyl-2(S)-pyrrolidinylmethoxy)pyridine

To a solution of the compound of example 1a (3 g, 11.1 mmol) in methanol (125 mL) was added CuBr (1.38 g). The resultant mixture was allowed to stir with ammonia at 130°C in a pressure vessel for 24 hours. The excess ammonia was evaporated, methanol was removed, and the resultant residue was dissolved in water. The aqueous solution was

then extracted with chloroform (3x50 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and filtered. The mixture was concentrated *in vacuo* and the residue was purified on silica gel to give 2.0 g (86%) of the title compound. MS (DCI/NH_3) m/e: 208 $(M+H)^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.77 (d, 1H, J= 3.0 Hz)), 7.72 (d, 1H, J= 3.0 Hz), 6.54 (t, 1H, J= 3.0 Hz), 4.00-3.85 (m, 2H), 3.66 (m, 1H), 3.10 (m, 1H), 2.64 (m, 1H), 2.47 (s, 3H), 2.30 (m, 1H), 2.02 (m, 1H), 1.54-1.90 (m, 2H).

Step 1c. 5-Acetamido-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine

To neat 5-amino-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine (from step 1b) was added excess acetic anhydride (2mL) at room temperature, and the reaction mixture was stirred at 60 °C for 18 h. Judged by TLC, a substantial amount of starting material remained. A catalytic amount of dimethylaminopyridine was then added to the reaction mixture and the resultant solution was allowed to stir for an additional 24 h. Methylene chloride was added to the reaction mixture followed by the addition of saturated sodium bicarbonate solution. The organic layer was separated, evaporated *in vacuo*, , and the residue was chromatographed on a silica gel column, eluting with $CHCl_3$/MeOH, 10:1, to afford an oil (88 mg, 68%). MS (CI/NH_3) m/z 250 $(M+H)^+$. ^1H NMR ($CDCl_3$ 300 MHz) δ 1.66-1.90 (m, 3H), 2.04 (m, 1H), 2.22 (s, 3H), 2.31 (m, 1H), 2.48 (s, 3H), 2.66 (m, 1H), 3.12 (m, 1H), 3.93-4.05 (m, 2H), 7.93 (m, 1H), 8.03 (d, J = 2.9 Hz, 1H), 8.08 (d, J = 2.9 Hz, 1H).

Step 1d. 5-Ethylamino-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine dihydrochloride

The product from step 1c above (540 mg, 2.17 mmol) in tetrahydrofuran (5 mL) was treated dropwise with a 1M solution of borane (6.50 mL, 6.50 mmol) in tetrahydrofuran at room temperature. After reflux for 15 h, the reaction was quenched by addition of a large excess of methanol. The resultant solution was allowed to stir at room temperature for an additional 1 h. Solvent was then removed under reduced pressure to give a white solid. The crude reaction product was dissolved in ethanol and treated with excess cesium fluoride. The organic solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with $CHCl_3$/MeOH (10:1) to give 120 mg of the title compound (407 mg, 80%) as a colorless oil. MS(DCI/NH_3) m/z 236 $(M+H)^+$. ^1H NMR($CDCl_3$) δ 1.27 (t, J=7.5 Hz, 3H), 1.54-1.94 (m, 4H), 2.02 (m, 1H), 2.31 (m, 1H), 2.48 (s, 3H), 3.08-3.20 (m, 3H), 3.60 (m, 1H), 3.91 (dd, J = 6.0, 10 Hz, 1H), 4.01 (dd, J = 6.0, 10 Hz, 1H), 6.43 (t, J= 3.0 Hz, 1H), 7.66 (d, J = 3.0 Hz, 1H), 7.68 (d, J = 3.0 Hz, 1H).

To the solution of the product obtained above in diethyl ether (1.5 mL) was added hydrogen chloride in diethyl ether dropwise at 0°C. After stirring at 0°C for 15 minutes, the precipitate was collected by centrifugation, washed with diethyl ether three times and dried *in vacuo* to yield the title compound as a white powder. mp 190-192°C. MS(DCI/NH3)

m/z 236(M+H)+. ^{1}H NMR(300MHz, D_2O) δ 1.24 (t, J = 7.5 Hz, 3H), 2.05-2.28 (m, 3H), 2.41 (m, 1H), 3.04 (s, 3H), 3.21 (dd, J = 7.3, 14.3 Hz, 2H), 3.23 (m, 1H), 3.73 (m, 1H), 3.93 (m, 1H), 4.40 (dd, J = 5.8, 11.0 Hz), 4.56 (dd, J = 3.0, 11.0 Hz), 7.14 (t, J = 2.2 Hz, 1H), 7.72 (br s, 2H). Anal. Calcd. for $C_{13}H_{21}N_3O$•2HCl: C, 50.66; H, 7.52; N, 13.63. Found: C, 50.92; H, 7.63; N, 13.44. $[\alpha]^{25}_D$=+1.58° (c 0.19, MeOH).

Example 2

5-Bromo-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine hydrochloride

Step 2a. 5-Bromo-6-chloro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine

To a solution of diethyl azodicarboxylate (1.52 mL, 9.6 mmol) in THF (56 mL) was added triphenylphosphine (2.52 g, 9.6 mmol) at 0°C, and the reaction mixture was stirred for 0.5 hour. 1-BOC-2-(S)-azetidinemethanol (1.44 g, 7.7 mmol) and 5-bromo-6-chloropyridin-3-ol (1.4 g, 6.4 mmol; prepared from 2-hydroxy-5-nitropyridine according to V. Koch and S. Schnatterer, *Synthesis* **1990**, 499-501) were then added. The reaction mixture was allowed to warm slowly to room temperature and stir overnight. Solvent was removed, and the residue was chromatographed on a silica gel column, eluting with chloroform:methanol (100:1) to afford the title compound. MS (DCI/NH_3) m/z 377, 379 $(M+H)^+$.

Step 2b. 5-Bromo-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine hydrochloride

To 5-bromo-6-chloro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine from step 2a (360 mg, 0.95 mmol) was added TFA in methylene chloride at 0°C, and the mixture was stirred for 30 minutes. The volatile components were then removed under vacuum. The residue was neutralized with $NaHCO_3$, then extracted with methylene chloride, which was dried over $MgSO_4$ and concentrated. The residue was chromatographed on a silica gel column, eluting with methylene chloride:methanol:NH_4OH 10:1:0.1 to afford to give the free base of the title compound. The base was converted to the salt by treatment with hydrogen chloride in ether to give the title compound (224 mg). mp 168-169°C. MS (DCI/NH_3) m/z 277, 279 $(M+H)^+$. ^{1}H NMR (D_2O, 300 MHz) δ 2.69 (dd, J=7.0, 8.5, 2H), 4.06-4.20 (m, 3H), 4.43 (d, J=4.5, 2H), 4.95 (m, 1H), 7.94 (d, J=3.0, 1H), 8.17 (d, J=3.0, 1H). Anal. Calcd. for $C_9H_{10}N_2OBrCl$•0.9 HCl: C, 34.83; H, 3.54; N, 9.03. Found: C, 34.85; H, 3.56; N, 8.82. $[\alpha]^{25}_D$=-4.81° (c 0.13, MeOH).

Example 3

5-Bromo-6-chloro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine hydrochloride

A sample of 5-bromo-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine (from Example 2b, 140 mg, 0.51 mmol) was stirred with excess paraformaldehyde (0.5 mL) in ethanol (3 mL), on ice and under nitrogen at pH 5 (pH adjusted with acetic acid). The reaction was

stirred for 15 minutes and sodium cyanoborohydride (94 mg, 1.5 mmol) was added. A very small amount of bromocresol green was added directly to the reaction mixture as indicator. The reaction was stirred 18 hours, allowed to warm to room temperature, and additional formaldehyde (0.25 mL) and sodium cyanoborohydride (20 mg, 0.32 mmol) were added. The reaction mixture was then acidified to pH 1 with 10% solution of potassium hydrogen sulfate, and the volatile components were evaporated. The aqueous phase was washed with ethyl acetate (3x10 mL), basified with sodium carbonate (pH 9.5), and the products were extracted with ethyl acetate (5x15 mL). These extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residual oil was purified by flash silica gel chromatography ($CHCl_3$:MeOH:NH_4OH/10:1:0.1), yielding the pure free base (101 mg, 68% yield), which was dissolved in ethanol and converted to the hydrochloride salt by treatment with hydrogen chloride in ethanol to give the title compound. mp 155-157°C (dec). MS (DCI/NH_3) m/z 291, 293 $(M+2H)^+$. ^1H NMR (D_2O, 300 MHz) δ 2.54-2.77 (m, 2H), 2.98 (s, 3H), 3.99 (m, 1H), 4.27 (m, 1H), 4.37-4.55 (m, 2H), 7.93 (d, J=3 Hz, 1H), 8.17 (s, J=3 Hz, 1H). Anal. Calcd. for $C_{10}H_{12}N_2OBrCl \cdot 1HCl \cdot 0.8\ H_2O$·: C, 35.07; H, 4.30; N, 8.18. Found: C, 35.08; H, 4.12; N, 8.08. $[\alpha]^{25}_D$=-13.1° (c 0.16, MeOH).

Example 4

5-Bromo-6-chloro-3-(2-(S)-pyrrolidinylmethoxy)pyridine dihydrochloride

Step 4a. 5-Bromo-6-chloro-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine

To a solution of diethyl azodicarboxylate (1.89 mL, 12.0 mmol) in THF (30 mL) was added triphenylphosphine (3.15 g, 12.0 mmol) at 0°C, and the reaction mixture was stirred for 0.5 hour. 1-BOC-(S)-pyrrolidinemethanol (2.41 g, 12.0 mmol) and 5-bromo-6-chloropyridine-3-ol (2.09 g, 10.0 mmol) were then added. The reaction mixture was allowed to warm to room temperature overnight. The solvent was removed, and the residue was chromatographed on a silica gel column, eluting with EtOAc/hexane (1:5 and 1:2) to afford an oil (3.80 g, 97%). MS (CI/NH_3) m/z 391,393 $(M+H)^+$. ^1H NMR (DMSO-d_6, 300 MHz) δ 1.65-2.05 (m, 4H), 3.20-3.35 (m, 2H), 3.95-4.15 (m, 3H), 7.98 (d, J = 2.9 Hz, 1H), 8.21 (d, J = 2.9 Hz, 1H).

Step 4b. 5-Bromo-6-chloro-3-(2-(S)-pyrrolidinylmethoxy)pyridine dihydrochloride

To 5-bromo-6-chloro-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine from step 4a (150 mg, 0.38 mmol) was added hydrogen chloride (4.0 M in 1,4-dioxane, 3.0 mL), and the reaction mixture was allowed to stir at room temperature for two days. A precipitate formed which was filtered, washed with Et_2O and vacuum-dried to afford the title compound (119 mg, 94%). mp 264-268°C. MS (CI/NH_3) m/z 291,293 $(M+H)^+$, 308,310 $(M+NH_4)^+$. ^1H NMR (D_2O, 300 MHz) δ 1.90-2.35 (m, 4H), 3.38-3.46 (m,

2H), 4.12 (m, 1H), 4.27 (m, 1H), 4.47 (m, 1H), 7.90 (d, J = 2.9 Hz, 1H), 8.13 (d, J = 2.9 Hz, 1H). Anal. Calcd. for $C_{10}H_{12}N_2OBrCl \cdot 1.0$ HCl: C, 36.61; H, 3.99; N, 8.54. Found: C, 36.61; H, 3.95; N, 8.42. $[\alpha]^{25}_D = +9.2^\circ$ (c 0.90, MeOH).

Example 5

5-Bromo-6-chloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine dihydrochloride

Step 5a. 5-(Bromo-6-chloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine (50722-139)

To 5-bromo-6-chloro-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine (from Example 4a, 300 mg, 0.77 mmol) was added formalin (38%, 3.0 mL) and formic acid (88%, 1.5 mL). The mixture was refluxed for 5 hours and cooled to room temperature. Hydrochloric acid (36%, 0.3 mL) was added, and the mixture was extracted with Et_2O (3 x 8 mL). The aqueous layer was concentrated to dryness under vacuum. Water (2 mL) was added, and solid sodium bicarbonate was added until the aqueous layer was saturated. The mixture was extracted with EtOAc, which was dried over MgSO4, filtered and concentrated. The residue was chromatographed on a silica gel column, eluting with $CHCl_3$/MeOH 10:1 to afford an oil (214 mg, 91%). MS (CI/NH_3) m/z 305,307 $(M+H)^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.60-2.11 (m, 4H), 2.33 (m, 1H), 2.48 (s, 3H), 2.67 (m, 1H), 3.11 (m, 1H), 3.89-4.02 (m, 2H), 7.52 (d, J = 3.0 Hz, 1H), 8.04 (d, J = 3.0 Hz, 1H).

Step 5b. 5-Bromo-6-chloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine dihydrochloride

To 5-bromo-6-chloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine from step 5a (100 mg, 0.33 mmol) in THF (3.0 mL) was added hydrogen chloride (1.0 M in Et_2O, 0.75 mL, 0.75 mmol). A precipitate formed which was filtered, washed (Et_2O) and vacuum-dried to afford the title compound (85 mg, 76%). mp 189-191°C. MS (CI/NH_3) m/z 305,307 $(M+H)^+$. ^1H NMR (D_2O, 300 MHz) δ 2.02-2.47 (m, 4H), 3.03 (s, 3H), 3.28 (m, 1H), 3.73 (m, 1H), 3.94 (m, 1H), 4.36 (m, 1H), 4.51 (m, 1H), 7.92 (d, J = 3.0 Hz, 1H), 8.14 (d, J = 3.0 Hz, 1H). Anal. Calcd. for $C_{11}H_{14}N_2OBrCl \cdot 1.0$ HCl: C, 38.63; H, 4.51; N, 8.19. Found: C, 38.67; H, 4.49; N, 8.13. $[\alpha]^{25}_D = -3.8^\circ$ (c 0.50, MeOH).

Example 6

3-(1-Methyl-2-(S)-pyrrolidinylmethoxy)-5-nitro-pyridine hydrochloride (47449-238)

Step 6a. 3,5- Dinitro-2-pyridinylhydrazine

2-Chloro-3,5-dinitropyridine (3.01g, 14.8mmol, Lancaster) was dissolved in MeOH (20 mL), then hydrazine (0.5ml, 15.9mmol) was added. The mixture was stirred at room temperature overnight. The solvent was evaporated, and the residue was washed with water and MeOH. A dark solid was obtained (2.78g, 94.4%). MS (CI/NH3) m/z 200 $(M+H)^+$. NMR (DMSO-d_6, 300MHz) δ 9.07 (m, 1H), 9.26 (m, 1H).

Step 6b. 3,5-Dinitropyridine

The crude 3,5-dinitro-2-pyridinylhydrazine from step 6a (2.2g, 11.1mmol) and silver acetate (2.2g, 13.2mmol) were dissolved in a mixture of MeOH-H_2O (1:1). The resultant solution was stirred and heated under reflux overnight. Solvent was evaporated, then water and concentrated ammonia were added to the residue. The aqueous solution was extracted with ethyl ether, dried (MgSO4), concentrated and chromatographed (silica gel; hexane/EtOAc, 2:1). An orange solid was obtained (0.40g, 21.8%). MS (CI/NH3) m/z 140 $(M-NO)^+$. NMR ($CDCl_3$, 300MHz) δ 9.26 (m, 1H), 9.78 (m, 2H).

6c. (S)-(1-Methyl-2-pyrrolidinylmethoxy)-5-nitropyridine

(S)-1-Methyl-2-pyrrolidinemethanol (0.46ml 3.9mmol) was added to the suspension of NaH (0.16g, 4.0mmol) in DMF. After 30 minutes, 3,5-dinitropyridine (from step 6b, 0.34g, 2.0mmol) in DMF (4ml) was added. The mixture was allowed to stir at room temperature for 3 days. The mixture was diluted with CH_2Cl_2 (30ml), and washed three times with H2O-Brine (1:1). The organic layer was dried (MgSO4), concentrated and chromatographed (silica gel: CH_2Cl_2/MeOH, 10:0.5). An oil was obtained (70mg, 7.6%). MS (CI/NH3) m/z 238 $(M+H)^+$. NMR ($CDCl_3$, 300MHz) δ 1.70-1.90 (m, 3H), 2.06 (m, 1H), 2.35 (m, 1H), 2.50 (s, 3H), 2.74 (m, 1H), 3.12 (m, 1H), 4.07 (m, 2H). 7.98 (m, 1H), 8.62 (m, 1H), 9.07 (m, 1H).

6d. (S)-(1-Methyl-2-pyrrolidinylmethoxy)-5-nitropyridine Hydrochloride

The product of step 6c above (60mg, 0.25mmol) was dissolved in ethyl ether and MeOH. 1M HCl (in Et_2O) was added dropwise. The solvent was removed, and the residue was triturated with Et_2O and dried under vacuum to afford the title compound. MS (CI/NH3) m/z 238 $(M+H)^+$ NMR (CD_3OD, 300MHz) δ 2.02-2.30 (m, 3H), 3.10 (s, 3H), 3.24 (m, 1H), 3.78 (m, 1H), 3.98 (m, 1H), 4.50 (dd, J=6.5, 11.2 Hz, 1H), 4.63 (dd, J=3.4, 11.2 Hz, 1H), 8.29 (m, 1H), 8.76 (s, 1H), 9.09 (s, 1H). Anal. Calcd. for $C_{11}H_{15}N_3O_3 \cdot 1.2\ HCl \cdot 0.5\ MeOH$: C, 46.50; H, 6.18; N, 14.15. Found: C, 46.52; H, 6.01; N, 13.92.

Example 7

5-bromo-6-chloro-3-(2-(R)-pyrrolidinylmethoxy)pyridine dihydrochloride

Following the procedure of Example 4, except substituting 1-BOC-(R)-pyrrolidinemethanol for the 1-BOC-(S)-pyrrolidinemethanol thereof, the 5-bromo-6-chloro-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine was prepared. MS (CI/NH_3) m/z 391,393 $(M+H)^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.65-2.05 (m, 4H), 3.20-3.35 (m, 2H), 3.95-4.15 (m, 3H), 7.55 (d, J = 2.9 Hz, 1H), 8.12 (d, J = 2.9 Hz, 1H). The 5-bromo-6-chloro-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine (150 mg) was stirred with 4N HCl in dioxane (3 mL) at room temperature for 16 hours . The precipitate formed was triturated with ether, and the solid was dried under high vacuum to afford the title compound (99.2 mg). mp 230°C. MS (DCI/NH_3) m/z 291,293 $(M+H)^+$. ^1H NMR (D_2O, 300 MHz) δ 1.89-2.02 (m, 1H), 2.05-2.21 (m, 2H), 2.28 (m, 1H), 3.42 (t, J=7.2 Hz, 2H), 4.12 (m, 1H)), 4.25 (dd, J=7.8, 10.5 Hz, 1H), 4.47 (dd, J=3.2, 10.5 Hz, 1H), 7.90 (d, J=2.7 Hz, 1H), 8.13 (d, J=2.7 Hz, 1H). Anal. Calcd. for $C_{10}H_{12}N_2OBrCl \cdot 2$ HCl: C, 36.61; H, 3.99; N, 8.54. Found: C, 36.69; H, 3.91; N, 8.41. $[\alpha]^{25}_D = -14.80^\circ$ (c 0.25, MeOH).

Example 8

5-bromo-6-chloro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine hydrochloride

To 5-bromo-6-chloro-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine from Example 7 (210 mg, 0.54 mmol) was added formalin (37%, 7 mL) and formic acid (3.5 mL), and the mixture was heated at 70°C for 2.5 hours. The solvent was concentrated, and excess solid $NaHCO_3$ was added to the residue. The mixture was extracted with methylene chloride, which was dried over $MgSO_4$ and concentrated. The residue was chromatographed on a silica gel column, eluting with methylene chloride:methanol 100:5-100:10 to give the free base of the title compound (110 mg, 67% yield). MS (DCI/NH_3) m/z 305, 307 $(M+H)^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.68 (m, 3H), 2.02 (m, 1H), 2.32 (m, 1H), 2.48 (s, 3H), 2.67 (m, 1H), 3.12 (m, 1H), 3.96 (m, 2H), 7.52 (m, 1H), 8.06 (m, 1H). The base was converted to the salt by treatment with hydrogen chloride in THF to give the title compound. MS (DCI/NH_3) m/z 305, 307 $(M+H)^+$. ^1H NMR (D_2O, 300 MHz) δ 2.20-2.17 (m, 2H), 2.24 (m, 1H), 2.39 (m, 1H), 3.03 (s, 3H), 3.27 (m, 1H), 3.73 (m, 1H), 3.96 (m, 1H), 4.36 (dd, J=6.1, 11.2 Hz, 1H), 4.53 (dd, J=3.1, 11.2 Hz, 1H), 7.91 (d, J=2.7 Hz, 1H), 8.13 (d, J=2.7 Hz, 1H). Anal. Calcd. for $C_{11}H_{14}N_2OBrCl \cdot 1.1$ HCl: C, 38.22; H, 4.40; N, 8.10. Found: C, 37.95; H, 4.81; N, 7.76. $[\alpha]^{25}_D = +11.06^\circ$ (c 0.24, MeOH).

Example 9

5,6-Dichloro-3-(2-(R)-pyrrolidinylmethoxy)pyridine hydrochloride

Step 9a. 5,6-Dichloro-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine

To a solution of triphenylphosphine (2.6 g, 9.88 mmol) in THF (30 mL) was added diethyl azodicarboxylate (1.56 mL, 9.88 mmol) at 0°C, and the reaction mixture was stirred for 0.5 hour. 1-BOC-(R)-pyrrolidinemethanol (2.0 g, 9.88 mmol) and 5,6-dichloropyridine-3-ol (1.35 g, 8.23 mmol; prepared from 2-hydroxy-5-nitropyridine according to the procedure of V. Koch and S. Schnatterer, *Synthesis* **1990**, 499-501) were then added. The reaction mixture was slowly warmed up to room temperature overnight. The solvent was removed, and the residue was chromatographed on a silica gel column, eluting with EtOAc/hexane 1:6 to afford an oil (2.16 g). MS (CI/NH_3) m/z 347, 349 $(M+H)^+$, 364, 366 $(M+NH_4)^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.47 (s, 9H), 1.85-2.05 (m, 4H), 3.35-3.45 (m, 2H), 3.85-4.2 (m, 3H), 7.35-7.45 (br d, 1H), 8.02 (d, J = 2.5 Hz, 1H).

Step 9b. 5,6-Dichloro-3-(2-(R)-pyrrolidinylmethoxy)pyridine hydrochloride

To 5,6-dichloro-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine from step 9a (9.88 mmol) was added trifluoroacetic acid in methylene chloride (1:1, 20 mL) at 0°C, and the mixture was stirred for 30 minutes. The residue was neutralized with saturated $KHCO_3$ solution, then extracted with methylene chloride, which was dried over $MgSO_4$ and concentrated to afford the free base of the title compound (1.24 g, oil). The base (800 mg, 3.2 mmol) was converted to the salt by treatment with saturated hydrogen chloride in ether to give the title compound (398 mg). mp 250-252°C. MS (CI/NH_3) m/z 247, 249, 251 $(M+H)^+$, 264, 266 $(M+NH_4)^+$. ^1H NMR (D_2O, 300 MHz) δ 1.90-2.35 (m, 4H), 3.40-3.45 (m, 2H), 4.13 (m, 1H), 4.27 (m, 1H), 4.47 (m, 1H), 7.74 (d, J = 2.7 Hz, 1H), 8.07 (d, J = 2.7 Hz, 1H). Anal. Calcd. for $C_{10}H_{12}N_2OCl_2 \cdot 1.0$ HCl: C, 42.35; H, 4.62; N, 9.88. Found: C, 42.41; H, 4.49; N, 9.79. $[\alpha]^{25}_D = -11.1^\circ$ (c 1.0, MeOH).

Example 10

5,6-Dichloro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine hydrochloride

Step 10a. (5,6-Dichloro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine (50722-139)

To 5,6-dichloro-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine (from Example 9b, 438 mg, 1.8 mmol) was added formalin (37%, excess) and formic acid (88%, excess). The mixture was treated by a procedure similar to that of Example 5a to afford a solid (338 mg, 72%). mp 38-39°C. MS (CI/NH_3) m/z 261/263 $(M+H)^+$. $[\alpha]^{25}_D = +59.3^\circ$ (c 1.00, $CHCl_3$).

Step 10b. 5,6-Dichloro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine dihydrochloride

To 5,6-dichloro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine from step 10a

(313 mg) in ether was added saturated HCl in ether. A precipitate formed which was washed with Et_2O, then recrystallized from methanol/ether, and vacuum dried to afford the title compound (272 mg). mp 187-189°C. MS (CI/NH_3) m/z 262, 263, 265 $(M+H)^+$. ^1H NMR (D_2O, 300 MHz) δ 2.02-2.45 (m, 4H), 3.03 (S, 3H), 3.28 (m, 1H), 3.73 (m, 1H), 3.94 (m, 1H), 4.36 (m, 1H), 4.51 (m, 1H), 7.76 (d, J = 2.7 Hz, 1H), 8.10 (d, J = 2.7 Hz, 1H). Anal. Calcd. for $C_{11}H_{14}N_2OCl_2$•1.0 HCl•0.1 H_2O: C, 44.13; H, 5.12; N, 9.36. Found: C, 43.89; H, 5.21; N, 9.19. $[\alpha]^{25}_D$=+6.8° (c 1.0, MeOH).

Example 11

5,6-Dichloro-3-(2-(S)-pyrrolidinylmethoxy)pyridine hydrochloride

Step 11a. 5,6-Dichloro-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine

To a solution of triphenylphosphine (2.9 g, 11.0 mmol) in THF (30 mL) was added diethyl azodicarboxylate (1.7 mL, 11.0 mmol) at 0°C, and the reaction mixture was stirred for 15 minutes. 1-BOC-(S)-pyrrolidinemethanol (2.21 g, 11.0 mmol) and 5,6-dichloropyridine-3-ol (1.5 g, 9.2 mmol) were then added. The reaction mixture was slowly warmed up to room temperature overnight. The solvent was removed, and the residue was chromatographed on a silica gel column, eluting with EtOAc/hexane (1:6) to afford an oil (3.5 g). MS (CI/NH_3) m/z 347, 349 $(M+H)^+$, 364/366 $(M+NH_4)^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.47 (s, 9H), 1.85-2.05 (m, 4H), 3.35-3.45 (m, 2H), 3.85-4.2 (m, 3H), 7.40 (m, 1H), 8.02 (d, J = 2.5 Hz, 1H).

Step 11b. 5,6-Dichloro-3-(2-(S)-pyrrolidinylmethoxy)pyridine hydrochloride

To 5,6-dichloro-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine from step 11a (3.5 g) was added trifluoroacetic acid in methylene chloride (1:1, 30 mL) at 0°C, and the mixture was stirred for 30 minutes. The residue was partitioned between saturated K_2CO_3 solution and methylene chloride, then the organic layer was dried over $MgSO_4$ and concentrated. The residue was flash chromatographed on silica gel eluting with 10% methanol/chloroform to afford the free base of the title compound (2.5 g, oil). The base (1.32 g, 5.3 mmol) was converted to the salt by treatment with saturated HCl in ether to give the title compound (224 mg). mp 253-254°C. MS (CI/NH_3) m/z 247, 249, 251 $(M+H)^+$, 264, 266 $(M+NH_4)^+$. ^1H NMR (D_2O, 300 MHz) δ 1.90-2.36 (m, 4H), 3.37-3.49 (m, 2H), 4.13 (m, 1H), 4.27 (m, 1H), 4.48 (dd, J=3.5, 10.5, 1H), 7.74 (d, J = 2.7 Hz, 1H), 8.07 (d, J = 2.7 Hz, 1H). Anal. Calcd. for $C_{10}H_{12}N_2OCl_2$•1.0 HCl: C, 42.35; H, 4.62; N, 9.88. Found: C, 42.41; H, 4.55; N, 9.73. $[\alpha]^{25}_D$=+12.2° (c 1.0, MeOH).

Example 12

5,6-Dichloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine hydrochloride

Step 12a. 5-(5,6-Dichloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine (50722-139)

To 5,6-dichloro-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine (from Example 11a, 1.06 g, 4.29 mmol) was added formalin (37%, excess) and formic acid (88%, excess). The mixture was heated for 2 hours, then hydrochloric acid (12 N) was added, and the mixture was washed with Et_2O. The aqueous layer was basified with 15% NaOH, and the mixture was extracted with methylene chloride, which was dried over $MgSO_4$, filtered and concentrated. The residue was chromatographed on a silica gel column, eluting with $CHCl_3$/MeOH (20:1) to afford an oil (360 mg). MS (CI/NH_3) m/z 261,263,265 $(M+H)^+$. $[\alpha]^{25}_D$=-48.8° (c 1.00, $CHCl_3$).

Step 12b. 5,6-Dichloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine hydrochloride

To 5,6-dichloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine from step 12a (360 mg) in ether was added saturated HCl in ether. A precipitate formed which was washed with Et_2O and dried under vacuum to afford the title compound (240 mg). mp 192-193°C. MS (CI/NH_3) m/z 261, 263, 265 $(M+H)^+$. ^1H NMR (D_2O, 300 MHz) δ 2.05-2.45 (m, 4H), 3.03 (S, 3H), 3.28 (m, 1H), 3.72 (m, 1H), 3.96 (m, 1H), 4.36 (dd, J=6.1, 11.2, 1H), 4.53 (dd, J=3,11.2 Hz, 1H), 7.76 (d, J = 2.7 Hz, 1H), 8.10 (d, J = 2.7 Hz, 1H). Anal. Calcd. for $C_{11}H_{14}N_2OCl_2$•1.0 HCl: C, 44.39; H, 5.08; N, 9.41. Found: C, 44.13; H, 5.05; N, 9.29. $[\alpha]^{25}_D$=-5.3° (c 1.0, MeOH).

Example 13

2-Chloro-3-(2-(S)-azetidinylmethoxy)pyridine hydrochloride

Step 13a. 2-chloro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine (50722-136)

To a solution of triphenylphosphine (1.73 g, 6.6 mmol) in THF (26 mL) was added diethyl azodicarboxylate (1.04 mL, 6.6 mmol) at 0°C, and the reaction mixture was stirred for 15 minutes. 1-BOC-2-(S)-azetidinemethanol (1.03 g, 5.5 mmol) and 2-chloro-3-pyridinol (785 mg, 6.0 mmol, Aldrich Chemical Co.) were then added. The reaction mixture was allowed to warm slowly to room temperature and stir overnight. Solvent was removed, and the residue was dissolved in ethyl acetate. The solution was washed with saturated aqueous K_2CO_3 and brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed on a silica gel column, eluting with ethyl acetate:hexane (1:4 to 1:1) to afford the title compound (611 mg) . MS (DCI/NH_3) m/z 299 $(M+H)^+$.

Step 13b. 2-chloro-3-(2-(S)-azetidinylmethoxy)pyridine hydrochloride (50722-141)

To 2-chloro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine from step 13a (469 mg, 1.66 mmol) was added TFA (5 mL) in methylene chloride (5 mL) at 0°C, and the mixture was stirred for 30 minutes. The volatile components were then removed under vacuum.

The residue was treated with saturated K_2CO_3 solution, then extracted with methylene chloride, which was dried over $MgSO_4$ and concentrated. The residue was chromatographed on a silica gel column, eluting with chloroform:methanol:NH_4OH (10:1:0-10:1:0.5) to afford the free base of the title compound (217 mg). The base (156 mg) was dissolved in methylene chloride (3 mL) and then converted to the salt by treatment with saturated HCl in ether to give the title compound (142 mg). mp 155-156°C. MS (DCI/NH_3) m/z 199, 201 $(M+H)^+$, 216 $(M+NH_4)^+$. ^1H NMR (D_2O, 300 MHz) δ 2.7-2.79 (m, 2H), 4.13-4.24 (m, 2H), 4.44-4.58 (m, 2H), 4.98 (m, 1H), 7.45 (dd, J=4.8, 8.1 Hz, 1H), 7.59 (dd, J=1.5, 8.2 Hz, 1H), 8.03 (dd, J=1.4, 4.5 Hz, 1H). Anal. Calcd. for $C_9H_{11}N_2OCl$•1.0 HCl: C, 45.98; H, 5.14; N, 11.91. Found: C, 45.76; H, 5.09; N, 11.64.

Example 14

2-chloro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine hydrochloride

A sample of 2-chloro-3-(2-(S)-azetidinylmethoxy)pyridine (from Example 13b, 60 mg, 0.30 mmol) was dissolved in 5 mL of a 5:1 formalin:acetic acid solution. Sodium cyanoborohydride was added slowly until tlc showed consumption of starting material. The reaction mixture was then acidified to pH 1 with HCl, and the mixture was extracted with ether. The aqueous layer was made basic with 15% NaOH, and this solution was extracted with methylene chloride. The extract was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash silica gel chromatography ($CHCl_3$:MeOH, 10:1), yielding the free base (29 mg, 45% yield), which was dissolved in ether and converted to the hydrochloride salt by treatment with saturated HCl in ether to give the title compound. mp 150-152°C (dec). MS (DCI/NH_3) m/z 213, 215 $(M+H)^+$. ^1H NMR (D_2O, 300 MHz) δ 2.65-3.06 (s, 3H), 4.03 (m, 1H), 4.35-4.48 (m, 2H), 4.61 (dd, J=2.5, 12 Hz, 1H), 4.82-4.87 (m, 1H), 7.45 (dd, J=5, 8 Hz, 1H), 7.58 (dd, J=1, 8 Hz, 1H), 8.03 (dd, J= 1.5, 4.8 Hz, 1H). Anal. Calcd. for $C_{10}H_{13}N_2OCl$ •1.2HCl·: C, 46.84; H, 5.58; N, 10.92. Found: C, 46.40; H, 5.51; N, 10.54.

Example 15

5,6-dichloro-3-(2-(S)-azetidinylmethoxy)pyridine hydrochloride

Step 15a. 5,6-dichloro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine

A solution of triphenylphosphine (2.6 g, 9.94 mmol) and diethyl azodicarboxylate (1.6 mL, 9.94 mmol) in THF (16 mL) was stirred at 0°C for 15 minutes. 1-BOC-2-(S)-azetidinemethanol (1.55 g, 8.28 mmol) and 5,6-dichloro-3-pyridinol (1.5 g, 9.1 mmol) were then added. The reaction mixture was allowed to warm slowly to room temperature and stir overnight. Solvent was removed, and the residue was redissolved in methylene

chloride. The solution was washed with saturated aqueous K_2CO_3 and brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed on a silica gel column, eluting with ethyl acetate:hexane (1:5) to afford the title compound (1.08 g) . MS (DCI/NH_3) m/z 333 $(M+H)^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.42 (s, 9H), 2.22-2.42 (m, 2H), 3.85-3.92 (m, 2H), 4.12 (dd, J=2.7, 10.1 Hz, 1H), 4.30-4.40 (m, 1H), 4.48-4.56 (m, 1H), 7.41 (d, J=2.8 Hz, 1H), 7.97 (d, J =2.8 Hz, 1H).

Step 15b. 5,6-dichloro-3-(2-(S)-azetidinylmethoxy)pyridine hydrochloride

To 5,6-dichloro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine from step 15a (1.06 g, 3.11 mmol) was added TFA (10 mL) in methylene chloride (10 mL) at 0°C, and the mixture was stirred for 30 minutes. The solution was allowed to warm to room temperature while stirring for an additional 45 minutes. The volatile components were then removed under vacuum. The residue was treated with saturated K_2CO_3 solution, then extracted with methylene chloride, which was dried over $MgSO_4$ and concentrated. The residue was chromatographed on a silica gel column, eluting with MeOH:$CHCl_3$:NH_4OH (1:10:0 to 1:10:0.05) to afford the free base of the title compound (475 mg, 64% yield). mp 59-60°C. MS (DCI/NH_3) m/z 233 $(M+H)^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.21-2.44 (m, 2H), 3.45 (m, 1H), 3.73 (dd, J=8.4, 15.8 Hz, 1H), 3.98-4.08 (m, 2H), 4.28 (m, 1H), 7.37 (d, J=2.8 Hz, 1H), 8.01 (d, J=2.8 Hz, 1H). The base (336 mg) was slurried in ether and converted to the salt by treatment with saturated HCl in ether to give the title compound. Recrystallization from methanol/ether gave the title compound (317 mg, 81% yield). mp 181-182°C. MS (DCI/NH_3) m/z 233 $(M+H)^+$. ^1H NMR (D_2O, 300 MHz) δ 2.65-2.74 (m, 2H), 4.03-4.21 (m, 2H), 4.44 (d, J=4.4 Hz, 1H), 4.95 (m, 1H), 7.79 (d, J=2.9 Hz, 1H), 8.13 (d, J=2.9 Hz, 1H). Anal. Calcd. for $C_9H_{11}N_2OCl_2$•1.0 HCl: C, 40.10; H, 4.11; N, 10.39. Found: C, 39.89; H, 4.08; N, 10.25.

Example 16

5,6-dichloro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine hydrochloride

A sample of 5,6-dichloro-3-(2-(S)-azetidinylmethoxy)pyridine (from Example 15b, 126 mg, 0.54 mmol) was slurried in 4 mL of H_2O and acetic acid was added (ca 3 mL) until the solution became homogeneous. An excess of formalin was added, followed by sodium cyanoborohydride until tlc showed consumption of starting material. The reaction mixture was then acidified to pH 1 with HCl, and the mixture was extracted with ether. The aqueous layer was made basic with solid K_2CO_3 and 15% NaOH, and this solution was extracted with methylene chloride. The extract was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash silica gel chromatography ($CHCl_3$:MeOH, 20:1), yielding the free base as an oil (105 mg, 79% yield). MS (DCI/NH_3) m/z 247 $(M+H)^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.04-2.12 (m, 2H), 2.39

(m, 3H), 2.87 (m, 1H), 3.33-3.49 (m, 2H), 4.00 (d, J=4.8 Hz, 2H), 7.36 (d, J=2.7 Hz, 1H), 8.01 (d, J=2.7 Hz, 1H). The base was dissolved in ether and converted to the hydrochloride salt by treatment with saturated HCl in ether to give the title compound (75 mg, 66% yield). The salt was crystallized from methanol/ether. mp 144-145°C. MS (DCI/NH_3) m/z 247 $(M+H)^+$. ^1H NMR (D_2O, 300 MHz) δ 2.57-2.75 (m, 2H), 2.99 (s, 3H), 3.97-4.08 (m, 1H), 4.22-4.30 (m, 2H), 4.43-4.53 (m, 2H), 4.83 (m, 1H), 7.78 (d, J=2.7 Hz, 1H), 8.13 (d, J=2.7 Hz, 1H). Anal. Calcd. for $C_{10}H_{13}N_2OCl_2 \cdot 1.1HCl \cdot$: C, 42.09; H, 4.66; N, 9.82. Found: C, 41.86; H, 4.57; N, 9.62.

Example 17

5,6-dichloro-3-(2-(R)-azetidinylmethoxy)pyridine hydrochloride

Following the procedures of Example 15, replacing the 1-BOC-2-(S)-azetidinemethanol thereof with 1-BOC-2-(R)-azetidinemethanol (3 mmol), the title compound was prepared (212 mg, 83% yield). mp 166-168°C. MS (DCI/NH_3) m/z 233, 235, 237 $(M+H)^+$. ^1H NMR (D_2O, 300 MHz) δ 2.65-2.74 (m, 2H), 4.03-4.20 (m, 2H), 4.44 (d, J=4.4 Hz, 1H), 4.91-5.00 (m, 1H), 7.79 (d, J=2.7 Hz, 1H), 8.13 (d, J=2.7 Hz, 1H). Anal. Calcd. for $C_9H_{11}N_2OCl_2 \cdot 1.0$ HCl: C, 40.10; H, 4.11; N, 10.39. Found: C, 40.01; H, 4.02; N, 10.33. $[\alpha]^{25}_D = +9.5°$ (c 0.55, MeOH).

Example 18

5,6-dichloro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine hydrochloride

Following the procedures of Example 16, replacing the 5,6-dichloro-3-(2-(S)-azetidinylmethoxy)pyridine thereof with a sample of 5,6-dichloro-3-(2-(R)-azetidinylmethoxy)pyridine (98.6 mg, from Example 17), the title compound was prepared (45.6 mg, 74% yield). mp 136-137°C. MS (DCI/NH_3) m/z 247/249/251 $(M+H)^+$. ^1H NMR (D_2O, 300 MHz) δ 2.58-2.70 (m, 2H), 2.96 (s, 3H), 3.95-4.05 (m, 1H), 4.18-4.26 (m, 2H), 4.42-4.52 (m, 2H), 4.77 (m, 1H), 7.78 (d, J=2.7 Hz, 1H), 8.13 (d, J=2.7 Hz, 1H). Anal. Calcd. for $C_{10}H_{13}N_2OCl_2 \cdot 1.0$ HCl· • 0.1 H_2O: C, 42.09; H, 4.66; N, 9.82. Found: C, 41.70; H, 4.49; N, 9.48.

Example 19

3-((*cis*-1,5-dimethyl-2-(S)-pyrrolidinyl)methoxy)pyridine dihydrochloride

Step 19a. 3-((5-oxo-2-(S)-pyrrolidinyl)methoxy)pyridine

To a solution of triphenylphosphine (52.46 g, 0.20 mol) in 400 mL of anhydrous THF at 0°C was added diethyl azodicarboxylate (31.49 mL, 0.20 mol) dropwise. The mixture was stirred at 0°C for 30 minutes, then brought to room temperature. (S)-5-(Hydroxymethyl)-2-pyrrolidinone (Aldrich Chemical Co., 15.19 g, 0.13 mol) and 3-

hydroxypyridine (19.02 g, 0.20 mol) were added, and the mixture was stirred for 16 hours. Solvent was removed *in vacuo*, then the residue was diluted with CH_2Cl_2 and washed with 1N NaOH and brine (2X), then dried over $MgSO_4$ and concentrated. The residue was purified by silica gel flash chromatography using a gradient from 100% $CHCl_3$ to 10% MeOH/$CHCl_3$, then the recovered product was recrystallized from ethyl acetate to give 4.0 g (16%) of the title compound as a white powder. mp 121-122°C. TLC R_f=0.31 (10%MeOH/$CHCl_3$). MS (DCI/NH_3) m/e: 193 $(M + H)^+$ and 210 $(M + NH_4)^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.32-8.30 (m, 1H), 8.27 (dd, J=4.40, 1.5 Hz, 1H), 7.25-7.16 (m, 2H), 6.17 (br s, 1H), 4.11 (m, 1H), 4.05 (dd, J=8.8, 3.7 Hz, 1H), 3.89 (dd, J=8.8, 7.7 Hz, 1H), 2.49-2.23 (m, 3H), 1.93 (m, 1H). Anal. Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57; Found C, 62.53; H, 6.25; N, 14.71.

Step 19b. 3-((1-methyl-5-oxo-2-(S)-pyrrolidinyl)methoxy)pyridine

To a solution of the compound from step 19a above (0.100 g, 0.52 mmol) in anhydrous THF at 0°C was added NaH (80% dispersion, 0.02 g, 0.83 mmol), and the reaction mixture was stirred for 20 minutes. The reaction was then allowed to warm to room temperature, and iodomethane (0.06 mL, 0.89 mmol) was added via syringe. After starting material was consumed, the mixture was partitioned between aqueous $NaHCO_3$ and methylene chloride, then the organic layer was washed with brine (2x), dried ($MgSO_4$) and concentrated. The residue was purified by silica gel flash chromatography (5% MeOH/$CHCl_3$) to give 0.107 g (100%) of the title compound as a white powder. mp 73-74°C. MS (DCI/NH_3) m/e: 207 $(M + H)^+$, 224 $(M + NH_4)^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.33-8.28 (m, 2H), 7.24-7.18 (m, 2H), 4.14 (dd, J=9.5, 4 Hz, 1H), 4.04 (dd, J=9.5, 4.4 Hz, 1H), 3.93 (m, 1H), 2.92 (s, 3H), 2.52 (m, 1H), 2.45-2.21 (m, 2H), 1.98 (m, 1H). Anal. Calcd. for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 8.84; N, 13.58; Found C, 64.07; H, 6.67; N, 13.67. $[\alpha]^{25}_D$=+37.30° (c=1.03, MeOH).

Step 19c. 3-((*cis*-1,5-dimethyl-2-(S)-pyrrolidinyl)methoxy)pyridine

To a solution of the compound of step 19b above (0.400g, 1.94 mmol) in anhydrous THF at 0°C was added methylmagnesium chloride (Aldrich Chemical Co., 3M solution in THF, 1.94 mL, 5.80 mmol). The reaction mixture was stirred at this temperature for 2 hours, then brought to room temperature and sonicated for 30 minutes followed by stirring for 1 hour. After the starting material was consumed the reaction was quenched with MeOH. Bromocresol green indicator was added followed by enough 2N HCl/MeOH to turn give a yellow color (acidic pH). Sodium cyanoborohydride (.182g, 2.92 mmol) was added to the reaction and the mixture was stirred for an additional 3 hours (adding 2N HCl/MeOH to maintain the pH). Saturated K_2CO_3 was added until the mixture was basic, then CH_2Cl_2 was added to extract the desired material. The organic layer was then washed with a brine solution (2X) and dried over $MgSO_4$. The resulting material was

purified by silica gel flash chromatography (10%MeOH/$CHCl_3$) to give 0.170g (42.5%) of the *cis* -5'-methyl compound and 0.057g (14%) of the *trans* -5'-compound (the data for the *cis* compound given). MS (DCI/NH_3) m/e: 207 $(M + H)^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.32 (m, 1H), 8.20 (t, J=3 Hz, 1H), 7.20-7.18 (m, 2H), 4.05 (dd, J=9.2, 5.5 Hz, 1H), 3.89 (dd, J=9.2, 6.2 Hz, 1H), 2.77 (m, 1H), 2.41 (s, 3H), 2.38 (m, 1H), 2.01-1.87 (m, 2H), 1.63 (m, 1H), 1.45 (m, 1H), 1.13 (d, J=6.2 Hz, 3H).

Step 19d. 3-((*cis*-1,5-dimethyl-2-(S)-pyrrolidinyl)methoxy)pyridine dihydrochloride

The free base from step 19c above was dissolved in diethyl ether and brought to 0°C with stirring. The solution was treated with diethyl ether saturated with hydrogen chloride gas. The solvent was removed *in vacuo*. The resulting salt was triturated with diethyl ether (2X) and dried under vacuum to give a white powder. MS (DCI/NH_3) m/e: 207 $(M + H)^+$. ^1H NMR (D_2O, 300 MHz) δ 8.41 (br s, 1H), 8.31 (d, J=4.4 Hz, 1H), 7.81-7.77 (m, 1H), 7.66 (dd, J=8.8, 5.1 Hz, 1H), 4.57 (dd, J=11.4, 3 Hz, 1H), 4.44 (dd, J=8.8, 5.9 Hz, 1H), 3.99 (m, 1H), 3.57 (m, 1H), 3.03 (s, 3H), 2.43-2.30 (m, 2H), 2.09 (m, 1H), 1.87 (m, 1H), 1.47 (d, J=6.6 Hz, 3H). Anal. Calcd. for $C_{12}H_{18}N_2O$•2.20 HCl: C, 50.31; H, 7.11; N, 9.78; Found C, 50.07; H, 7.10; N, 9.77. $[\alpha]_D^{25}$=+8.60° (c 1, MeOH).

Example 20

3-(1-methyl-2-(S)-pyrrolidinylmethoxy)-5-trifluoromethylpyridine dihydrochloride

Step 20a. 3-(1-methyl-2-(S)-pyrrolidinylmethoxy)-5-trifluoromethylpyridine

(S)-(-)-1-Methyl-2-pyrrolidinemethanol (Aldrich Chemical Co., 0.5 g, 4.34 mmol) was reacted with 3-chloro-5-trifluoromethylpyridine according to the method of Example 3, except using DMF in place of THF as solvent and reducing reaction time to less than 2 hours. The solvent was removed, the residue dissolved in ethyl acetate, and the product purified by chromatography over silica gel to give 170 mg of the title compound. MS (DCI/NH_3) m/e: 261 $(M + H)^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.50 (d, J=0.6 Hz, 1H), 8.49 (d, J=3.0 Hz, 1H), 7.41 (dd, J=0.6 Hz, 1H), 4.12-3.96 (m, 2H), 3.16 (m, 1H), 2.73 (m, 1H), 2.51 (s, 3H), 2.44 (m, 1H), 2.14-1.73 (m, 4H).

Step 20b. 3-(1-methyl-2-(S)-pyrrolidinylmethoxy)-5-trifluoromethylpyridine dihydrochloride

The compound from step 20a was treated with HCl and the product isolated as described in Example 1b, affording the title compound. mp 243-246°C. MS (DCI/NH_3) m/e: 261 $(M + H)^+$. ^1H NMR (D_2O, 300 MHz) δ 8.58 (d, J=0.6 Hz, 1H), 8.55 (d, J=3.0 Hz, 1H), 7.82 (dd, J=0.6, 3.0 Hz, 1H), 4.60 (dd, J=11, 2.9 Hz, 1H), 4.43 (dd, J=10.6, 6.2 Hz, 1H), 3.99 (m, 1H), 3.77 (m, 1H), 3.30 (m, 1H), 3.06 (s, 3H), 2.49-2.05 (m, 4H). Anal. Calcd. for $C_{12}H_{16}N_2OF_3Cl$•0.50 H_2O: C, 45.76; H, 5.28; N, 8.89; Found C, 45.51; H, 5.25; N, 9.16. $[\alpha]_D^{25}$=-1.1° (c 0.57, MeOH).

Example 21

3-((*trans*-4-cyanomethyl-1-methyl-2-(S)-pyrrolidinyl)methoxy)pyridine dihydrochloride

Step 21a. 3-(1-methyl-4-hydroxymethyl-5-oxo-2-(S)-pyrrolidinylmethoxy)pyridine

A 4.12 g (20 mmol) sample of 3-((1-methyl-5-oxo-2-(S)-pyrrolidinyl)methoxy)pyridine, from Example 19b above, was dissolved in 50 mL of dry THF and cooled to -78°C. To this solution was added 14.67 mL (22 mmol) of LDA, and the mixture was stirred for 1 hour. The temperature of the reaction mixture was allowed to warm to between -20°C and -10°C, and 4 g (200 mmol) of paraformaldehyde was added. The mixture was stirred at this temperature for 3 hours, then quenched by addition of H_2O, and taken to dryness. The residue was repeatedly triturated with ethyl acetate to dissolve the product. The solvent was removed, and the residue was purified on a silica gel column, eluting with 100:1 to 100:10 $CHCl_3$:methanol, to afford 2.90 g of the title compound.

Step 21b. 3-((4-hydroxymethyl-1-methyl-2-(S)-pyrrolidinyl)methoxy)pyridine

A 401 mg (2 mmol) sample of 3-(1-methyl-4-hydroxymethyl-5-oxo-2-(S)-pyrrolidinylmethoxy)pyridine, from step 21a above, was dissolved in 6 mL of THF and 6 mL of 1M BH_3•THF was added. The mixture was heated at reflux for 2 hours, then treated with methanol and stirred at room temperature for 15 minutes. The solvent was removed under pressure, and the residue was dissolved in 4 mL of ethanol. To this solution was added 251 mg of CsF, and the reaction mixture was heated at reflux for 16 hours. The solvent was removed, and the residue was purified on a column of silica gel, eluting with 100:5 to 10:1 chloroform:methanol to give 78 mg of a mixture of *cis* and *trans* product.

cis compound: MS (DCI/NH_3) m/e: 223 $(M+H)^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.32 (m, 1H), 8.23 (t, 1H, J=3 Hz), 7.21 (m, 1H), 4.16-3.94 (m, 2H), 3.77-3.54 (m, 2H), 3.05 (m, 1H), 2.71 (m, 1H), 2.53 (m, 1H), 2.46 (s, 1H), 2.33 (m, 1H), 1.90 (m, 1H).

trans compound: MS (DCI/NH_3) m/e: 223 $(M+H)^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.33 (m, 1H), 8.23 (m, 1H), 7.23 (m, 1H), 4.20-3.96 (m, 2H), 3.74-3.59 (m, 2H), 3.34 (m, 1H), 2.90 (m, 1H), 2.54 (s, 1H), 2.35 (m, 1H), 1.92 (m, 1H).

Step 21c. 3-((*trans*-4-methanesulfonyloxymethyl-1-methyl-2-(S)-pyrrolidinyl)-methoxy)pyridine

To a 386 mg (1.84 mmol) sample of 3-(*trans*-1-methyl-4-hydroxymethyl-2-(S)-pyrrolidinylmethoxy)pyridine (from step 21b above) dissolved in 12 mL of methylene chloride were added 262 µL (3.38 mmol) of methanesulfonyl chloride, 470 µL of triethylamine and a catalytic amount of DMAP, and the reaction mixture was stirred for 5 hours at room temperature. The reaction was quenched with water, the product extracted from the mixture, the solvent removed, and the product purified by column

chromatography on silica gel, eluting with 20:1 chloroform:methanol to afford 320 mg of the title compound.

Step 21d. 3-((*trans*-4-cyanomethyl-1-methyl-2-(S)-pyrrolidinyl)methoxy)pyridine

A 132 mg sample of the compound from step 21c above was dissolved 4 mL of a 6:1 solution of DMF:H_2O, 240 mg of NaCN was added, and the reaction mixture was stirred at 95°C for 16 hours. The solvent was removed, and the residue was purified by column chromatography on silica gel, eluting with 10:1 chloroform:methanol to afford 62 mg of the title compound. MS (DCI/NH_3) m/e: 232 $(M+H)^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.34 (m, 1H), 8.28 (m, 1H), 7.30-7.20 (m, 2H), 4.28-4.06 (m, 2H), 3.05-2.72 (m, 5H), 2.65-2.52 (br s, 3H), 2.33 (m, 1H), 2.23-2.0 (m, 2H).

Step 21e. 3-((*trans*-4-cyanomethyl-1-methyl-2-(S)-pyrrolidinyl)methoxy)pyridine dihydrochloride

The compound from step 21d was treated with HCl in ether to afford the title compound. mp 203-205°C. MS (DCI/NH_3) m/e: 232 $(M+H)^+$. ^1H NMR (D_2O, 300 MHz) δ 8.48 (d, 1H, J=3 Hz), 8.38 (dd, 1H, J=1.0, 5.2 Hz), 7.96 (m, 1H), 7.80 (dd, 1H, J=5.1, 8.8 Hz), 4.64 (dd, 1H, J=2.9, 11.4 Hz), 4.49 (dd, 1H, J=5.2, 11.1 Hz), 4.17 (m, 1H), 3.98 (m, 1H), 3.09 (s, 3H), 3.25-3.02 (m, 2H), 3.0-2.8 (m, 2H), 2.47 (m, 1H), 2.30 (m, 1H). Anal. Calcd. for $C_{13}H_{17}N_3O$•1.7 HCl: C, 53.24; H, 14.33; N, 6.43; Found C, 53.21; H, 14.36; N, 6.07.

Example 22

3-((1-methyl-2-(R)-pyrrolidinyl)methoxy)-5-trifluoromethylpyridine hydrochloride

Step 22a. 3-((1-methyl-2-(R)-pyrrolidinyl)methoxy)-5-trifluoromethylpyridine

(R)-1-methyl-2-pyrrolidinemethanol (Aldrich Chemical Co.) was dissolved in 8 mL of DMF and stirred under N_2, then 240 mg of NaH (80% dispersion in mineral oil) was added. The mixture was stirred for fifteen minutes, and 363 mg of 3-chloro-5-trifluoromethylpyridine (2.0 mmol) was added. The reaction mixture was stirred at 50°C for 16 hours. The volatile components were removed under vacuum, and the residue was purified by chromatography on silica gel, eluting with 2:1 ethyl acetate:hexane to give 336 mg of the title product. MS (DCI/NH_3) m/e: 261 $(M+H)^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.50 (d, J=0.6 Hz, 1H), 8.49 (d, J=3.0 Hz, 1H), 7.41 (dd, J=0.6, 3.0 Hz, 1H), 4.12-3.96 (m, 2H), 3.16 (m, 1H), 2.73 (m, 1H), 2.51 (s, 3H), 2.37 (m, 1H), 2.13-1.73 (m, 4H).

Step 22b. 3-((1-methyl-2-(R)-pyrrolidinyl)methoxy)-5-trifluoromethylpyridine hydrochloride

The compound from step 22a was treated with HCl in ether according to Example 2b to afford 282 mg of the title compound. mp 246-248°C. MS (DCI/NH_3) m/e: 261

(M+H)+. ^{1}H NMR (D_2O, 300 MHz) δ 8.58 (d, J=0.6 Hz, 1H), 8.56 (d, J=3.0 Hz, 1H), 7.83 (dd, J=0.6, 3.0 Hz, 1H), 4.60 (dd, J=11.0, 2.9 Hz, 1H), 4.33 (dd, J=10.6, 6.2 Hz, 1H), 3.98 (m, 1H), 3.77 (m, 1H), 3.29 (m, 1H), 3.06 (s, 3H), 2.49-2.05 (m, 4H). Anal. Calcd. for $C_{12}H_{16}N_2OF_3Cl$: C, 47.99; H, 5.50; N, 9.29; Found C, 48.07; H, 5.40; N, 9.29. $[\alpha]_D^{25}$=+5.0° (c 1.00, methanol).

Example 23

3-((*cis*-3-propyl-2-pyrrolidinyl)methoxy)pyridine dihydrochloride

Step 23a. *cis*-1-BOC-3-propyl-2-pyrrolidinemethanol

A 400 mg (1.6 mmol) sample of 1-BOC-3-propyl-2-carboxylic acid methyl ester (prepared according to Chung *et al., J. Org. Chem.*, 55:270-275 (**1990**)) was dissolved in 12 mL of THF and cooled to 0°C. To this solution was added 3.0 mL of 1M LAH, and the mixture was stirred at 0°C for 30 minutes. The reaction was quenched by sequential addition of 0.11 mL of H_2O, 0.11 mL of 40% NaOH and 3.00 mL of H2O, and the mixture was stirred for 30 minutes. The mixture was filtered, and the filtrate was concentrated. The residue was purified by chromatography on silica gel to give 240 mg of the title compound.

Step 23b. 3-((*cis*-1-BOC-3-propyl-2-pyrrolidinyl)methoxy)pyridine

A 220 mg (0.96 mmol) sample of cis-1-BOC-3-propyl-2-pyrrolidinemethanol, prepared from Example 23a above, and 137 mg (1.44 mmol) of 3-hydroxypyridine were treated with triphenylphosphine and DEAD (1.44 mmol each) in 10 mL of THF according to the procedure of Example 4a, to give 190 mg of the title compound. MS (DCI/NH_3) m/e: 321 (M+H)+. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.29 (s, 1H), 8.19 (m, 1H), 7.27 (m, 1H), 7.21 (m, 1H), 4.33 (q, 1H), 4.18-3.80 (m, 2H), 3.52-3.2 (m, 2H), 2.26 (m, 1H), 2.00 (m, 1H), 1.77 (m, 1H), 1.40 (m, 4H), 1.48 (s, 9H), 0.92 (m, 3H).

Step 23c. 3-((*cis*-3-propyl-2-pyrrolidinyl)methoxy)pyridine

A 160 mg (0.5 mmol) sample of 3-(cis-1-BOC-3-propyl-2-pyrrolidinylmethoxy)pyridine, from step 23b above, was dissolved in 2 mL of methylene chloride and stirred with 1 mL of TFA for 16 hours at room temperature. The solvent was removed under vacuum, and the residue was adjusted to pH 8 with $NaHCO_3$. The mixture was extracted with methylene chloride, and the extract was dried over $MgSO_4$. The residue was purified by chromatography on silica gel, eluting with 10:2:0.2 $CHCl_3$:methanol:concd ammonium hydroxide, to give 60 mg of the title product. MS (DCI/NH_3) m/e: 221 (M+H)+. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.33 (m, 1H), 8.24 (m, 1H), 7.22 (m, 2H), 4.10 (m, 1H), 4.00 (m, 1H), 3.69 (m, 1H), 3.24 (m, 1H), 3.07 (m, 1H), 2.33 (m, 1H), 2.07 (m, 1H), 1.65 (m, 1H), 1.39 (m, 4H), 0.92 (m, 3H).

Step 23d. 3-((*cis*-3-propyl-2-pyrrolidinyl)methoxy)pyridine dihydrochloride

A 120 mg sample of the compound from step 23c was treated with HCl in ether according to Example 6d to afford 120 mg of the title compound. mp 183-185°C. MS (DCI/NH_3) m/e: 221 $(M+H)^+$. ^1H NMR (D_2O, 300 MHz) δ 8.34 (s, 1H), 8.25 (d, J=4.04 Hz, 1H), 7.61 (m, 1H), 7.52 (m, 1H), 4.45 (dd, J=3.7, 10.7 Hz, 1H), 4.27 (m, 1H), 4.16 (m, 1H), 3.54 (m, 1H), 3.35 (m, 1H), 2.55 (m, 1H), 2.30 (m, 1H), 1.92 (m, 1H), 1.57-1.30 (m, 4H), 0.92 (t, J=6.9 Hz, 3H). Anal. Calcd. for $C_{13}H_{20}N_2O$•1.6 HCl • 0.3 H_2O: C, 54.97; H, 7.88; N, 9.85; Found C, 55.37; H, 7.48; N, 9.43.

Example 24

3-(2-(S)-pyrrolidinylmethoxy)-5-trifluoromethylpyridine dihydrochloride

Step 24a. 3-benzyloxy-5-trifluoromethylpyridine

To a 3.63 g (20 mmol) sample of 3-chloro-5-trifluoromethylpyridine dissolved in 15 mL of DMF and cooled to 0°C was added 960 mg of NaH (60%), then 2.07 mL of benzyl alcohol was added slowly. The reaction mixture was stirred for 2 hours at 40°C. The solvent was then evaporated *in vacuo* and the mixture diluted with chloroform, washed with saturated $NaHCO_3$ and brine. The organic layer was then dried over $MgSO_4$ and concentrated. The resulting crude material was purified by flash chromatography on silica gel to give the title product. MS (DCI/NH_3) m/z 163 $(M+H)^+$, 181 $(M+NH_4)^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.57 (d, J=1.8 Hz, 1H), 8.51 (d, J=0.9 Hz, 1H), 7.48-7.25 (m, 6H), 5.17 (s, 2H).

Step 24b. 3-hydroxy-5-trifluoromethylpyridine

The product from step 24a above (1.95 g) was dissolved in 10 mL of methanol and hydrogenated over Pd/C (5%, 97.5 mg) at 1 atm H_2 for 16 hours. The catalyst was removed, and the solvent was evaporated. The residue was purified by flash chromatography on silica gel to give the title compound. MS (DCI/NH_3) m/z 163 $(M+H)^+$, 181 $(M+NH_4)^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.57 (d, J=1.8 Hz, 1H), 8.51 (d, J=0.9 Hz, 1H), 7.48-7.25 (m, 6h), 5.17 (s, 2H). MS (DCI/NH_3) m/z 154 $(M+H)^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.56 (d, J=1.8 Hz, 1H), 8.47 (d, J=0.9 Hz, 1H), 7.51 (dd, J=1, 0.9 Hz, 1H).

Step 24c. 3-((1-BOC-2-(S)-pyrrolidinyl)methoxy)-5-trifluoromethylpyridine

A 333 mg (1.20 mmol) sample of 1-BOC-2-(S)-azetidinemethanol, and 230 mg (1.30 mmol) of 3-hydroxy-5-trifluoromethylpyridine, from step 24b above, were reacted with triphenylphosphine and DEAD (1.2 mmol each) in 5 mL of THF according to the procedure of Example 4a, to give 360 mg of the title compound. MS (DCI/NH_3) m/z 347 $(M+H)^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.50 (s, 1H), 8.48 (s, 1H), 7.46 (s, 1H), 4.28-3.90 (m, 3H), 3.84-3.48 (m, 2H), 2.12-1.87 (m, 4H).

Step 24d. 3-(2-(S)-pyrrolidinylmethoxy)-5-trifluoromethylpyridine dihydrochloride

The BOC group was removed from the compound of 24c as in the procedure of Example 2b to give the free base of the title compound. The base was converted to the salt with HCl/ethanol as in Example 2b. mp 158-161°C. MS (DCI/NH_3) m/z 247 $(M+H)^+$, 264 $(M+NH_4)^+$. ^1H NMR (D_2O, 300 MHz) δ 8.60 (d, J=0.6 Hz, 1H), 8.55 (d, J=3.0 Hz, 1H), 7.88 (dd, J=0.6, 3.0 Hz, 1H), 4.54 (dd, J=10.6, 3.7 Hz, 1H), 4.32 (dd, J=10.6, 7.7 Hz, 1H), 4.15 (m, 1H), 3.42 (t, J=6.9 Hz, 2H), 2.35-1.90 (m, 4H). Anal. Calcd. for $C_{11}H_{14}N_2OClF_3$: C, 41.40; H, 4.74; N, 8.78; Found: C, 41.38; H, 4.57; N, 8.77. $[\alpha]^{25}_D$=+13.0° (c 0.50, methanol).

Example 25

3-(2-(R)-pyrrolidinylmethoxy)-5-trifluoromethylpyridine dihydrochloride

Step 25a. 3-(1-BOC-2-(R)-pyrrolidinylmethoxy)-5-trifluoromethylpyridine

A 332.9 mg (1.56 mmol) sample of (R)-1-BOC-2-pyrrolidinemethanol and 224.9 mg (1.30 mmol) of 3-hydroxy-5-trifluoromethylpyridine were reacted with triphenylphosphine and DEAD (1.56 mmol each) in 5 mL of THF according to the procedure of Example 2a, to give 386 mg of the title compound. MS (DCI/NH_3) m/z 347 $(M+H)^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.50 (s, 1H), 8.48 (s, 1H), 7.46 (s, 1H), 4.28-3.90 (m, 3H), 3.84-3.48 (m, 2H), 2.12-1.87 (m, 4H), 1.47 (s, 9H).

Step 25b. 3-(2-(R)-pyrrolidinylmethoxy)-5-trifluoromethylpyridine dihydrochloride

A 380 mg sample of the compound from step 25a above was dissolved in 5 mL of dioxane and treated with 4 M HCl in dioxane. The salt was collected, washed and dried, to afford 129 mg of the title compound. mp 169-171°C. MS (DCI/NH_3) m/z 347 $(M+H)^+$. ^1H NMR (D_2O, 300 MHz) δ 8.60 (d, J=0.6 Hz, 1H), 8.55 (d, J=3.0 Hz, 1H), 7.88 (dd, J=0.6, 3.0 Hz, 1H), 4.54 (dd, J=10.6, 3.7 Hz, 1H), 4.32 (dd, J=10.6, 7.7 Hz, 1H), 4.20-4.11 (m, 1H), 3.42 (t, J=6.9 Hz, 2H), 2.35-1.90 (m, 4H). Anal. Calcd. for $C_{11}H_{14}N_2OF_3Cl$•0.7 HCl: C, 42.87; H, 4.81; N, 9.09; Found C, 42.96; H, 4.55; N, 9.05. $[\alpha]^{25}_D$=-9.2° (c 0.52, MeOH).

Example 26

3-(2-(S)-azetidinylmethoxy)-5-trifluoromethylpyridine dihydrochloride

Step 26a. 3-((1-BOC-2-(S)-azetidinyl)methoxy)-5-trifluoromethylpyridine

A sample of 1-BOC-2-(S)-azetidinemethanol (771.9 mg, 4.13 mmol) and 3-hydroxy-5-trifluoromethylpyridine (560 mg, 3.44 mmol), from Example 24b above, were reacted with triphenylphosphine and DEAD (4.13 mmol each) in 15 mL of THF according to the procedure of Example 4a, to give 683 mg of the title compound. MS (DCI/NH_3) m/z 333 $(M+H)^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.54 (d, 1.8 Hz, 1H), 8.51 (d, J=0.9

Hz, 1H), 7.93 (dd, J=0.9, 1.8 Hz, 1H), 4.54 (m, 1H), 4.90 (m, 1H), 4.19 (m, 1H), 3.90 (t, J=7.3 Hz, 2H), 2.43-2.27 (m, 2H), 1.43 (s, 9H).

Step 26b. 3-(2-(S)-azetidinylmethoxy)-5-trifluoromethylpyridine dihydrochloride

A 680 mg sample of the compound from step 26a above was dissolved in 5 mL of dioxane and treated with 1.13 mL of 4M HCl in HCl in dioxane at 0°C for 1.5 hours. The salt was collected, washed and dried, to afford 60 mg of the title compound. mp 154-156°C. MS (DCI/NH_3) m/z 233 $(M+H)^+$, 250 $(M+NH_4)^+$. ^1H NMR (D_2O, 300 MHz) δ 8.61 (d, J=0.9 Hz, 1H), 8.60 (d, J=1.8 Hz, 1H), 7.93 (dd, J=0.9, 1.8 Hz, 1H), 5.04-4.95 (m, 1H), 4.51 (d, J=4.1 Hz, 2H), 4.22-4.04 (m, 2H), 2.70 (q, J=8.4 Hz, 2H). Anal. Calcd. for $C_{10}H_{11}N_2OF_3 \cdot 1.8$ HCl: C, 40.33; H, 4.33; N, 9.41; Found C, 40.09; H, 4.37; N, 9.35. $[\alpha]^{25}_D$=-3.3° (c 0.52, MeOH).

Example 27

3-((*trans*-4-methanesulfonyloxy-1-methyl-2-(S)-pyrrolidinyl)methoxy)pyridine dihydrochloride

Step 27a. 3-((*trans*-1-methyl-4-hydroxy-5-oxo-2-(S)-pyrrolidinyl)methoxy)pyridine

A sample of the compound from Example 19b (1.0 g, 5.6 mmol) was dissolved in 25 mL of THF and cooled to -78°C. LDA (1.5 M in hexane, 7.5 mL, 11.2 mmol) was added, and the solution was stirred at -78°C for 30 min. Next a solution of 1.17 g (5.12 mmol) of (+)-(camphorsulfonyl)oxaziridine in 24 mL of THF was added. After stirring at -78°C for 1 h, the reaction mixture was gradually allowed to warm to room temperature and stirred for an additional 2 hours . The reaction was then quenched by addition of methanol. The resultant mixture was stirred for 15 min, and the solvent was removed. The residue was subjected to flash chromatography on silica gel using chloroform:methanol (10:1) as eluant. The title compound was isolated as an oil (0.76 g, 69% yield). MS m/z : 223 $(M+H)^+$, 240 $(M+NH_4)^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.37-8.26 (m, 2H), 7.31-7.16 (m, 2H), 4.59 (t, J=7.5 Hz, 1H,), 4.18 (dd, J= 4.5, 9 Hz, 1H), 4.04 (dd, J=4.5, 9 Hz, 1H), 3.92 (m, 1H), 2.96 (s, 3H), 2.47 (m, 1H), 2.11 (m, 1H).

Step 27b. 3-((*trans*-1-methyl-4-methanesulfonyloxy-5-oxo-2-(S)-pyrrolidinyl)-methoxy)pyridine

A 570 mg (2.6 mmol) sample of 3-((*trans*-1-methyl-4-hydroxy-5-oxo-2-(S)-pyrrolidinyl)methoxy)pyridine, prepared in step 27a, was dissolved in 17 mL of methylene chloride, and 0.72 mL (5.2 mmol) of triethylamine, a catalytic amount of DMAP and 0.302 mL (3.9 mmol) of methanesulfonyl chloride were added. The reaction mixture was stirred at room temperature for 16 hours then quenched by the addition of H_2O. The solvent was stripped from the mixture under vacuum, $NaHCO_3$ was added, and the mixture was

extracted with chloroform. The solvent was removed, and the residue was purified by chromatography on silica gel to give 780 mg of title compound.

Step 27c. 3-((*trans*-1-methyl-4-hydroxy-2-(S)-pyrrolidinyl)methoxy)pyridine dihydrochloride

A sample of the compound from step 27b was reacted under nitrogen with borane in THF (2.5 mL, 2.48 mmol, of a 1 M solution of borane in THF added dropwise over a period of 5 minutes). After stirring under reflux for 3 hours, methanol was added dropwise, and the mixture was stirred for an additional 15 minutes. The solvent was then removed *in vacuo*, affording a white solid. This solid was dissolved in anhydrous ethanol. cesium fluoride (0.286 g, 2.48 mmol) was added, and the resultant solution was stirred at room temperature for 16 hr. Evaporation of the solvent provided a residue which was purified on a silica gel column to give 50 mg of base. This compound was converted to the salt by treatment with HCl in ethanol. mp 65-67°C. MS (DCI/NH_3) m/e: 287 $(M+H)^+$. ^1H NMR (D_2O, 300 MHz) δ 8.44 (d, J=2.6 Hz, 1H), 8.34 (m, 1H), 7.84 (m, 1H), 7.70 (dd, J=8.9, 5.2 Hz, 1H), 5.62 (m, 1H), 4.69 (dd, J=11.8, 2.9 Hz, 1H), 4.52 (m, 1H), 4.35 (m, 1H), 4.19 (dd, J=14.0, 4.8 Hz, 1H), 3.76 (m, 1H), 3.33 (s, 3H), 3.17 (s, 3H), 2.80-2.59 (m, 2H). Anal. Calcd. for $C_{12}H_{18}N_2O4 \cdot 1.5$ HCl: C, 42.26; H, 5.76; N, 8.24; Found C, 42.59; H, 5.60; N, 8.10.

Example 28

6-hydroxymethyl-3-(1-methyl-2-(S)-pyrrolidinyl)methoxypyridine dihydrochloride

Step 28a. 6-acetyloxymethyl-3-((1-BOC-2-(S)-pyrrolidinyl)methoxy)pyridine

A sample of (S)-1-BOC-2-pyrrolidinemethanol (1.64 g, 8.18 mmol and 1.05 g (6.29 mmol) of 6-acetyloxymethyl-3-hydroxypyridine (prepared as described by Deady and Dayhe, *Aust. J. Chem.*, 2565:36 (**1983**)), were reacted with triphenylphosphine and DEAD (8.18 mmol each) in 25 mL of THF according to the procedure of Example 2a. Workup gave 1.90 g of title compound. MS (DCI/NH_3) m/e: 309 $(M+H)^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.32-8.28 (m, 1H), 7.33-7.25 (m, 2H), 5.15 (s, 2H), 4.30-3.90 (m, 2H), 3.65-3.25 (m, 3H), 2.13 (s, 3H), 2.10-1.80 (m, 3H), 1.49 (s, 9H).

Step 28b. 6-hydroxymethyl-3-((1-BOC-2-(S)-pyrrolidinyl)methoxy)pyridine

To a solution of 1.0 g of the compound from step 28b in methanol was added a solution of 342 mg of KOH in 1 mL of methanol while cooling in a water bath. The reaction mixture was stirred at room temperature for 30 minutes, then neutralized an concentrated. The residue was purified by chromatography on silica gel, eluting with 1:1 ether:hexane followed by ethyl acetate to give 1.22 g of title compound. MS (DCI/NH_3) m/e: 351 $(M+H)^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.27 (d, J=3.0 Hz, 1H), 7.28 (dd,

J=9.3, 3.0 Hz, 1H), 7.16 (d, J=9.3 Hz, 1H), 4.70 (s, 2H), 4.25-3.80 (m, 3H), 3.48-3.30 (m, 3H), 2.10-1.83 (m, 3H), 1.49 (s, 9H).

Step 28c. 6-hydroxymethyl-3-((1-methyl-2-(S)-pyrrolidinyl)methoxy)pyridine

A 669 mg sample of the compound of step 28b above was heated with 2 mL of 37% HCHO and 1 mL of HCOOH, and the mixture was stirred at 100°C for 40 minutes. The reaction was quenched by addition of H_2O, and the mixture was adjusted to pH 7 with $NaHCO_3$ and extracted with methylene chloride. The extract was dried over $MgSO_4$, and the solvent was removed to give the title compound. MS (DCI/NH_3) m/e: 223 $(M+H)^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.28 (d, J=3.0 Hz, 1H), 7.24 (dd, J=9.3, 3.0 Hz, 1H), 7.17 (d, J=9.3 Hz, 1H), 4.71 (s, 2H), 4.01 (m, 1H), 3.94 (m, 1H), 3.13 (m, 1H), 2.73-2.63 (m, 1H), 2.51 (s, 3H), 2.33 (m, 1H), 2.11-1.68 (m, 4H).

Step 28d. 6-hydroxymethyl-3-(1-methyl-2-(S)-pyrrolidinyl)methoxypyridine dihydrochloride

A 60 mg sample of the compound from step 28c was treated with HCl in ether to afford 66 mg of the title compound. MS (DCI/NH_3) m/e: 223 $(M+H)^+$. ^1H NMR (D_2O, 300 MHz) δ 8.38 (d, J=3.0 Hz, 1H), 7.92 (dd, J=9.3, 3.0 Hz, 1H), 7.74 (d, J=9.3 Hz, 1H), 4.85 (s, 2H), 4.59 (m, 1H), 3.95 (m, 1H), 3.77 (m, 1H), 3.27 (m, 1H), 3.04 (s, 3H), 2.47-2.03 (m, 4H). Anal. Calcd. for $C_{12}H_{20}Cl_2N_3O \cdot 0.4\ H_2O$: C, 47.66; H, 6.93; N, 9.26; Found: C, 47.58; H, 7.05; N, 9.23. $[\alpha]^{25}_D$=-4.4° (c 0.50, methanol).

Example 29

3-((*trans*-1,5-dimethyl-2-(S)-pyrrolidinyl)methoxy)pyridine hydrochloride

Step 29a. 3-((1,5-dimethyl-2-(S)-pyrrolidinyl)methoxy)pyridine

A 1.24 g (6.0 mmol) sample of 3-(1-methyl-2-oxo-5-(S)-pyrrolidinylmethoxy)pyridine, from Example 19b above, was dissolved in 50 mL of ether and cooled to -78°C. To this solution was added 4.71 mL (6.6 mmol) of methyl lithium, and the solution was allowed to warm to room temperature and stirred for 2 hours. The solution was cooled to 0°C, 6.6 mL of a 1 M solution of $LAlH_4$ was added, and the reaction mixture was stirred for 2 hours at room temperature. The reaction was quenched by addition of 1 mL of methanol, the solvents removed, and the residue purified by chromatography on silica gel, eluting with 200:1 to 100:1 chloroform:methanol. MS (DCI/NH_3) m/e: 207 $(M+H)^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.34-8.30 (m, 1H), 8.24-8.17 (m, 1H), 7.25-7.27 (m, 2H), 4.05 (m, 1H), 3.90 (m, 1H), 2.78 (m, 1H), 2.43 (s, 3H), 2.39 (m, 1H), 2.03-1.82 (m, 2H), 1.70-1.40 (m, 2H), 1.13 (d, J=6.7 Hz, 3H).

Step 29b. 3-((*trans*-1,5-dimethyl-2-(S)-pyrrolidinyl)methoxy)pyridine hydrochloride

A 25 mg sample of the compound of compound from step 29a was treated with HCl in ether to afford 37 mg of the title compound. MS (DCI/NH_3) m/e: 207 $(M+H)^+$. ^1H

NMR (D_2O, 300 MHz) δ 8.42-8.38 (m, 1H), 8.34-8.28 (m, 1H), 7.80-7.76 (m, 1H), 7.67-7.63 (m, 1H), 4.60-4.54 (m, 1H), 4.47-4.41 (m, 1H), 4.03-3.95 (m, 1H), 3.62-3.52 (m, 1H), 3.03 (s, 3H), 2.40-2.30 (m, 2H), 2.13-2.03 (m, 1H), 1.93-1.80 (m, 1H), 1.47 (d, J=6.7 Hz, 3H). $[\alpha]^{25}_D$=+15.4° (c 0.50, methanol). Anal. Calcd. for $C_{12}H_{18}N_2O$•0.40 HCl: C, 49.06; H, 7.00; N, 9.54; Found: C, 49.22; H, 6.47; N, 9.69.

Example 30

3-((*cis*-4-cyano-1-methyl-2(S)-pyrrolidinyl)methoxy)pyridine dihydrochloride

Step 30a 3-((*cis*-4-cyano-1-methyl-2(S)-pyrrolidinyl)methoxy)pyridine

To a solution of 300 mg (1.05 mmol) of 3-((*trans*-1-methyl-4-methanesulfonyloxy-2-(S)-pyrrolidinyl)methoxy)pyridine, prepared as in Example 27c above, in 7 mL of 6:1 DMF:H_2O was added 0.51 g (10.5 mmol) of NaCN, and the mixture was heated at 100°C for 5 hours. The mixture was cooled, diluted with water, and extracted with chloroform. The extract was dried over MgSO4 and concentrated. The residue was purified on a silica gel column, eluting with 100:2 chloroform:methanol, to give 80 mg of the title compound.

Step 30b 3-((*cis*-4-cyano-1-methyl-2(S)-pyrrolidinyl)methoxy)pyridine dihydrochloride

The compound from step 30a was treated with HCl in ether to afford 75 mg of the title compound. mp 220-222°C. MS (DCI/NH_3) m/e: 218 $(M+H)^+$. ^1H NMR (D_2O, 300 MHz) δ 8.46 (d, J=2.9 Hz, 1H), 8.34 (m, 1H), 7.86 (m, 1H), 7.70 (m, 1H), 4.62 (m, 1H), 4.49 (m, 1H), 4.04 (m, 2H), 3.85 (m, 1H), 3.66 (m, 1H), 3.05 (s, 3H), 2.91 (m, 1H), 2.55 (m, 1H). Anal. Calcd. for $C_{12}H_{15}N_3O$•2 HCl•0.6 H_2O: C, 47.88; H, 6.09; N, 13.96; Found C, 47.70; H, 5.95; N, 14.14. $[\alpha]^{25}_D$=+15.14° (c 0.50, methanol).

Example 31

3-((cis-4-fluoromethyl-1-methyl-2-(S)-pyrrolidinyl)methoxy)pyridine dihydrochloride

Step 31a. 3-((cis-4-fluoromethyl-1-methyl-2-(S)-pyrrolidinyl)methoxy)pyridine

A 1.57 g (7.1 mmol) sample of 3-((4-hydroxymethyl-1-methyl-2-(S)-pyrrolidinyl)methoxy)pyridine, prepared as described in Example 21b above, was dissolved in 40 mL of methylene chloride, and the solution was cooled to -78°C. To this solution was added 2.80 mL (21.2 mmol) of diethylaminosulfur trifluoride, then the solution was stirred at -35°C for 1.5 hours. The reaction mixture was allowed to warm to room temperature, and the reaction was quenched by the addition of saturated $NaHCO_3$. The mixture was extracted with chloroform, the chloroform was removed, and the residue was purified on a silica gel column, eluting with 100:2 chloroform:methanol to 10:1:0.02 chloroform:methanol:concd NH_4OH, to give 120 mg of the title compound.

Step 31b. 3-((cis-4-fluoromethyl-1-methyl-2-(S)-pyrrolidinyl)methoxy)pyridine dihydrochloride

The compound from step 31a was treated with HCl in ether according to Example 14c to afford the title compound. MS (DCI/NH_3) m/e: 225 $(M+H)^+$. ^1H NMR (D_2O, 300 MHz) δ 8.63 (d, J=0.9 Hz, 1H), 8.44 (m, 1H), 7.97 (m, 1H), 4.64-4.43 (m, 5H), 3.49 (m, 1H), 3.31 (m, 1H), 2.92 (s, 3H), 2.90 (m, 1H), 2.41 (m, 1H), 1.63 (m, 1H). 2D NOE data are consistent with the *cis* configuration. Anal. Calcd. for $C_{12}H_{17}N_2OF$•2 HCl: C, 48.50; H, 6.44; N, 9.43; Found C, 48.22; H, 6.65; N, 9.26. $[\alpha]^{25}_D$=+5.83° (methanol).

Example 32

5-Amino-3-(1-methyl-2(S)-pyrrolidinylmethoxy)pyridine hydrochloride

The compound from Example 1b was treated with HCl in ether, then again with HCl in dioxane, and the precipitate was collected. The salt was triturated with ether and dried under vacuum to give the title compound. MS (DCI/NH_3) m/e: 208 $(M+H)^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.77-7.80 (m, 2H), 7.09 (t, 1H, J= 2.4Hz), 4.50 (dd, 1H, J= 3.4, 11 Hz), 4.34 (dd, 1H, J= 5.8, 11 Hz), 3.93 (m, 1H), 3.76 (m, 1H), 3.26 (m, 1H), 3.03 (s, 3H), 2.38 (m, 1H), 2.15 (m, 1H). Anal. Calcd. for $C_{11}H_{17}N_3O$• 1.6 HCl• 1.0 H_2O: C, 46.58 H, 7.32 N, 14.82. Found: C, 46.84; H, 7.46; N, 14.42.

Example 33

3-(2-(2-(S)-pyrrolidinyl)ethoxy)pyridine dihydrochloride

Step 33a. 1-BOC-2-(S)-2-cyanomethylpyrrolidine

To 1-Boc-2-(S)-pyrrolidinemethanol (1.58g, 7.90 mmol) was added pyridine (15 mL) and tosyl chloride (2.25 g, 11.80 mmol) and the mixture was stirred for 16 hours at room temperature. The mixture was then poured into CH_2Cl_2 and washed with citric acid (100 mL), sat $NaHCO_3$ (100 mL) and brine (100 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. The crude material (2.70g) was taken up in DMSO (20 mL) and sodium cyanide was added (1.54g, 23.70mmol), then mixture was sonicated for 16 overnight. The mixture was poured into EtOAc and washed with sat $NaHCO_3$ (100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude material was chromatographed (silica gel; MeOH/CH_2Cl_2, 20/1) to afford a yellow oil (1.17g, 71%). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.48 (s, 9H), 1.72-2.08 (m, 3H), 2.10-2.25 (m, 1H), 2.51-2.83 (m, 2H), 3.37-3.53 (m, 2H), 3.93-4.10 (m, 1H). MS (DCI/NH_3) m/e: 210 $(M+H)^+$, 228 $(M+NH_4)^+$.

Step 33b. 1-BOC-2-(S)-2-methoxycarbonylmethylpyrrolidine

To the product of Example 33a was added a saturated solution of HCl in EtOH and the mixture was heated to reflux for 4 hours. The mixture was cooled to room temperature and concentrated *in vacuo*. To the residue was added CH_2Cl_2 (200 mL), triethylamine (5.85 g, 57.80 mmol), di-*t*-butyl dicarbonate (9.46 g, 43.40 mmol) and 4-dimethylaminopyridine (0.353 g, 2.90 mmol), and the mixture was stirred at room temperature for 16 hours. The mixture was poured into CH_2Cl_2 (200 mL) and washed with H_2O (150 mL) and brine (150 mL), then dried ($MgSO_4$) and concentrated in vacuo. The crude mixture was chromatographed (silica gel; MeOH/CH_2Cl_2, 20/1) to afford a yellow oil (6.43g, 87%). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.26 (m, J=6.0 Hz, 3H), 1.48 (s, 9H), 1.72-1.92 (m, 2H), 2.0-2.11 (m, 1H), 2.30 (q, J=9.0, 15.0 Hz, 2H), 2.71-3.01 (m, 2H), 3.28-3.41 (m, 2H), 4.07-4.21 (m, 2H). MS (DCI/NH_3) m/e: 258 $(M+H)^+$

Step 33c. 1-BOC-2-(S)-2-(2-hydroxyethyl)pyrrolidine

To a solution of the product of Example 33b (6.80 g, 26.5 mmol) in anhydrous toluene (100 mL), cooled to -78°C was added a 1M solution of diisobutylaluminum hydride in toluene (132.5 mL, 132.5 mmol). The mixture was stirred at -78°C for 2 hours, then the reaction was quenched at -78°C with methanol (150 mL). The mixture was poured into 1M Rochelle salt (500 mL), and the emulsified solution was extracted with ethyl acetate (200 mL). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified on silica gel, eluting with methanol/methylene chloride (5:95) to yield a colorless oil (3.82 g, 67%). ^1H NMR (CDCl3, 300 MHz) δ 1.47 (s, 9H), 1.58-1.76 (m, 2H), 1.82-2.05 (m, 3H), 3.31 (t, J=6.0 Hz, 2H), 3.50-3.69 (m, 2H), 4.10-4.21 (m, 1H), 4.43 (dd, J=4.0, 7.0 Hz, 1H). MS (DCI/NH3) m/e: 216 $(M+H)^+$.

Step 33d. 3-(2-(1-BOC-2-(S)-pyrrolidinyl)ethoxy)pyridine

To a solution of triphenylphosphine (3.39 g, 12.9 mmol) in THF (10 mL) was added DEAD (2.03 mL, 15.5 mmol), and the mixture was stirred at room temperature for 20 minutes. Then 3-hydroxypyridine (1.23 g, 15.5 mmol) in 10 mL of THF was added, and the mixture was stirred at room temperature for 10 minutes. The alcohol from step 33c above (2.31 g, 10.80 mmol) in 10 mL of THF was then added, and the mixture was stirred for 16 hours and concentrated *in vacuo*. The residue was triturated with hexane, then the filtrate was concentrated and purified on silica gel, eluting with ethyl acetate/hexane (1:1) to afford an oil (2.58 g, 84%). MS(DCI/NH_3) m/e: 293 $(M+H)^+$. 1H NMR ($CDCl_3$, 300 MHz) δ 1.49 (s, 9H), 1.74-2.06 (m, 5H), 2.22 (m, 1H), 3.37-3.40 (m, 2H), 3.95-4.12 (m, 3H), 7.19 (m, 1H), 8.21 (d, J=8.0 Hz, 1H), 8.30 (m, 1H).

Step 33e. 3-(2-(2-(S)-pyrrolidinyl)ethoxy)pyridine dihydrochloride

To a solution of the compound from step 33d above (60 mg, 0.20 mmol) in 3 mL of ethanol at 0°C was added saturated HCl in ethanol (10 mL), and the reaction mixture was stirred for 30 minutes at 0°C. The volatile components were removed under vacuum, and the residue was purified on a column of silica gel, eluting with methanol/methylene chloride (5:95). The product was treated with a saturated solution of HCl in EtOH, then was concentrated and the residue was held under vacuum for 24 hours to afford a white solid. MS (DCI/NH_3) m/e: 193 $(M+H)^+$, 210 $(M+NH_4)^+$. ^1H NMR (D_2O, 300 MHz) δ 1.77 (m, 1H), 1.91-2.20 (m, 3H), 2.26-2.43 (m, 2H), 3.28-3.47 (m, 2H), 3.77 (m, 1H), 4.27-4.45 (m, 2H), 7.82 (dd, J=8.5, 5.0 Hz, 1H), 7.98 (dd, J=9.0, 4.0 Hz, 1H), 8.35 (d, J=6.0 Hz, 1H), 8.45 (d, J=2.0 Hz, 1H). Anal. Calcd. for $C_{11}H_{16}N_2O$•2.3 HCl: C, 47.84; H, 6.68; N, 10.14; Found C, 47.48; H, 6.92; N, 9.94. $[\alpha]^{25}_D$=+41.62° (c 0.41, methanol).

Example 34

3-(2-(1-methyl-2-(S)-pyrrolidinyl)ethoxy)pyridine dihydrochloride

A 400 mg sample of 3-(2-(2-(S)-pyrrolidinyl)ethoxy)pyridine dihydrochloride, from Example 33 above, was dissolved in 14 mL of 37% HCHO, 14 mL of 80% HCOOH was added, and the reaction mixture was stirred at reflux for 2.5 hours. The solution was washed with ether, adjusted to basic pH with K_2CO_3 and extracted with methylene chloride. The extract was dried over $MgSO_4$ and concentrated. The residue was purified on a column of silica gel, eluting with 10% methanol in methylene chloride. The compound was converted to the salt by treatment with HCl in ether to afford the title compound. MS (DCI/NH_3) m/e: 207 $(M+H)^+$. ^1H NMR (D_2O, 300 MHz) δ 1.84 (m, 1H), 2.00-2.23 (m, 3H), 2.41 (m, 1H), 2.56 (m, 1H), 2.98 (s, 3H), 3.19 (m, 1H), 3.60 (m, 1H), 3.73 (m, 1H), 4.31-4.48 (m, 2H), 8.00 (dd, J=11.0, 7.0 Hz, 1H), 8.20 (dd, J=10.5, 5.0 Hz, 1H), 8.42 (d, J=6.5 Hz, 1H), 8.50 (d, J=5.0 Hz, 1H). Anal. Calcd. for $C_{12}H_{18}N_2O$•1.9 HCl•1.1 H_2O: C, 48.49; H, 7.46; N, 9.42; Found C, 48.51; H, 7.69; N, 9.61. $[\alpha]^{25}_D$=+36.28° (c 0.5, H_2O).

Example 35

3-(2-(2-(S)-pyrrolidinyl)ethoxy)-6-chloropyridine dihydrochloride

Step 35a. 3-(2-(1-BOC-2-(S)-pyrrolidinyl)ethoxy)-6-chloropyridine

To a solution of triphenylphosphine (5.90 mmol, 1.54 g) in THF (17 mL) was added DEAD (5.90 mmol, 1.03 g) and the mixture was stirred at room temperature for 10 minutes. To the mixture was added a solution of 2-chloro-5-hydroxypyridine (5.90 mmol, 0.7611g) in THF (5.0 mL) and stirring was continued for 10 minutes. The alcohol (1.06

g, 4.90 mmol) from Example 33a in THF (10 mL) was added and the mixture was stirred at room temperature for 16 hours. The mixture was concentrated *in vacuo*, triturated with hexane, filtered and the volatile components were removed. The residue was purified on silica gel, eluting with ethyl acetate/hexane (1:1) which afforded 1.57 g (98%) of a yellow oil. MS(DCI/NH_3) 327 $(M+H)^+$, 344 $(M+NH_4)^+$. ^1H NMR($CDCl_3$, 300MHz) δ 1.18-1.80 (m, 2H), 1.45 (s, 9H), 1.71-2.03 (m, 5H), 2.20 (br s, 1H), 3.34 (m, 1H), 3.96-4.10 (m, 2H), 7.14-7.25 (m, 2H), 8.04 (m, 1H).

Step 35b. 3-(2-(2-(S)-pyrrolidinyl)ethoxy)-6-chloropyridine dihydrochloride

To a solution of 124 mg (0.40 mmol) of the compound from step 35a above in 3 mL of ethanol was added 10 mL of saturated HCl in ethanol, and the mixture was stirred for 1 hour at room temperature. The volatile components were removed under vacuum, and the residue was treated with aqueous acid and extracted with methylene chloride. The aqueous solution was made basic and extracted with methylene chloride. The extract was dried over $MgSO_4$ and concentrated. The residue was purified on a column of silica gel, eluting with 10% methanol in methylene chloride. The compound was converted to the salt with HCl in ether to afford the title compound. MS (DCI/NH_3) m/e: 227 $(M+H)^+$. ^1H NMR (D_2O, 300 MHz) δ 1.77 (m, 1H), 1.91-2.18 (m, 2H), 2.21-2.37 (m, 3H), 3.23-3.43 (m, 2H), 3.74 (m, 1H), 4.15-4.46 (m, 2H), 7.47 (m, 2H), 8.06 (d, J=3.5 Hz, 1H). Anal. Calcd. for $C_{11}H_{15}N_2OCl \cdot 2$ HCl: C, 45.09; H, 5.71; N, 9.34; Found C, 45.04; H, 6.01; N, 9.05. $[\alpha]^{25}_D$=+19.00° (c 0.15, H_2O).

Example 36

3-(2-(1-methyl-2-(S)-pyrrolidinyl)ethoxy)-6-chloropyridine dihydrochloride

A 565 mg sample of 3-(2-(2-(S)-pyrrolidinyl)ethoxy)6-chloropyridine dihydrochloride, from Example 35 above, was dissolved in 27 mL of 37% HCHO, then 27 mL of 80% HCOOH was added, and the mixture was stirred at reflux for 30 minutes. The solution was washed with ether, adjusted to basic pH with K_2CO_3 and extracted with methylene chloride and chloroform. The combined extracts were dried over $MgSO_4$ and concentrated. The residue was purified on a column of silica gel, eluting with 10% methanol in methylene chloride. The compound was converted to the salt with HCl in ether to afford the title compound. MS (DCI/NH_3) m/e: 241 $(M+H)^+$. ^1H NMR (D_2O, 300 MHz) δ 1.89 (m, 1H), 2.01-2.20 (m, 3H), 2.38-2.54 (m, 2H), 2.98 (s, 3H), 3.15 (m, 1H), 3.56 (m, 1H), 3.72 (m, 1H), 4.13-4.32 (m, 2H), 7.40 (d, J=10 Hz, 1H), 7.48 (dd, J=10.5, 4.0 Hz, 1H), 8.10 (d, J=3.0 Hz, 1H). Anal. Calcd. for $C_{12}H_{17}N_2OCl \cdot 1.9$ HCl: C, 46.49; H, 6.14; N, 9.03; Found: C, 46.70; H, 6.06; N, 9.04. $[\alpha]^{25}_D$=+21.00° (c 0.20, H_2O).

Example 37

3-(2-(S)-pyrrolidinylmethylthioxy)pyridine dihydrochloride

Step 37a. 3-(1-BOC-2-(S)-pyrrolidinylmethylthioxy)pyridine

To a solution of triphenylphosphine (1.8 mmol, 0.472 g) in THF (8 mL) at 0°C was added DEAD (1.8 mmol, 0.283 mL) and the mixture was stirred for 20 minutes. To this mixture was added 166.5 mg (1.5 mmol) of 3-mercaptopyridine (prepared from 3-pyridinesulfonic acid according to the procedure of A. Albert and G.B. Barlin, *J. Chem. Soc.*, **1959**, 2384) and 361.8 mg (1.8 mmol) of (S)-1-BOC-2-pyrrolidinemethanol. The reaction mixture was allowed to warm to room temperature and stirred for 16 hours. The mixture was concentrated *in vacuo*. The residue was purified on silica gel to give 440 mg of the title compound. MS (DCI/NH_3) m/e: 295 $(M+H)^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.62 (m, 1H), 8.41 (m, 1H), 7.78 (m, 1H), 3.97 (m, 1H), 3.65-32.8 (m, 4H), 2.18-1.74 (m, 4H), 1.44 (s, 9H).

Step 37b. 3-(2-(S)-pyrrolidinylmethylthioxy)pyridine dihydrochloride

The compound from step 37a was treated with HCl in ether, then again with HCl in dioxane, and the precipitate was collected. The salt was triturated with ether and dried under vacuum to give the title compound. MS (DCI/NH_3) m/e: 195 $(M+H)^+$. ^1H NMR (D_2O, 300 MHz) δ 8.91-8.84 (m, 1H), 8.60 (m, 1H), 8.44 (m, 1H), 7.86 (m, 1H), 3.78 (m, 1H), 3.61 (m, 1H), 3.44-3.28 (m, 3H), 2.29 (m, 1H), 2.18-1.97 (m, 2H), 1.82 (m, 1H). Anal. Calcd. for $C_{10}H_{16}N_2SCl_2$: C, 44.95; H, 6.04; N, 10.48; Found C, 45.07; H, 5.80; N, 10.40.

Example 38

3-(1-methyl-2-(S)-pyrrolidinylmethylthioxy)pyridine dihydrochloride

A 120 mg sample of 3-(2-(S)-pyrrolidinylmethylthioxy)pyridine dihydrochloride, from Example 37b above, was dissolved in 2 mL of 37% HCHO, 1 mL of HCOOH was added, and the reaction mixture was stirred at reflux for 30 minutes. The solution was washed with ether, adjusted to basic pH with K_2CO_3 and extracted with methylene chloride and chloroform. The extract was dried over $MgSO_4$ and concentrated. The residue was purified on a column of silica gel, eluting with 10% methanol in methylene chloride. The compound was converted to the salt by HCl in ether to afford 84.5 mg of the title compound. MS (DCI/NH_3) m/e: 209 $(M+H)^+$. ^1H NMR (D_2O, 300 MHz) δ 8.67 (m, 1H), 8.50 (m, 1H), 8.11 (m, 1H), 7.57 (m, 1H), 3.74 (m, 1H), 3.61-3.48 (m, 2H), 3.36 (m, 1H), 3.27 (m, 1H), 2.93 (s, 3H), 2.39 (m, 1H), 2.18-1.97 (m, 2H), 1.87 (m, 1H). Anal. Calcd. for $C_{11}H_{18}N_2SCl_2$: C, 46.98; H, 6.45; N, 9.96; Found: C, 46.55; H, 6.56; N, 9.69.

Example 39

2-Fluoro-3-(2(S)-azetidinylmethoxy)pyridine hydrochloride

Step 39a. 2-Fluoro-3-hydroxypyridine.

2-Amino-3-hydroxypyridine (8.25 g, 75 mmol; from Aldrich) was dissolved in hydrogen fluoride-pyridine (100 g, Aldrich) and cooled to 0 °C. Then sodium nitrite (5.4 g 78 mmol) was added over 30 min. The solution was stirred for an additional 30 minutes and then slowly poured into 300 mL of 25% NaOH at 0 °C. The aqueous mixture was filtered and then extracted with CH_2Cl_2 (6 X 75 mL). The aqueous solution was adjusted to pH 6 with 20% aq NaOH and extracted with EtOAc (6 x 100 mL), then the combined EtOAc extracts were dried over $MgSO_4$ and concentrated. The residue was chromatographed (silica gel; hexane/ EtOAc, 9:1 to 6:4) to afford 3.93 g of the title compound ^1H NMR ($CDCl_3$, 300 MHz) δ 7.75(m, 1H), 7.37 (m, 1H), 7.11 (m, 1H). MS (DCI/NH_3) m/z 114 $(M+H)^+$, 131 $(M+NH_4)^+$.

Step 39b. 2-Fluoro-3-(1-Cbz-2-(S)-azetidinylmethoxy)pyridine

The procedure of example 2a was followed, substituting 2-fluoro-3-hydroxypyridine and 1-Cbz-2-(S)-azetidinemethanol for 5-bromo-9-chloropyridine-3-ol and 1-BOC-2-(S)-azetidinemethanol, respectively. Yield: 56 %. ^1H NMR (DMSO-*d6*, 130° C, 300 MHz) : δ 7.72 (m. 1H), 7.55 (m, 1H), 7.30-7.20 (m, 5H), 7.17 (m, 1H), 5.01 (s, 1H), 4.56 (m, 1H), 4.41 (dd, J=11.11, 1H), 4.5 (dd, J=10.68, 1H), 3.90-3.85 (t, J=7.26, 2H), 2.42 (m, 1H), 2.25 (m, 1H). MS (DCI/NH_3) m/z 334 $(M+H)^+$, 317 $(M+NH_4)^+$.

Step 39c. 2-Fluoro-3-(2-azetidinylmethoxy)pyridine hydrochloride

2-Fluoro-3-(1-Cbz-2-(S)-azetidinylmethoxy)pyridine (1.1 g 34.8 mmol) was combined with 100 mg of 5% Pd/C in EtOH (25 mL) and the mixture was stirred under an H_2 atmosphere for 16 hours. The mixture was filtered and concentrated, and the crude product was chromatographed (silica gel; $CHCl_3$, 99:1 to 94:6) to afford 480 mg (76%) of the free base. The base was converted to the salt by treatment with 1M hydrogen chloride in ether. The salt was recrystallized three times from EtOH/EtOAc/ Et_2O to give 150 mg of the title compound ^1H NMR (D_2O 300 MHz) δ 7.81 (m. 1H), 7.67 (m, 1H), 7.35 (m, 1H), 4.97 (m, 1H), 4.5-4.48 (t, J=2.04 Hz, 2H), 4.21-4.06 (m, 2H), 2.75-2.66 (tt, J=6.95 Hz, 2H). MS (DCI/NH_3) m/z 183 $(M+H)^+$, 200 $(M+NH_4)^+$ Anal. Calcd. for $C_9H_{11}N_2OF \cdot HCl \cdot 0.3\ H_2O$: C, 48.24; H, 5.67; N, 12.50. Found: C,48.30: H, 5.56; N, 12.15.

Example 40

2-Fluoro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine hydrochloride

2-Fluoro-3-(1-Cbz-2-(S)-azetidinylmethoxy)pyridine from Example 39b (450 mg, 14.2 mmol) was combined with 100 mg of 5% Pd/C and paraformaldehyde (300 mg) in 10

mL of EtOH and the mixture was stirred under an H_2 atmosphere for 16 hours. The mixture was filtered and concentrated. The crude product was chromatographed (silica gel; $CHCl_3$/MeOH, 95:5) to afford 100 mg (30%) of the free base . The base was converted to the salt by treatment with 1M hydrogen chloride in ether. The salt was recrystallized three times from EtOH/EtOAc/ Et_2O to give 29 mg (9%) of the title compound. ^1H NMR (D_2O, 300 MHz) δ 7.81 (m, 1H), 7.66 (m, 1H), 7.35 (dd, J=7.94 Hz, 1H), 4.82 (br s, 1H), 4.56 (dd, J=11.6 Hz, 1H), 4.49 (br s, 1H), 4.27 (br s, 1H), 4.04 (br s, 1H), 3.01 (s, 3H), 2.71-2.63 (m, 2H). MS (DCI/NH_3) m/z 197 $(M+H)^+$, 211 $(M+NH_4)^+$. Anal. Calcd. for $C_{10}H_{13}FN_2O$•HCl·: C, 51.62; H, 6.06; N, 12.04. Found: C,51.87; H, 5.9;1 N, 11.77.

Example 41

5-nitro-3-(2-(S)-pyrrolidinylmethoxy)pyridine hydrochloride

Step 41a. 3-benzyloxy-5-bromopyridine

NaH (60% in mineral oil) (40.9 g 1.0225 mol) in 800 mL of DMF was cooled to 0°C, and benzyl alcohol (105 mL 1.014 mol) was added slowly. The reaction mixture was stirred for 1 hour at 20°C, then 3,5-dibromopyridine (200.4 g, 846 mmol) was added and the mixture was stirred for 16 hours. The mixture was quenched with saturated NH_4Cl (500 mL), diluted with 400 mL water and extracted with Et_2O (5 x 300 mL). The combined Et_2O extracts were washed with 50 % brine (6x 300 mL) and dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the crude product was recrystallized from Et_2O to afford 161 g (72 %) of the title product, mp 63-68 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.37-8.27 (m, 2H), 7.5-7.35 (m, 6H), 5.1 (s, 1H). MS (DCI/NH_3) m/z 264, 266 $(M+H)^+$.

Step 41b. 3-amino-5-benzyloxypyridine

The product of Example 41a (41.3 g 156 mmol), copper(I) bromide (22.43 g 156 mmol), MeOH (275 mL), and liquid NH_3 (50 mL) were combined in a stainless steel reactor and heated to 130° C for 24 hours. The mixture was allowed to cool to ambient temperature, then concentrated. The residue was suspended in 300 mL of saturated aqueous Na_2CO_3 and extracted with CH_2Cl_2 (4 x 500 mL) . The combined CH_2Cl_2 extracts were washed with brine, dried ($MgSO_4$), and concentrated. The crude product was chromatographed (silica gel; hexane/ EtOAc, 9:1 to 7:3) to afford 15.6 g (50 %) of the title compound. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.21-8.29 (m, 2H), 7.44-1.26 (m, 6H), 5.10 (s, 2H). MS (DCI/NH_3) m/z 201 $(M+H)^+$.

Step 41c. 3-amino-5-hydroxypyridine

The product of Example 41b (15.47 g, 77.25 mmol) in MeOH (25 mL) was stirred under an atmosphere of H_2 in the presence of 5% Pd/C (100 mg) for 48 hours. The

mixture was filtered and concentrated, then the crude product was chromatographed (silica gel; $CHCl_3$/MeOH, 9:1) to afford 4.5 g (53 %) of the title compound MS (DCI/NH_3) m/z 111 $(M+H)^+$, 128 $(M+NH_4)^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.4 (d, J = 3 Hz, 1H), 7.3 (d, J = 2.5 Hz, 1H), 6.33 (dd, J = 2.6 Hz, 1H).

Step 41d. 3-hydroxy-5-nitropyridine

Potassium persulfate (56.8 g 210 mmol) was ground into 31.5 mL of concd sulfuric acid, and the solution was added to a solution of the product of Example 41c (2.75 g 25 mmol) in concd sulfuric acid (27 mL). The mixture was allowed to stand for 72 hours, then was poured over ice and adjusted to pH 6 with concd NH_4OH. The solution was extracted with EtOAc (4 x 100 mL), then the EtOAc extracts were dried ($MgSO_4$) and concentrated. The crude product was chromatographed (silica gel; $CHCl_3$/ MeOH, 99:1to 9:1) to afford 1.65 g (47 %) of the title compound. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.81(d, J = 3 Hz, 1H), 8.51 (d, H = 3 Hz, 1H), 7.82 (dd, J = 2.5 Hz, 1H). MS (DCI/NH_3) m/z 141 $(M+H)^+$, 158 $(M+NH_4)^+$.

Step 41e. 5-nitro-3-(2-(1-BOC-2-(S)-pyrrolidinyl)methoxy)pyridine

The procedures of Example 2a were followed, substituting 3-hydroxy-5-nitropyridine for 5-bromo-6-chloro-3-hydroxypyridine. Yield: 23 %. ^1H NMR (DMSO-d_6, 120° C, 300 MHz) δ 8.94 (d, J= 1.8 Hz, 1H), 8.68 (d, J= 2.5 Hz, 1H), 8.08 (t, J= 2.4 Hz, 1H), 4.31-4.28 (dd, J= 9.3 Hz, 1H).4.24 (dd, J=10.4 Hz, 1H), 4.09 (m 1H), 3.38 (m, 1H), 3.28 (m, 1H), 2.05 (m, 1H) 1.98-1.92 (m, 2H) 1.82 (m, 1H), 1.41 (s, 9H). MS (DCI/NH_3) m/z 324 $(M+H)^+$, 341 $(M+NH_4)^+$.

Step 41f. 5-nitro-3-(2-(S)-pyrrolidinyl)methoxy)pyridine

The procedures of Example 2b were followed, replacing 5-bromo-6-chloro-3-(2-(1-BOC-2-(S)-pyrrolidinyl)methoxy)pyridine with 5-nitro-3-(2-(1-BOC-2-(S)-pyrrolidinyl)methoxy)pyridine. Yield 54%. ^1H NMR (D_2O, 300 MHz) δ 9.02 (d, J= 2 Hz, 1H), 8.66 (d, J= 2.7 Hz, 1H), 8.27 (dd, J= 2.72, 1H), 4.58 (dd, J=0.9, 1H), 4.37 (dd, J=10.9, 1H), 4.16 (m, 1H), 3.84-3.4 (m, 2H), 2.30 (m, 1H), 2.07 (m, 3H). MS (DCI/NH_3) m/z 224 $(M+H)^+$, 241 $(M+NH_4)^+$. Anal. Calcd. for $C_{10}H_{13}N_3O_3 \cdot 1.2$ HCl: C, 4.99; H 5.36; N, 15.74. Found: C, 45.08: H, 5.43; N, 15.66.

Example 42

2-Fluoro-3-(2(R)-azetidinylmethoxy)pyridine hydrochloride

The procedures of Examples 39b and 39c were followed, replacing 1-Cbz-2-(S)-azetidinemethanol in Example 39b with the corresponding (R) isomer. ^1H NMR (D_2O) δ 2.68-2.77 (m, 2H), 4.15-4.22 (m, 2H), 4.48 (d, J=4.1 Hz, 2H), 4.92-5.01 (m, 1H), 7.34 (dd, J=5.0, 8.1 Hz, 1H), 7.66 (ddd, J=1.3, 8.1, 9.5 Hz, 1H), 7.79 (dd, J=1.3, 5.0 Hz,

1H). MS (CI/NH_3) m/z 183 ($M+H^+$), 200 ($M+NH_4^+$). Anal. Calcd. for $C_9H_{11}FN_2O \cdot HCl$: C, 49.44; H, 5.53; N, 12.81. Found: C, 49.69; H, 5.72; N, 12.67.

Example 43

6-Cyano-3-(2(S)-azetidinylmethoxy)pyridine hydrochloride

Step 43a. 3-amino-6-bromopyridine

A mixture of 2-bromo-5-nitropyridine (30.75 g, 151.5 mmol), water (250 mL), and acetic acid (110 mL) was heated to 45°C. Iron powder (24.5 g, 439 mmol) was added at a rate which kept the temperature below 53°C, then the mixture was stirred at 48°C ± 5°C for one hour. The mixture was cooled to room temperature and filtered through diatomaceous earth filter aid, washing with ethyl acetate. The layers were separated and the aqueous phase was extracted with ethyl acetate. The combined organic fractions were washed with saturated Na_2CO_3 (4X 50 mL) and brine (50 mL), dried over $MgSO_4$, and the solvent was removed *in vacuo*. The residue was chromatographed [silica gel, hexane:EtOAc, 100:0 to 50:50) to give 20.4 g of the title compound. MS (CI/NH_3) m/e: 173 $(M+H)^+$, 190 $(M+NH_4)^+$. ^1H NMR ($CDCl_3$ 300 MHz) δ 6.86-6.90 (dd, 1H, J=8.5, 2.4 Hz) 7.21-7.23 (d, 1H, J=8.2 Hz) 7.85-7.86 (d, 1H, J=3 Hz).

Step 43b. 3-acetoxy-6-bromopyridine.

To 25.6 mL of boron trifluoride etherate (208 mmol, Aldrich) cooled to -15°C under N_2 was added 18 g (104 mmol) of 3-amino-6-bromopyridine (from step 28a above) dissolved in 35mL of dimethoxyethane. Then *t*-Butyl nitrite (14.7 mL, 125 mmol, Aldrich) was added at a rate which kept the temperature below 0°C. Dimethoxyethane (65 mL) and methylene chloride (60 mL) were then added to aid stirring. After 10 minutes at -10°C the mixture was allowed to warm to 5°C and stirred for 30 min. Pentane (400 mL) was then added to the reaction mixture, the solid was collected by suction filtration, washed with cold ether, air dried, and dissolved in 125 mL of acetic anhydride. The resulting solution was heated to 100°C ± 5°C for 1 hour. The solvent was removed *in vacuo,* and the residue was suspended in saturated aqueous Na_2CO_3, and extracted with ethyl ether. The ether solution was dried over $MgSO_4$, the solvent was removed *in vacuo,* and the residue was chromatographed on silica gel, eluting with 100:0 to 60:40 hexane:ethyl acetate to give 13.6 g of the title compound. ^1H NMR ($CDCl_3$ 300 MHz) δ 8.20 (m, 1H).7.51 (d, J = 8.5 Hz 1H),7.38 (dd, J = 2.9, 7.5 Hz, 1H), 2.35 (s, 3H). MS (CI/NH_3) m/e: 216 $(M+H)^+$, 233 $(M+NH_4)^+$.

Step 43c. 2-Bromo-5-hydroxypyridine.

The product of Example 43b (12.8 g, 60 mmol was dissolved in 15% aqueous NaOH (50 mL) at 0°C, and the solution was allowed to warm to room temperature and stirred for 60 minutes. After complete consumption of the starting material the solution was

neutralized by addition of HCl. The aqueous mixture was extracted with ethyl acetate (3 X 200 mL). The organic extracts were washed with water (2 X 50 mL) and brine (4 X 50 mL), then dried ($MgSO_4$), and the solvent was evaporated to yield 9.8 g of the title compound. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.12-7.16 (dd, 1H, J=3.2 Hz),7.36-7.39 (d, 1H, J=8.5Hz), 8.04-8.05 (d, 1H, J=2.4 Hz). MS m/e: 174 $(M+H)^+$

Step 43d. 6-Bromo-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine

The product of Example 43c was coupled to 1-BOC-2-(S)-azetidinemethanol using the procedure described in Example 2a. ^1H NMR ($CDCl_3$, 300 MHz) : 1.42 (s, 9H), 2.20-2.43 (m, 2H), 4.88 (t, J=8.0 Hz, 2H), 4.17 (dd, J=3.0, 9.0 Hz, 1H), 4.30-4.39 (m, 1H), 4.43-4.58 (m,1H), 7.42 (t, J=2.0 Hz, 1H), 8.25-8.32 (m, 2H). MS (DCI/NH_3) m/e: 343 $(M+H)^+$, 360 $(M+NH_4)^+$.

Step 43e. 6-Cyano-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine

To the product of Example 43d (1.22g, 3.60mmol) in degassed DMF (10 mL) were added zinc cyanide (0.295 g, 2.50 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.249 g, 0.20mmol) and the mixture was heated at 80°C for 5 hours. The mixture was cooled to room temperature and poured into saturated sodium bicarbonate. The aqueous layer was extracted with EtOAc (400 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude product was chromatographed (silica gel; EtOAc/hexane 1/1) to afford a colorless oil (0.784 g, 75%).

^1H NMR ($CDCl_3$, 300 MHz) δ 1.42 (s, 9H), 2.22-2.42 (m, 2H), 3.82-3.87 (m, 2H), 3.18 (dd, J=3.0, 9.0 Hz, 1H), 4.38-4.45 (m, 1H), 4.48-4.60 (m, 1H), 7.32-7.58 (m, 1H), 7.62 (d, J=11.5 Hz, 1H), 8.42 (d, J=4.0 Hz, 1H). MS (DCI/NH_3) m/e: 290 $(M+H)^+$, 307 $(M+NH_4)^+$.

Step 43f. 6-Cyano-3-(2(S)-azetidinylmethoxy)pyridine hydrochloride

The product of Example 43e was deprotected and converted to the hydrochloride salt according to the procedure described in Example 2b. ^1H NMR ($CDCl_3$) δ 2.66-2.74 (m, 2H), 4.02-4.19 (m, 2H), 4.50 (d, 2H, J=4.4 Hz), 4.84-4.99 (m, 1H), 7.63 (dd, 1H, J=3.0, 11.5 Hz), 7.97 (d, 1H, J=8.8 Hz), 8.48 (d, 1H, J=3.0 Hz). MS (CI/NH3): m/z 190.00 $(M+H^+)$, 207.00 $(M+NH_4^+)$. Anal. Calcd. for $C_{10}H_{11}N_3O \cdot 1.0\ HCl \cdot 0.1\ Et_2O \cdot 0.1\ H_2O$: C, 53.18; H, 5.66; N, 17.89. Found: C, 53.07; H, 5.46; N, 17.87.

Example 44

5-cyano-3-(2-(S)-azetidinylmethoxy)pyridine hydrochloride

Step 44a. 3-Bromo-5-hydroxypyridine.

3-Benzyloxy-5-bromopyridine from Example 41a was heated at reflux with 48% HBr/HOAc (60 mL) for 16 hours. The reaction was quenched with excess $NaHCO_3$, the basic mixture was extracted with ethyl acetate, and the extract was dried over Na_2SO_4.

The solvent was removed, and the residue was chromatographed (silica gel; MeOH/CCl_4, 1/10) to afford the title compound. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.27 (d, J=1.8 Hz, 1H), 8.23 (d, J=2.6 Hz, 1H), 7.44 (dd, J=1.8, 2.6 Hz, 1H). MS (DCI/NH3) m/z 174, 176 $(M+H)^+$, 191, 193 $(M+NH_4)^+$.

Step 44b. 5-Bromo-3-(2-(1-BOC-2-(S)-azetidinyl)methoxy)pyridine

Triphenylphosphine (4.01 g, 15.3 mmol) and DEAD (2.43 mL, 15.3 mmol) were dissolved in 30 mL of THF at 0 °C, and the mixture was stirred for 10 minutes. Samples of 1-BOC-2-(S)-azetidinemethanol (2.86 g , 15.3 mmol) and the product of Example 44a (1.505 g, 10.2 mmol) were added, and the mixture was stirred for 40 hours at room temperature. The volatile components were removed under vacuum, and the residue was triturated with hexane. The separated hexane fraction was concentrated, and the residue was chromatographed on a silica gel column, eluting with hexane/ether (10:1 to 10:2) to afford the title compound as a colorless oil (1.669 g). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.42 (s, 9H), 2.31 (m, 2H), 3.89 (m, 2H), 4.12 (m, 1H), 4.322 (m, 1H), 4.52 (m, 1H), 7.43 (m, 1H), 8.29 (m, 2H). MS (CI/NH_3) m/z 344 $(M+H)^+$.

Step 44c. 5-Cyano-3-(2-(1-BOC-2-(S)-azetidinyl)methoxy)pyridine

The procedure of Example 43d was followed, replacing the product of Example 43c with the product of Example 44b. The crude product was chromatographed (silica gel; CH_2Cl_2/ MeOH/concd NH_4OH, 10:1:0.1) to afford 1.3 g (86%) of the title compound. ^1H NMR ($CDCl_3$, 300 MHz) : δ 1.42 (s, 9H), 2.23-2.43 (m, 2H), 3.85-3.87 (m, 2H), 3.18 (dd, J=3.0, 9.0 Hz, 1H), 3.35-3.42 (m, 1H), 4.48-4.58 (m, 1H), 7.45-7.50 (m, 1H), 8.50 (d, J=1.5 Hz, 1H), 8.55 (d, J=4.0 Hz, 1H).
MS (DCI/NH_3) m/e: 290 $(M+H)^+$, 307$(M+NH_4)^+$.

Step 44d. 5-Cyano-3-(2-(S)-azetidinylmethoxy)pyridine hydrochloride

The product of Example 44c was deprotected and converted to the hydrochloride salt according to the procedure described in Example 2b. ^1H NMR (D_2O) δ 2.63-2.78 (m, 2H), 4.03-4.22 (m, 2H), 4.48 (d, 2H, J=4.0 Hz), 4.95-5.03 (m, 1H), 7.90-7.95 (m, 1H), 8.58 (d, 1H, J=2.0 Hz), 8.62 (d, 1H, J=3.0 Hz). MS (CI/NH3): m/z 190.00 $(M+H^+)$, 207.00 $(M+NH_4^+)$. Anal. Calcd. for $C_{10}H_{11}N_3O$•1.1 HCl•0.10 H_2O: C, 51.97; H, 5.36; N, 18.18. Found: C, 52.11; H, 5.27; N, 17.95.

Example 45

5-Ethyl-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine hydrochloride

Step 45a. 5-Vinyl-6-chloro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine

To 5-bromo-6-chloro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine from Example 2a (1.00g, 2.65mmol) in toluene (30mL) was added tetrakis(triphenylphosphine) palladium (0) (93mg, 0.081mmo) and vinyltributyltin (0.93mL, 3.18mmol). The mixture was stirred

and heated at 95° C overnight, then the solvent was evaporated. The residue was chromatographed (silica gel; CH_2Cl_2/MeOH, 100:2) to afford an oil (720mg, 84%). ^1H NMR ($CDCl_3$, 300MHz) δ 1.42 (s, 9H), 2.33 (m, 2H), 3.89 (t, J=8.5 Hz, 2H), 4.14 (m, 1H), 4.36 (m, 1H), 4.52 (m, 1H), 5.50 (d, J=10.9 Hz, 1H), 5.80 (d, J=17 Hz, 1H), 6.98 (dd, J=17.6 Hz, J=11.2 Hz, 1H), 7.44 (d, J=2.7 Hz, 1H), 8.02 (d, J=2.7 Hz, 1H). MS (CI/NH_3) m/e: 325 $(M+H)^+$.

Step 45b. 5-Ethyl-6-chloro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine

The product from Example 45a (440 mg, 1.36 mmol) in MeOH (10mL) was stirred overnight under 1 atm of H_2 in the presence of 5% Pt-C (440mg). The mixture was filtered and the filtrate was concentrated to afford a colorless oil (219mg, 51%). NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, J=7.46Hz, 3H), 1.42 (s, 9H), 2.32 (m, 2H), 2.71 (q, J=7.5Hz, 2H), 3.89 (t, J=7.8 Hz, 2H), 4.12 (dd, J=3.0, 9.8 Hz, 1H), 4.30 (m, 1H), 4.50 (m, 1H), 7.16 (d, J=3.1 Hz, 1H), 7.94 (d, J=3.0 Hz, 1H). MS (CI/NH_3) m/z 327 $(M+H)^+$.

Step 45c. 5-Ethyl-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine hydrochloride

To the product from Example 45b (216 mg, 0.66 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added trifluoroacetic acid (1.8 mL). The solution was stirred and allowed to warm to room temperature, then adjusted to pH 11 with aqueous 10% NaOH, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated. The residue was chromatographed (silica gel; CH_2Cl_2/MeOH, 100:3 to 100:15) to afford an oil (60mg, 40%). NMR ($CDCl_3$, 300 MHz) δ 1.22(m 3H), 2.38 (m, 2H), 2.71 (q, J=7.5Hz, 2H), 3.57 (m, 1H), 3.80 (m, 1H), 4.08 (m, 2H), 4.38 (m, 1H), 7.15 (d, J=2.4 Hz, 1H), 7.92 (d, J=3.0 Hz, 1H). MS (CI/NH_3) m/e: 227 $(M+H)^+$. The free base was dissolved in THF and treated with 1 M HCl in Et_2O to afford the salt, which was triturated with Et_2O and dried under vacuum. mp 102-104 °C . ^1H NMR (D_2O) δ 1.24 (t, 3H, J=7.5 Hz), 2.71 (m, 4H), 4.11 (m, 2H), 4.42 (d, 2H, J=4 Hz), 4.95 (m, 1H), 7.51 (d, 1H, J=3 Hz), 8.00 (d, 1H, J=3 Hz). Anal. Calcd. for $C_{11}H_{15}N_2OCl \cdot 1.1$ HCl: C, 49.52; H, 6.08; N, 10.50. Found: C, 49.63; H, 5.89; N, 10.20.

Example 46

5-Ethyl-6-chloro-3-(2-(S)-pyrrolidinylmethoxy)pyridine hydrochloride

Step 46a. 5-Vinyl-6-chloro-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine

5-Bromo-6-chloro-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine from Example 4a (0.95 g, 2.4 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.14g, 0.12 mmol) were dissolved in toluene (50 mL) and the solution was purged with nitrogen gas for 5 minutes. Vinyl tributyltin (0.78 mL, 2.67 mmol) was added and the mixture was heated to 90°C for 1 day. The solvent was evaporated and the residue was chromatographed (silica gel; hexanes/EtOAc, 4:1) to provide 0.69 g (85%) of the title compound. TLC R_f 0.3 (4:1

hexanes/EtOAc). MS (DCI/NH3) m/z 339 $(M+H)^+$. Continued elution provided a minor amount of 5,6-divinyl-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine (0.044g, 5.5%). TLC R_f 0.25 (4:1 hexanes/EtOAc). MS (DCI/NH3) m/z 331 $(M+H)^+$.

Step 46b. 5-Ethyl-6-chloro-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine

A solution of the compound of Example 46a (0.33 g, 0.97 mmol) in MeOH (20 mL) was stirred under 1 atm of hydrogen in the presence of 10% Pd/C for 4 days. The mixture was filtered and the solvent was evaporated. The residue was chromatographed (silica gel ; hexanes/EtOAc , 4:1) to provide 0.24 g (72%) of the title compound. TLC R_f 0.5 (2:1 hexanes/EtOAc). MS (DCI/NH3) m/z 341 $(M+H)^+$.

Step 46c. 5-Ethyl-6-chloro-3-(2-(S)-pyrrolidinylmethoxy)pyridine hydrochloride

The product of example 46b (115 mg, 0.34 mmol) was treated with 4N HCl (10 mL) in dioxane at 0 °C. The solution was allowed to warm to ambient temperature for 30 minutes, then ether was added and the resulting solid was collected, rinsed with fresh ether and dried in vacuo to provide 85 mg (quantitative yield) of the title compound, mp 144-145 °C . $[\alpha]_D$ -4.5° (c 0.44, MeOH). ^1H NMR (CD_3OD) δ 1.26 (t, 3H, J=7 Hz), 2.03-2.27 (m, 3H), 2.34-2.44 (m, 1H), 2.77 (q, 2H, J=7 Hz), 3.06 (s, 3H), 3.72 (br s, 1H), 3.91 (br s, 1H), 4.32 (dd, 1H, J=7,11 Hz), 4.50 (dd, 1H, J=4,11 Hz), 7.49 (d, 1H, J=3 Hz), 8.03 (d, 1H, J=3 Hz). MS (CI/NH3): m/z 255 $(M+H^+)$. Anal. Calcd. for $C_{13}H_{19}ClN_2O \cdot HCl$: C, 53.62; H, 6.92; N, 9.62. Found: C, 53.58; H, 6.72; N, 9.51.

Example 47

5-Ethyl-6-chloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine hydrochloride

The product of Example 45b was treated with formalin (6 mL) and formic acid (3 mL) at 80°C for 4 hours. The mixture was cooled to ambient temperature and poured into saturated sodium bicarbonate solution. The solution was extracted with EtOAc, and the organic layer was washed with water and dried ($MgSO_4$). The solvent was evaporated and the crude product was dissolved in ether and treated with 1M HCl in ether (1 mL). The resulting solid was filtered and washed with fresh ether to provide 41 mg (0.14 mmol, 38%) of the title compound. An additional 44 mg (42%) of the product was recovered by similar treatment of the mother liquors. mp 188-9 °C . $[\alpha]_D$ +15° (c 0.3, MeOH). ^1H NMR (CD_3OD) δ 1.42 (t, 3H, J=7 Hz), 2.02-2.13 (m, 1H), 2.20-2.33 (m, 2H), 2.39-2.49 (m, 1H), 2.91 (q, 2H, J=7 Hz), 3.53 (bt, 2H, J=7 Hz), 4.15-4.25 (m, 1H), 4.34 (dd, 1H, J=8,10 Hz), 4.58 (dd, 1H, J=3,10 Hz), 7.62 (d, 1H, J=3 Hz), 8.13 (d, 1H, J=3 Hz). MS (CI/NH3): m/z 241 $(M+H^+)$. Anal. Calcd. for $C_{12}H_{17}ClN_2O \cdot 1.1$ HCl: C, 51.32; H, 6.50; N, 9.97. Found: C, 51.47; H, 6.45; N, 9.77.

Example 48

5-Ethyl-6-chloro-3-(2-(R)-pyrrolidinylmethoxy)pyridine hydrochloride

Step 48a. 5-Vinyl-6-chloro-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine

The procedure of Example 45a was followed, replacing the starting material 5-bromo-6-chloro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine with 5-bromo-6-chloro-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine from Example 7. Yield: 71%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.47 (s, 9H), 1.88 (m, 2H), 2.02 (m 2H), 3.40 (m, 2H), 4.00 (m, 1H), 4.18 (m, 2H), 5.50 (d, J=11.2 Hz, 1H), 5.85 (m, 1H), 6.98 (dd, J=10.8, 17.3 Hz, 1H), 7.58 (br s, 1H), 7.99 (d, J=3.0 Hz, 1H). MS (CI/NH_3) m/e: 339 $(M+H)^+$.

Step 48b. 5-Ethyl-6-chloro-3-(1-BOC-2-(R)-methoxy)pyridine

The product of Example 48a was treated under the conditions of Example 45b. Yield: 57%. NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, J=7.5 Hz, 3H), 1.47 (s, 9H), 1.88 (m, 2H), 2.02 (m, 2H), 2.69 (q, J=7.5 Hz, 2H), 3.38 (m, 2H), 3.90 (m, 1H), 4.15 (m, 2H), 7.17 (m, 1H), 7.92 (d, J=2.4 Hz, 1H). MS (CI/NH_3) m/e: 341 $(M+H)^+$.

Step 48c. 5-Ethyl-6-chloro-3-(2-(R)-pyrrolidinylmethoxy)pyridine hydrochloride

The product of Example 48b was treated under the conditions of Example 45c. Yield of free base: 100%. ^{1}H NMR ($CDCl_3$, 300MHz) δ 1.22 (t, J=7.5 Hz, 3H), 1.85 (m, 1H), 2.04 (m, 2H), 2.15 (m, 1H), 2.68 (q, J=7.4 Hz, 2H), 3.19 (m, 2H), 3.84 (m, 1H), 4.11 (m, 2H), 7.12 (d, J=3.0 Hz, 1H), 7.89 (d, J=2.7 Hz, 1H). MS (CI/NH_3) m/z : 241 $(M+H)^+$. The free base was converted to the hydrochloride salt as described in Example 45c: mp 185-187 °C. ^{1}H NMR (D_2O) δ 1.23 (t, 3H, J=7.5 Hz), 1.95 (m, 1H), 2.13 (m, 2H), 2.74 (q, 2H, J=7.5 Hz), 3.43 (t, 2H, J=7.2 Hz), 4.12 (m, 1H), 4.24 (dd, 2H, J=7.8, 10.5 Hz), 4.46 (dd, 1H, J=3.4, 10.5 Hz), 7.45 (d, 1H, J=3.0 Hz), 7.94 (d, 1H, J=3.0 Hz). MS (CI/NH3): m/z 241 $(M+H^+)$, 258 $(M+NH_4^+)$. Anal. Calcd. for $C_{12}H_{17}N_2OCl \cdot HCl$: C, 52.00; H, 6.55; N, 10.11. Found: C, 51.73; H, 6.44; N, 9.82.

Example 49

5-Cyano-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine hydrochloride

Step 49a. 5-Cyano-6-chloro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine

The procedure of Example 43d was followed, replacing the product of Example 43c with 5-Bromo-6-chloro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine from Example 2 . The crude product was chromatographed (silica gel; CH_2Cl_2/ MeOH/concd NH_4OH, 10:1:0.1) to afford 0.61 g (39%) of the title compound: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.41 (s, 9H), 2.01-2.23 (m, 2H), 3.78-3.95 (m, 2H), 4.17 (dd, J=3.0, 11.0 Hz, 1H), 4.35-4.45 (m, 1H), 4.47-4.58 (m, 1H), 7.58 (d, J = 5.0 Hz, 1H), 8.35 (d, J = 3.5 Hz, 1H). MS (DCI/NH_3) m/e: 324 $(M+H)^+$, 341 $(M+NH_4)^+$.

Step 49b. 5-Cyano-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine hydrochloride

The product of Example 49a was deprotected and converted to the hydrochloride salt according to the procedure of Example 2b. ^{1}H NMR (D_2O) δ 2.65-2.73 (m, 2H), 4.02-4.20 (m, 2H), 4.46 (d, 1H, J=6.0 Hz), 4.93-4.99 (m, 1H), 8.00 (d, 1H, J=3.0 Hz), 8.42 (d, 2H, J=3 Hz). MS (CI/NH3): m/z 224 ($M+H^+$), 241 ($M+NH_4^+$). Anal. Calcd. for $C_{10}H_{10}N_3OCl$• HCl: C, 46.17; H, 4.26; N, 16.15. Found: C, 46.28; H, 4.18; N, 15.93.

Example 50

5-Cyano-6-chloro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine hydrochloride

To the product of Example 49b (0.160 g, 0.70mmol) were added H_2O (5.0 mL), HOAc (0.75 mL), formalin (2.25 mL) and $NaCNBH_3$ (0.132 g, 2.10 mmol) and the mixture was stirred at room temperature for 1 hour. The reaction was basified with 15% NaOH and the aqueous solution was extracted with CH_2Cl_2 (250 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude material was chromatographed (silica gel; MeOH/CH_2Cl_2, 9/1) to afford a colorless oil (0.089g, 53%). Treatment with hydrogen chloride in ether afforded the hydrochloride as a white solid. ^{1}H NMR (D_2O) δ 2.57-2.78 (m, 2H), 3.0 (s, 3H), 3.83-4.12 (m, 1H), 4.19-4.36 (m, 1H), 4.43-4.60 (m, 2H), 4.78-4.90 (m, 1H), 8.01 (d, 1H, J=6.0 Hz), 8.22 (d, 1H, J=3.0 Hz). MS (DCI/NH3): m/z 238.00 ($M+H^+$). for $C_{11}H_{12}N_3OCl$•HCl•0.2 H2O: C, 47.53; H, 4.81; N, 15.18. Found: C, 47.57; H, 4.86; N, 15.13.

Example 51

5-Carbamoyl-6-chloro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine hydrochloride

Step 51a. 5-Carbamoyl-6-chloro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine

To the product of Example 49a (0.535 g, 1.70 mmol) were added 30% H_2O_2 (0.6347mL, 5.50mmol) and 6N NaOH (0.670mL, 4.0mmol) and the mixture was stirred at room temperature for 45 minutes. The mixture was then heated at 45°C for 75 minutes, cooled to room temperature, and poured into 15% NaOH. The aqueous solution was extracted with CH_2Cl_2 (250 mL), and the combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude material was chromatographed (silica gel; EtOAc/hexane, 1:2) to afford a colorless oil (0.414 g, 72%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.42 (s, 9H), 2.28-2.36 (m, 2H), 3.86-3,91 (m, 2H), 4.37-4.42 (m, 1H), 4.50-4.59 (m, 1H), 7.84 (d, J=3.4 Hz, 1H), 8.22 (d, J=3.0 Hz, 1H). MS (DCI/NH_3) m/e: 342, $(M+H)^+$, 359, $(M+NH_4)^+$.

Step 51b. 5-Carbamoyl-6-chloro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine hydrochloride.

The product of Example 51a was treated as in Example 2b to afford the title compound as a hygroscopic oil. ^{1}H NMR (CD_3OD) δ 2.50-2.65 (m, 2H), 3.91-3.99 (m, 2H), 4.35-4.40 (m, 2H), 4.70-4.80 (m, 1H), 7.62 (d, 1H, J=5.0 Hz), 8.22 (d, 1H, J=5.0 Hz). MS (APCI): m/z 242.00 $(M+H^+)$. Anal. Calcd. for $C_{10}H_{12}N_3O_2Cl \cdot 1.5\ HCl \cdot 0.2\ Et_2O$: C, 41.68; H, 5.02; N, 13.50. Found: C, 41.71; H, 5.04; N, 13.54.

Example 52

5-bromo-6-methyl-3-(2-(S)-azetidinylmethoxy)pyridine hydrochloride

Step 52a. 3-bromo-2-methyl-5-nitropyridine

3-Bromo-2-chloro-5-nitropyridine (25 g, 105 mmol; prepared from 2-hydroxy-5-nitropyridine according to the procedure of V. Koch and S. Schnatterer, *Synthesis* **1990**, 499-501) was treated with the sodium salt of diethylmalonate (17.6 mL, 116 mmol) according to the procedure of Odashima *et al.*, *Bull. Chem. Soc. Jpn.*, **1993**, 66: 797-803) to provide 17.1 g (78.8 mmol, 75%) of a dark red oil. TLC Rf 0.5 (4:1 hexanes/EtOAc). ^{1}H NMR (CDCl3, 300 MHz) δ 2.81 (s, 3H), 8.61 (d, 1H, J=2Hz), 9.26 (d, 1H, J=2Hz).

Step 52b. 5-amino-3-bromo-2-methylpyridine

The compound of Example 52a (17.1g, 78.8 mmol) was dissolved in HOAc (50 mL) and water (150 mL) and treated with iron powder (13.3 g, 236 mmol) added in portions over 2 hours. The mixture was filtered and the filter cake was washed with EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic fractions were washed with 1M sodium bicarbonate and water, then dried ($MgSO_4$) and concentrated to afford 12.65 g (86%) of the title compound. TLC R_f 0.25 (2:1 hexanes/EtOAc). MS (DCI/NH3) m/z 187 $(M+H)^+$, 204 $(M+NH_4)^+$.

Step 52c 5-Acetoxy-3-bromo-2-methylpyridine

The compound of Example 52b (12.6 g, 67 mmol) was treated with t-butyl nitrite and $BF_3 \cdot OEt_2$ followed by acetic anhydride according to the procedure of Example 43b. The crude product was chromatographed (silica gel; hexanes/EtOAc, 4:1) to afford the title compound (12.0 g, 58%). TLC Rf 0.5 (2:1 hexanes/EtOAc). MS (DCI/NH3) m/z 230 $(M+H)^+$, 188.

Step 52d. 3-bromo-5-hydroxy-2-methylpyridine

The product of Example 52c was stirred with 15% NaOH (75 mL) at 0 °C and then allowed to warm to ambient temperature. After 1 hour, the mixture was acidified with 6N HCl with cooling, and the resulting suspension was extracted with EtOAc. The EtOAc was washed with H_2O, dried ($MgSO_4$) and concentrated to provide 7.0 g (95%) of the title

compound. TLC R_f 0.25 (2:1 hexanes/EtOAc). ^1H NMR ($CDCl_3$, 300 MHz) δ 2.59 (s, 3H), 7.46 (d, 1H, J=2Hz), 8.10 (d, 1H, J=2Hz). MS (DCI/NH3) m/z 188 $(M+H)^+$, 207 $(M+NH_4)^+$.

Step 52e. 5-bromo-6-methyl-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine

Triphenylphosphine (6.3 g, 24 mmol) was dissolved in THF (100 mL), cooled to 0°C and treated with DEAD (3.8 mL, 24 mmol) for 15 minutes. Then the compound of Example 52d (3g, 16 mmol) and 1-BOC-2-(S)-azetidinemethanol(3.4 g, 18 mmol) were added, and the mixture was allowed to warm slowly to ambient temperature. After 3 days, the solvent was evaporated and the residue was chromatographed (silica gel; hexanes/EtOAc, 4:1) to provide the title compound as an oil, contaminated with byproduct derived from DEAD reagent. For the title compound: TLC R_f 0.6 (1:1 hexanes/EtOAc). MS (DCI/NH_3) m/z 357 $(M+H)^+$, 279.

Step 52f. 5-bromo-6-methyl-3-(2-(S)-azetidinylmethoxy)pyridine hydrochloride

The product of example 52e (0.4 g, 1.12 mmol) was dissolved in methylene chloride (4 mL) and treated with TFA (2 mL) at 0°C for 1 hour. The solution was concentrated, and the residue was mixed with saturated bicarbonate and extracted with methylene chloride. The combined organic layers were washed with H_2O, and dried ($MgSO_4$). Evaporation of the solvent provided 0.25 g (76%) of neutral product., which was dissolved in ether and treated with 1N HCl in ether. The resulting solid was collected and washed with fresh ether to provide 151 mg (41%) of the title compound: mp 153-155 °C; $[\alpha]_D$ -7.4 (c 0.54, MeOH); ^1H NMR (CD_3OD) δ 2.63-2.76 (m, 2H), 2.78 (s, 3H), 4.04-4.18 (m, 2H), 4.50-4.63 (m, 2H), 4.88-4.96 (m, 1H), 8.50 (d, 1H, J=2 Hz), 8.10 (d, 1H, J=2 Hz); MS (CI/NH3): m/z 257 $(M+H^+)$, 274 $(M+NH_4^+)$; Anal. Calcd. for $C_{10}H_{13}N_2OBr \cdot 2.0$ HCl: C, 36.39; H, 4.58; N, 8.49. Found: C, 36.31; H, 4.66; N, 8.41.

Example 53

5-nitro-3-(2-(S)-azetidinylmethoxy)pyridine hydrochloride

Step 53a. 5-nitro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine

1-BOC-2-(S)-azetidinylmethanol (868 mg, 4.64 mmol) and 3-hydroxy-5-nitropyridine from Example 41d (500 mg, 3.57 mmol) were coupled according the procedure of Example 2a. Solvent was removed, and the residue was chromatographed (silica gel, hexane/ethyl acetate, 5:1) to afford the title compound (800 mg, 73%). ^1H NMR ($CHCl_3$, 300 MHz) δ 1.45 (s, 9H), 2.56 (m, 2H), 4.52 (m, 4H), 4.82 (m, 1H), 8.25 (t, J = 3 Hz, 1H), 8.65 (d, J = 3 Hz, 1H), 9.05 (d, J = 3 Hz, 1H). MS (DCI/NH_3) m/z 310 $(M+H)^+$.

Step 53b. 5-nitro-3-(2-(S)-azetidinylmethoxy)pyridine hydrochloride

To the product of Example 53a (800 mg, 2.58 mmol) in methylene chloride at 0°C was added HCl/Et_2O and the solution was stirred for 1 h. Solvent was removed and the residue was recrystallized from EtOH/Et_2O to afford the title compound (750 mg): mp 162-164 °C (dec). ^1H NMR (D_2O, 300 MHz) δ 2.45 (m, 2H), 4.62 (m, 4H), 4.96 (m, 1H), 8.26 (t, J = 3 Hz, 1H), 8.75 (d, J = 3 Hz, 1H), 9.25 (d, J = 3 Hz, 1H). MS (APCI) m/z 210 $(M+H)^+$. Anal. Calcd. for $C_9H_{12}ClN_3O_3 \cdot 0.30$ HCl: C, 42.13; H, 4.83; N, 16.38. Found: C, 42.28; H, 4.87; N, 16.24.

Example 54

5-nitro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine hydrochloride

The product of Example 53b (200 mg, 0.956 mmol) was treated according to the procedure of Example 14. The mixture was then acidified to pH=1 with HCl, and extracted with ether. The aqueous layer was made basic with 15% NaOH, and this solution was extracted with methylene chloride. The extract was dried ($MgSO_4$), filtered, and concentrated in vacuo. The reside was purified (silica gel; $CHCl_3$:MeOH, 98:2) to afford the pure free base (168 mg, 78%). The free base was converted to the salt by treatment with saturated HCl in ether to give the title compound.

Example 55

6-Fluoro-5-methyl-3-(2-(S)-azetidinylmethoxy)pyridine hydrochloride

Step 55a. 2-fluoro-3-methyl-5-nitropyridine

2-Chloro-3-methyl-5-nitropyridine (15 g, 86.9 mmol; from Maybridge Chemical Co.), KF (12 g, 258 mmol), and tetraphenylphosphonium bromide (20 g, 47.7 mmol) were combined in 200 mL of acetonitrile and heated at reflux for 4 days. The mixture was diluted with Et_2O (500 mL), filtered, and the solution was concentrated. The residue was triturated with hot hexane (4 x 200 mL), then the combined hexane solutions were concentrated to give 8.4 g (60%) of the title compound. ^1H NMR (DMSO-d_6, 300 MHz) δ 8.95 (dd, J= 1.6 Hz, 1H), 8.43 (m, 1H), 2.42 (s, 1H). MS (DCI/NH_3) m/z 157 $(M+H)^+$.

Step 55b. 3-Amino-6-fluoro-5-methylpyridine

2-fluoro-3-methyl-5-nitropyridine was combined with 100 mg of 5% Pd/C in EtOH (100 mL) and the mixture was stirred under a H_2 atmosphere for 16 hours. The mixture was filtered and concentrated. The crude product was chromatographed (silica gel; $CHCl_3$/MeOH, 99:1 to 94:6) to yield 5.2 g (78%) of the title compound. ^1H NMR (DMSO-d_6, 300 MHz) δ 7.26 (t, J= 2.7 Hz, 1H), 6.95 (dd, J= 8.1 Hz, 1H), 5.11 (br, s, 2H), 2.10 (s, 3H) . MS (DCI/NH_3) m/z 127 $(M+H)^+$, 144 $(M+NH_4)^+$.

Step 55c. 3-acetoxy-6-fluoro-5-methylpyridine

To boron trifluoride etherate (10 mL, 81 mmol) at -15°C under N_2 was added the product of step 55b (5.1g, 40 mmol) in DME (30 mL). *t*-Butyl nitrite (5.5 mL, 46 mmol, Aldrich) was added at a such a rate that the temperature remained below 0 °C. Additional DME (25 mL) was then added. After 10 minutes at -10°C the reaction was allowed to warm to 5°C and stirred for 30 min. Pentane (400 mL) was then added to the reaction mixture, the solid was collected by suction filtration, washed with cold ether, air dried, and dissolved in 100 mL acetic anhydride. The resulting solution was heated to 77° C ± 5°C for 1 hour. The solvent was removed *in vacuo,* and the residue was suspended in saturated aqueous Na_2CO_3 (200 mL) and extracted with ethyl ether (2 x150). The ether solution was dried ($MgSO_4$) and concentrated The crude product was chromatographed (silica gel; hexane/EtOAc 9:1 to 7:3) yield 3.62g (53%) of the title compound. MS m/e: 170 $(M+H)^+$, 187 $(M+NH_4)^+$. ^1H NMR ($CDCl_3$ 300 MHz) δ 7.8 (m, 1H) 7.34 (m, 1H), 2.32 (s, 3H), 2.29 (s, 3H).

Step 55d. 2-Fluoro-5-hydroxy-3-methylpyridine

The product of step 55c (3.6 g, 21.3 mmol) was dissolved in 20% aqueous NaOH (25 mL). After complete consumption of the starting material the solution was neutralized by addition of HCl. The aqueous mixture was extracted with ethyl acetate (2 X 150 mL). The organic extracts were dried (MgSO4), and the solvent was evaporated. The crude product was triturated with hexane to yield 2.35 g (86.9%) of the title compound. MS m/e: 128 $(M+H)^+$, 145 $(M+NH_4)^+$.; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.61(t, 1H, J=2.2 Hz), 7.17 (m, 1 Hz), 2.25 (s, 3H)

Step 55e. 6-Fluoro-5-methyl-3-(1-Cbz-2-(S)-azetidinylmethoxy)pyridine

The procedure of example 2a was followed, substituting 2-fluoro-5-hydroxy-3-methylpyridine and 1-Cbz-2-(S)-azetidinemethanol for 5-bromo-9-chloropyridine-3-ol and 1-BOC-2-(S)-azetidinemethanol, respectively. Yield 60 %. MS (DCI/NH_3) m/z 331 $(M+H)^+$, 348 $(M+NH_4)^+$ ^1H NMR ($CDCl_3$ 300 MHz) : 7.63 (br s, 1H), 7.29 (m, 5H), 7.18 (br s, 1H), 5.05 (m, 2H), 4.59 (m, 1H), 4.3 (br s, 1H), 4.09 (m, 1H), 3.99 (m, 1H), 2.26-2.05 (m, 2H), 2.05 (s, 3H).

Step 55f. 6-Fluoro-5-methyl-3-(2-(S)-azetidinylmethoxy)pyridine benzoate

The procedure of example 39c was followed, substituting 6-fluoro-5-methyl-3-(1-Cbz-2-(S)-azetidinylmethoxy)pyridine for 2-fluoro-3-(1-Cbz-2-(S)-azetidinylmethoxy)pyridine, and benzoic acid for HCl, resulting in a 53% yield of the title compound as an off-white solid: mp 104-108 °C; $[\alpha]_D$ -5.545 (c 0.55, MeOH); ^1H NMR (DMSO) δ 7.90(m, 2H), 7.70 (s, 1H), 7.51-7.48 (m, 2H), 7.42-7.39 (t, 2H, J=7.2 Hz), 4.27(m, 1H), 4.17(dd, 1H, J=7.3, 10.4 Hz), 4.08 (dd, 1H, J=4.9, 10.4 Hz), 3.79 (m, 1H), 3.47 (m, 1H), 2.35 (m, 1H), 2.19 (s, 3H), 2.16 (m, 1H). MS (DCI/NH3): m/z 197

(M+H$^+$), 214 (M+NH4$^+$). Anal. Calcd. for $C_{10}H_{13}N_2OF \cdot C_7H_6O_2$: C, 64.14; H, 6.02; N, 8.80. Found: C, 63.90; H, 6.10; N, 8.70.

Example 56

6-Chloro-5-methyl-3-(2-(S)-azetidinylmethoxy)pyridine hydrochloride

Step 56a. 3-Amino-6-chloro-5-methylpyridine

2-Chloro-3-methyl-5-nitropyridine (3.2 g, 18.5 mmol; from Maybridge Chemical Co.) was dissolved in a mechanically stirred solution of H_2O/HOAc (60 mL, 5:1). Iron powder was added over a 5 h period, maintaining the temperature below 40°C, and stirring was continued until TLC showed consumption of starting material. The reaction mixture was filtered through filter aid and the filter cake was washed with EtOAc. The aqueous filtrate was extracted with EtOAc and the combined organic fractions were washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated. The residue was chromatographed (silica gel; $CHCl_3$/MeOH, 98:2) to afford an orange solid (2.34 g, 89%). MS (DCI/NH_3) m/e: 143 (M+H)$^+$. NMR (DMSO-*d*6, 300 MHz) δ 2.17 (s, 3H), 5.40 (br s, 2H), 6.90 (d, J=2.2 Hz, 1H), 7.54 (d, J=2.2 Hz, 1H).

Step 56b. 6-Chloro-5-methyl-3-(2-(S)-azetidinylmethoxy)pyridine benzoate

Starting with the product of Example 56a in place of 3-amino-6-fluoro-5-methylpyridine, the procedures of Examples 55c-55f are followed to prepare the title compound.

Example 57

5-Bromo-6-fluoro-3-(2-(S)-azetidinylmethoxy)pyridine hydrochloride

Step 57a. 3-Bromo-2-(4-nitrophenylazo)-5-hydroxypyridine

5-Bromo-3-pyridinol from Example 44a (8.7 g, 0.05 mmol) and KOH (1.1 g, 19.6 mmol) were dissolved in water (200 mL). A suspension of p-nitrobenzenediazonium tetrafluoroborate (11.84 g, 0.5 mol, prepared as described in *J. Org. Chem.*, 44: 1572-15783 (**1979**)) was added. The reaction was stirred for 1 hour, diluted with acetic acid (50 mL) and filtered. The crude product was allowed to air dry, then it was chromatographed (silica gel, eluting with chloroform/methanol 95:5-90:10) to provide the title compound (5.45 g, 33.7 % yield). MS (DCI/NH_3) m/z 323, 325 (M+H)$^+$. NMR (DMSO-*d*6, 300 MHz) δ 8.48-8.43 (m, 2H), 8.21 (d, J=2.4 Hz, 1H), 8.09-8.06 (m, 2H), 7.72 (d, J=2.4 Hz, 1H).

Step 57b. 2-Amino-3-bromo-5-hydroxypyridine

The compound from step 57a above (5.0 g, 15.8 mmol) and tin chloride (25 g, 111 mmol) were suspended in conc. HCl and ethanol (150 mL), and the mixture was heated at reflux for 1 hour. The mixture was cooled to 0°C, then filtered. The filtrate was neutralized with sodium bicarbonate (180 g) and extracted with ethyl acetate (4 x 200 mL).

The extracts were washed with brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed (silica gel, eluting with chloroform/methanol/NH_4OH 95:5:0.5-90:10:1) to afford the title compound (3.3 g, 33.7 % yield). MS (DCI/NH_3) m/z 189, 191 $(M+H)^+$. NMR (DMSO-d_6, 300 MHz) δ 7.57 (d, J=2.6 Hz, 1H), 7.43 (d, J=2.6 Hz, 1H).

Step 57c. 3-Bromo-2-fluoro-5-hydroxypyridine

The compound from step 57b (3.0 g, 15.9 mmol) was dissolved in HF•pyridine (50 mL). The solution was cooled to 0°C and stirred under nitrogen, then sodium nitrite (1.09 g, 15.8 mmol) was added in portions over 20 minutes. The mixture was heated to 50°C for 1 hour, cooled to 0°C and basified with 20% NaOH. The aqueous phase was washed with methylene chloride (5 x 100 mL), neutralized with HCl, and extracted with ethyl acetate (5 x 100 mL). The extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*, yielding the title compound as a tan solid. MS (DCI/NH_3) m/z 192, 194 $(M+H)^+$. NMR (DMSO-d_6, 300 MHz) δ 9.38 (d, J=2.6 Hz, 1H), 9.20 (d, J=2.6 Hz, 1H).

Step 57d. 5-Bromo-6-fluoro-3-(2-(S)-azetidinylmethoxy)pyridine hydrochloride

Following the procedures of Example 2a-b, except substituting the product from step 57c for the 5-bromo-6-chloropyridinol-3-ol thereof, the title compound is prepared.

Example 58

5-methoxy-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine hydrochloride

Step 58a. 3-bromo-5-methoxypyridine

To a suspension of 12 g of 3,5-dibromopyridine and 40 g of 60% NaH in DMF was added 4.05 mL of methanol, and the reaction mixture was stirred for 4 hours at room temperature and 1 hour at 60°C. The DMF was removed under reduced pressure, and the product was isolated following extractive work-up. MS (DCI/NH_3) m/z 188/190 $(M+H)^+$, 205/207 $(M+NH_4)^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.32 (d, J=1.8 Hz, 1H), 8.27 (d, J=2.6 Hz, 1H), 7.42 (dd, J=1.8, 2.6 Hz, 1H), 3.88 (s, 3H)

Step 58b. 3-amino-5-methoxypyridine

Treating the compound of step 58a according to the procedure of Example 41b, the title compound is prepared.

Step 58c. 3-hydroxy-5-methoxypyridine

Treating the compound of step 58b according to the procedures of Examples 55b and 55c, the title compound is prepared.

Step 58d. 2-amino-5-hydroxy-3-methyoxypyridine

Treating the compound of step 58c according to the procedures of Examples 57a and 57b, the title compound is prepared.

Step 58e. 2-chloro-5-hydroxy-3-methyoxypyridine

Treating the compound of step 58d with $NaNO_2$ and HCl according to standard procedures, the title compound is prepared

Step 58f. 5-methoxy-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine hydrochloride

Following the procedures of Examples 2a-b, except substituting the product from step 58e for the 5-bromo-6-chloropyridin-3-ol thereof, the title compound is prepared.

Example 59

5-ethoxy-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine hydrochloride

Following the procedures of Example 58, except substituting ethanol for the methanol reagent in Example 58a, the title compound is prepared.

Example 60

5-nitro-6-methyl-3-(2-(S)-azetidinylmethoxy)pyridine hydrochloride

Step 60a. 3-benzyloxy-5-bromo-6-methylpyridine

The hydroxy compound from Ex 44a is treated with 1 equivalent of sodium hydride in THF, followed by treatment with benzyl bromide to afford the title compound.

Step 60b. 3-benzyloxy-5-amino-6-methylpyridine

Treating the compound of step 60a according to the procedure of Example 41b, the title compound is prepared.

Step 60c. 3-amino-5-hydroxy-6-methylpyridine

Treating the compound of step 60b according to the procedure of Example 41c, the title compound is prepared.

Step 60d. 3-hydroxy-5-nitro-6-methylpyridine

Treating the compound of step 60a according to the procedure of Example 41d, the title compound is prepared.

Step 60e. 5-nitro-6-methyl-3-(2-(S)-azetidinylmethoxy)pyridine hydrochloride

Following the procedures of Examples 2a-b, except substituting the product from step 60d for the 5-bromo-6-chloropyridin-3-ol thereof, the title compound is prepared.

Example 61

5,6-dimethyl-3-(2-(S)-azetidinylmethoxy)pyridine hydrochloride

Step 61a. 2,3-dimethyl-5-nitropyridine

2-Chloro-3-methyl-5-nitropyridine (from Maybridge Chemical Co.) is treated according to the procedure of Ex. 52a to afford the title compound.

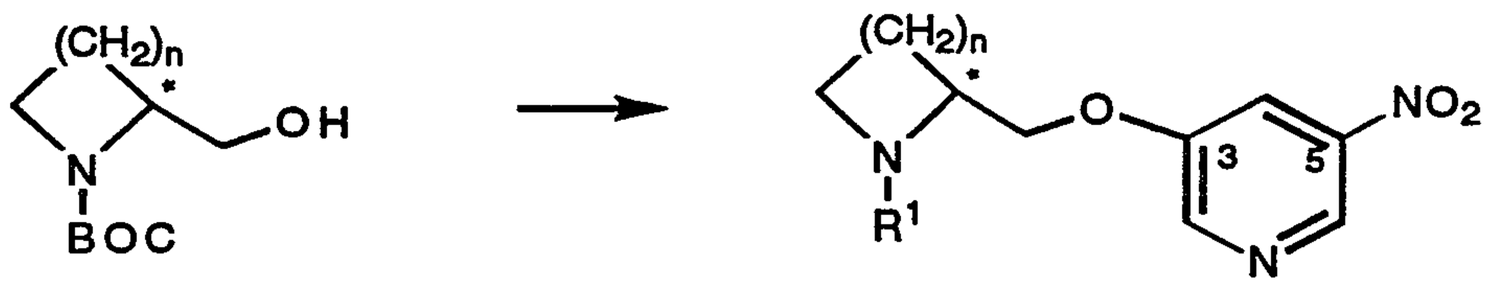
Step 61b. 5,6-dimethyl-3-(2-(S)-azetidinylmethoxy)pyridine hydrochloride

Following the procedures of Examples 2a-b, except substituting the product from step 61a for the 5-bromo-6-chloropyridin-3-ol thereof, the title compound is prepared.

Examples 62-66

Following the procedures of Example 2a-b, except substituting the 3-hydroxy-5-nitropyridine prepared in Example 41d for the 5-bromo-6-chloropyridin-3-ol in step 2a, and substituting the starting material indicated in the Table 2 below for the 1-BOC-2-(S)-azetidinemethanol in step 2a the compounds of examples 62-63 are prepared. Following the procedures of Examples 2 and 3, except substituting the 3-hydroxy-5-nitropyridine prepared in Example 41d for the 5-bromo-6-chloropyridin-3-ol in step 2a, and substituting the starting material indicated in the table below for the 1-BOC-2-(S)-azetidinemethanol in step 2a, the HCl salts of the compounds of examples 64-66 are prepared.

Table 2



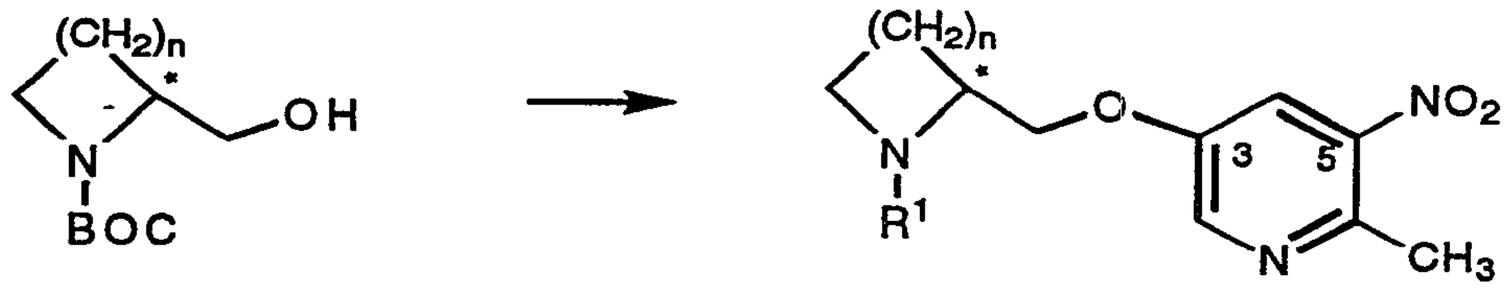
Ex. No.	Starting Material	Product
62	1-BOC-2-(R)-azetidinemethanol	5-nitro-3-(2-(R)-azetidinylmethoxy)pyridine
63	1-BOC-2-(R)-pyrrolidinemethanol	5-nitro-3-(2-(R)-pyrrolidinylmethoxy)pyridine
64	1-BOC-2-(R)-azetidinemethanol	5-nitro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine
65	1-BOC-(R)-pyrrolidinemethanol	5-nitro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine

Examples 66-72

Following the procedures of Example 2a-b, except substituting the 3-hydroxy-5-nitro-6-methylpyridine prepared in Example 60d for the 5-bromo-6-chloropyridin-3-ol in step 2a, and substituting the starting material indicated in the Table 3 below for the 1-BOC-2-(S)-azetidinemethanol in step 2a the compounds of examples 66-68 are prepared.

Following the procedures of Examples 2 and 3, except substituting the 3-hydroxy-5-nitro-6-methylpyridine prepared in Example 60d for the 5-bromo-6-chloropyridin-3-ol in step 2a, and substituting the starting material indicated in the table below for the 1-BOC-2-(S)-azetidinemethanol in step 2a, the HCl salts of the compounds of examples 69-72 are prepared.

Table 3

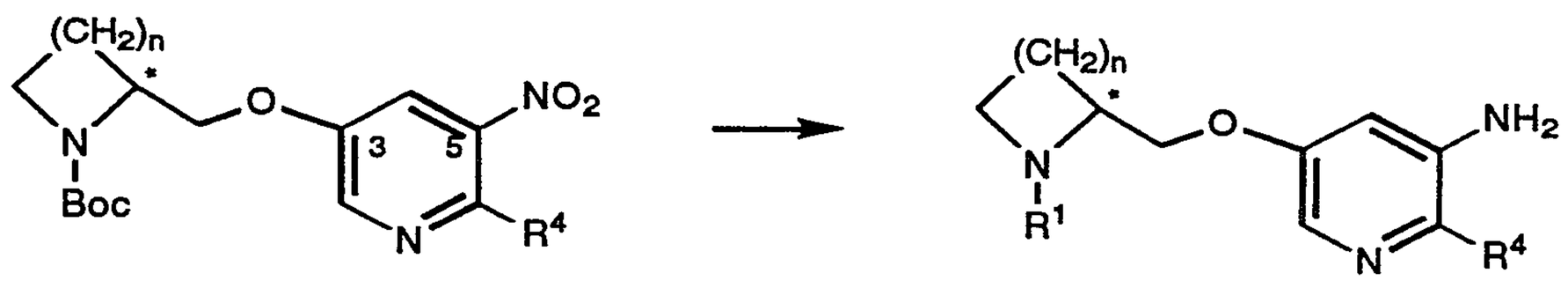


Ex. No.	Starting Material	Product
66	1-BOC-2-(R)-azetidinemethanol	5-nitro-6-methyl-3-(2-(R)-azetidinylmethoxy)pyridine
67	1-BOC-2-(S)-pyrrolidinemethanol	5-nitro-6-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine
68	1-BOC-2-(R)-pyrrolidinemethanol	5-nitro-6-methyl-3-(2-(R)-pyrrolidinylmethoxy)pyridine
69	1-BOC-2-(S)-azetidinemethanol	5-nitro-6-methyl-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine
70	1-BOC-2-(R)-azetidinemethanol	5-nitro-6-methyl-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine
71	1-BOC-(S)-pyrrolidinemethanol	5-nitro-6-methyl-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine
72	1-BOC-(R)-pyrrolidinemethanol	5-nitro-6-methyl-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine

Examples 73-87

In the following Examples, the starting materials (from Examples 41, 53, 60, and 62-72, as appropriate) are stirred under an atmosphere of hydrogen in the presence of 10% palladium on carbon and the progress of the reaction is monitored by TLC. When consumption of starting material is complete, the mixture is filtered, and the filtrate is concentrated. The residue is subjected to BOC deprotection under acidic conditions and isolation and salt formation as in Example 2b. Products with R^1 = methyl are obtained by treating the starting material under the conditions of Example 2b and 3 prior to conducting the above-described hydrogenation step.

Table 4



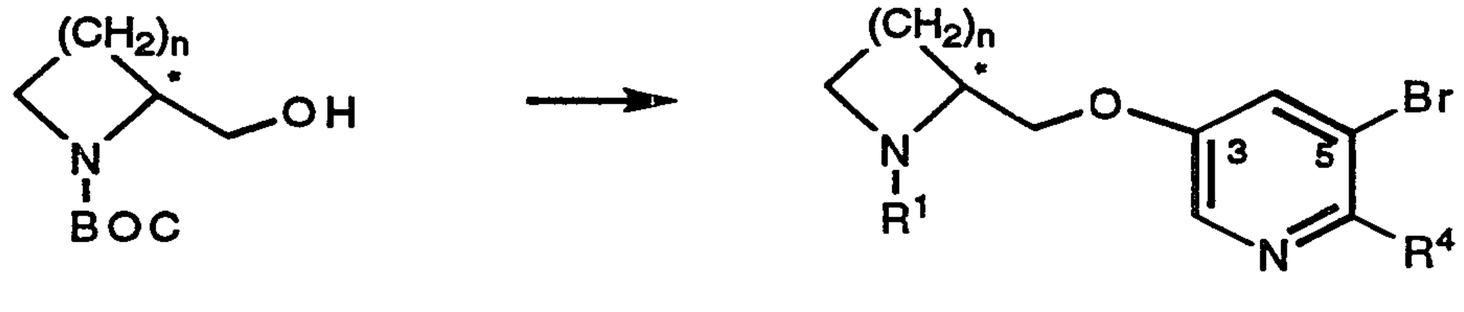
Ex. No.	Starting material	Product
73	5-nitro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine	5-amino-(2-(S)-azetidinylmethoxy)pyridine
74	5-nitro-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine	5-amino-3-(2-(R)-azetidinylmethoxy)pyridine
75	5-nitro-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine	5-amino-3-(2-(S)-pyrrolidinylmethoxy)pyridine
76	5-nitro-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine	5-amino-3-(2-(R)-pyrrolidinylmethoxy)pyridine
77	5-nitro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine	5-amino-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine
78	5-nitro-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine	5-amino-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine
79	5-nitro-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine	5-amino-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine
80	5-nitro-6-methyl-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine	5-amino-6-methyl-3-(2-(S)-azetidinylmethoxy)pyridine

81	5-nitro-6-methyl-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine	5-amino-6-methyl-3-(2-(R)-azetidinylmethoxy)pyridine
82	5-nitro-6-methyl-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine	5-amino-6-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine
83	5-nitro-6-methyl-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine	5-amino-6-methyl-3-(2-(R)-pyrrolidinylmethoxy)pyridine
84	5-nitro-6-methyl-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine	5-amino-6-methyl-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine
85	5-nitro-6-methyl-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine	5-amino-6-methyl-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine
86	5-nitro-6-methyl-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine	5-amino-6-methyl-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine
87	5-nitro-6-methyl-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine	5-amino-6-methyl-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine

Examples 88-94

Following the procedures of Example 52b-f, except substituting the starting material indicated below for the 1-BOC-2-(S)-azetidinemethanol in step 52b, and omitting the methylation step, the compounds of examples 88-91 are prepared. Following the procedures of Example 52b-f, except substituting the starting material indicated in the below for the 1-BOC-2-(S)-azetidinemethanol in step 52b the compounds of examples 92-94 are prepared.

Table 5



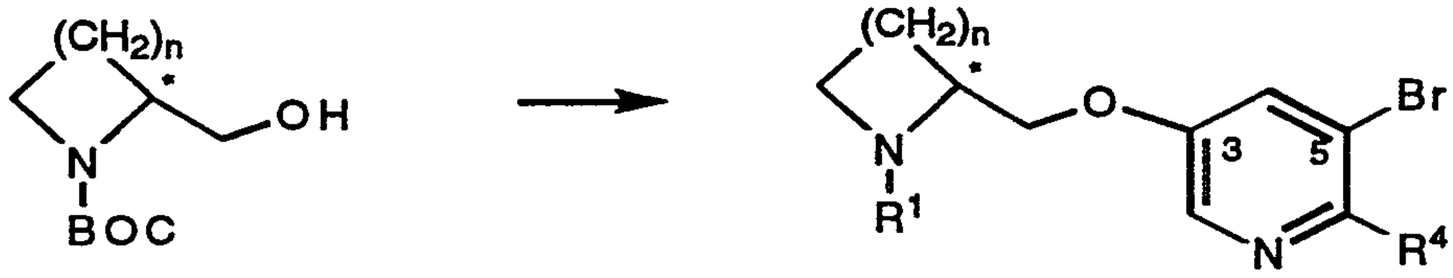
Ex. No.	Starting material	Product
88	1-BOC-2-(S)-azetidinemethanol	5-bromo-6-methyl-3-(2-(S)-azetidinylmethoxy)pyridine
89	1-BOC-2-(R)-azetidinemethanol	5-bromo-6-methyl-3-(2-(R)-azetidinylmethoxy)pyridine

90	1-BOC-2-(S)-pyrrolidinemethanol	5-bromo-6-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine
91	1-BOC-2-(R)-pyrrolidinemethanol	5-bromo-6-methyl-3-(2-(R)-pyrrolidinylmethoxy)pyridine
92	1-BOC-2-(R)-azetidinemethanol	5-bromo-6-methyl-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine
93	1-BOC-(S)-pyrrolidinemethanol	5-bromo-6-methyl-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine
94	1-BOC-(R)-pyrrolidinemethanol	5-bromo-6-methyl-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine

Examples 95-101

Following the procedure of Example 57d, except substituting the starting material indicated in the table below for the 1-BOC-2-(S)-azetidinemethanol in step 57d, the compounds of examples 95-97 are prepared. Following the procedures of Example 57d, except substituting the starting material indicated in the table below for the 1-BOC-2-(S)-azetidinemethanol in step 57d, then reacting the product thereof with paraformaldehyde and sodium cyanoborohydride according to the procedure of Example 3, the HCl salts of the compounds of examples 98-101 are prepared.

Table 6



Ex. No.	Starting material	Product
95	1-BOC-2-(R)-azetidinemethanol	5-bromo-6-fluoro-3-(2-(R)-azetidinylmethoxy)pyridine
96	1-BOC-2-(S)-pyrrolidinemethanol	5-bromo-6-fluoro-3-(2-(S)-pyrrolidinylmethoxy)pyridine
97	1-BOC-2-(R)-pyrrolidinemethanol	5-bromo-6-fluoro-3-(2-(R)-pyrrolidinylmethoxy)pyridine

98	1-BOC-2-(S)-azetidinemethanol	5-bromo-6-fluoro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine
99	1-BOC-2-(R)-azetidinemethanol	5-bromo-6-fluoro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine
100	1-BOC-(S)-pyrrolidinemethanol	5-bromo-6-fluoro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine
101	1-BOC-(R)-pyrrolidinemethanol	5-bromo-6-fluoro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine

Example 102

5-Bromo-6-chloro-3-(2-(R)-azetidinylmethoxy)pyridine hydrochloride

The title compound is prepared following the procedures of Example 2a-b, with the exception of substituting 1-BOC-2-(R)-azetidinemethanol for the 1-BOC-2-(S)-azetidinemethanol.

Example 103

5-Bromo-6-chloro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine hydrochloride

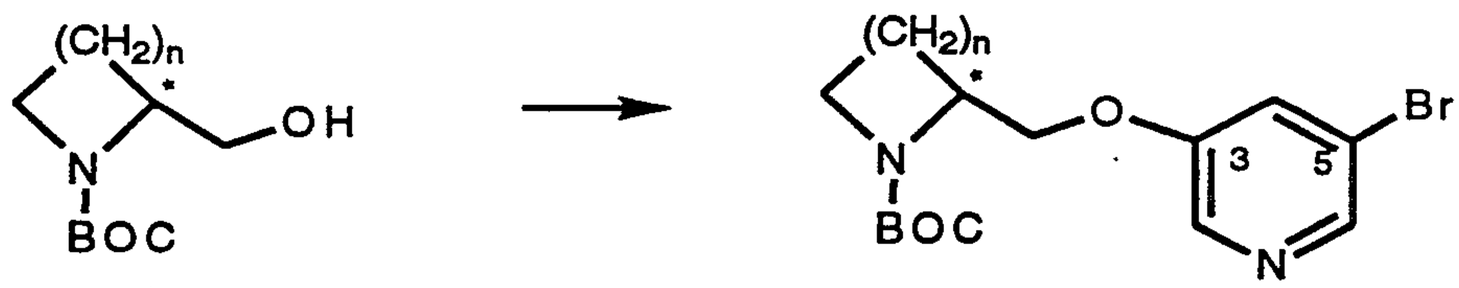
The title compound is prepared following the procedures of Example 3, with the exception of substituting 5-bromo-6-chloro-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine for the 5-bromo-6-chloro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine.

Examples 104-106

(Intermediate Compounds)

Following the procedure of Example 44b, except substituting the starting material indicated in the table below for the 1-BOC-2-(S)-azetidinemethanol in step 44b, the compounds of examples 104-106 are prepared.

Table 7

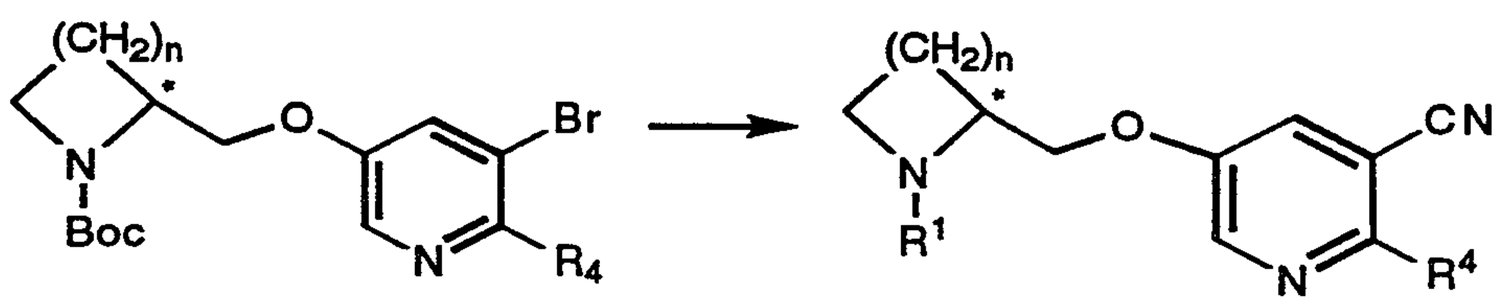


Ex. No.	Starting Material	Product
104	1-BOC-2-(R)-azetidinemethanol	5-bromo-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine
105	1-BOC-2-(S)-pyrrolidinemethanol	5-bromo-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine
106	1-BOC-2-(R)-pyrrolidinemethanol	5-bromo-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine

Examples 107-136

Following the procedures of Examples 49a-b and substituting the starting material of the table below for the 5-bromo-6-chloro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine of step 49a, the compounds of examples 107-110, 115-118, 123-126, and 131-133 are prepared. Following the procedures of Examples 49 and 50 and substituting the starting material of the table below for the 5-bromo-6-chloro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine of step 49a, the HCl salts of the compounds of examples 111-114, 119-122, 127-130, and 134-136 are prepared.

Table 8



Ex. No.	Starting material	Product
107	5-bromo-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine	5-cyano-3-(2-(S)-azetidinylmethoxy)pyridine

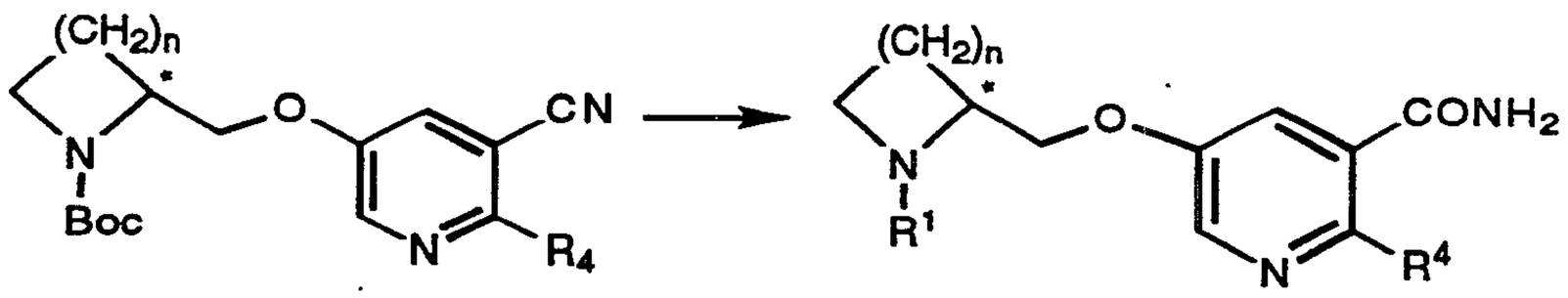
108	5-bromo-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine	5-cyano-3-(2-(R)-azetidinylmethoxy)pyridine
109	5-bromo-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine	5-cyano-3-(2-(S)-pyrrolidinylmethoxy)pyridine
110	5-bromo-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine	5-cyano-3-(2-(R)-pyrrolidinylmethoxy)pyridine
111	5-bromo-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine	5-cyano-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine
112	5-bromo-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine	5-cyano-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine
113	5-bromo-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine	5-cyano-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine
114	5-bromo-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine	5-cyano-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine
115	5-bromo-6-methyl-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine	5-cyano-6-methyl-3-(2-(S)-azetidinylmethoxy)pyridine
116	5-bromo-6-methyl-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine	5-cyano-6-methyl-3-(2-(R)-azetidinylmethoxy)pyridine
117	5-bromo-6-methyl-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine	5-cyano-6-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine
118	5-bromo-6-methyl-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine	5-cyano-6-methyl-3-(2-(R)-pyrrolidinylmethoxy)pyridine
119	5-bromo-6-methyl-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine	5-cyano-6-methyl-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine
120	5-bromo-6-methyl-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine	5-cyano-6-methyl-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine
121	5-bromo-6-methyl-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine	5-cyano-6-methyl-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine
122	5-bromo-6-methyl-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine	5-cyano-6-methyl-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine
123	5-bromo-6-fluoro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine	5-cyano-6-fluoro-3-(2-(S)-azetidinylmethoxy)pyridine
124	5-bromo-6-fluoro-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine	5-cyano-6-fluoro-3-(2-(R)-azetidinylmethoxy)pyridine

125	5-bromo-6-fluoro-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine	5-cyano-6-fluoro-3-(2-(S)-pyrrolidinylmethoxy)pyridine
126	5-bromo-6-fluoro-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine	5-cyano-6-fluoro-3-(2-(R)-pyrrolidinylmethoxy)pyridine
127	5-bromo-6-fluoro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine	5-cyano-6-fluoro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine
128	5-bromo-6-fluoro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine	5-cyano-6-fluoro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine
129	5-bromo-6-fluoro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine	5-cyano-6-fluoro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine
130	5-bromo-6-fluoro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine	5-cyano-6-fluoro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine
131	5-bromo-6-chloro-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine	5-cyano-6-chloro-3-(2-(R)-azetidinylmethoxy)pyridine
132	5-bromo-6-chloro-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine	5-cyano-6-chloro-3-(2-(S)-pyrrolidinylmethoxy)pyridine
133	5-bromo-6-chloro-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine	5-cyano-6-chloro-3-(2-(R)-pyrrolidinylmethoxy)pyridine
134	5-bromo-6-chloro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine	5-cyano-6-chloro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine
135	5-bromo-6-chloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine	5-cyano-6-chloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine
136	5-bromo-6-chloro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine	5-cyano-6-chloro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine

Examples 137-167

Following the procedures of Examples 49a-b and substituting the starting material of the table below for the 5-cyano-6-chloro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine of step 49a, the compounds of examples 137-140, 145-148, 153-156, and 161-164 are prepared. Following the procedures of Examples 49 and 50 and substituting the starting material of the table below for the 5-cyano-6-chloro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine of step 49a, the HCl salts of the compounds of examples 141-144, 149-152, 157-160, and 165-167 are prepared.

Table 9



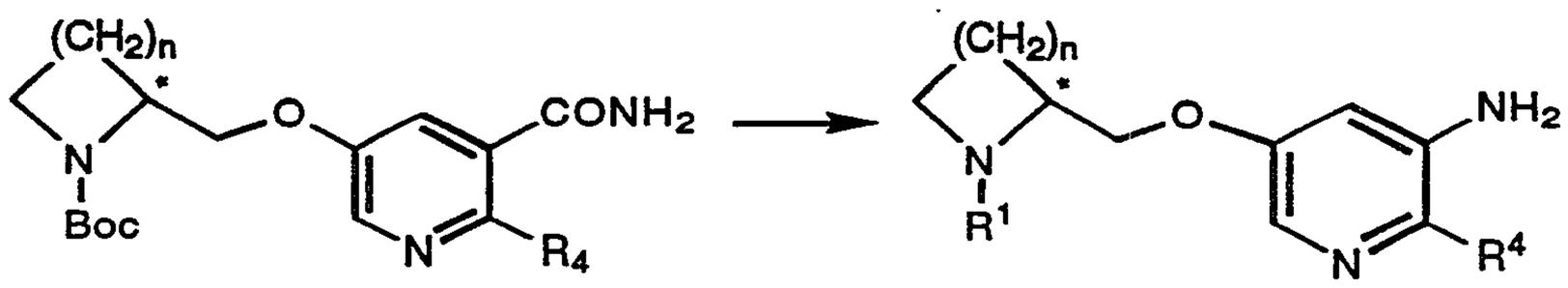
Ex. No.	Starting material	Product
137	5-bromo-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine	5-carbamoyl-3-(2-(S)-azetidinylmethoxy)pyridine
138	5-bromo-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine	5-carbamoyl-3-(2-(R)-azetidinylmethoxy)pyridine
139	5-bromo-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine	5-carbamoyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine
140	5-bromo-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine	5-carbamoyl-3-(2-(R)-pyrrolidinylmethoxy)pyridine
141	5-bromo-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine	5-carbamoyl-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine
142	5-bromo-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine	5-carbamoyl-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine
143	5-bromo-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine	5-carbamoyl-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine
144	5-bromo-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine	5-carbamoyl-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine
145	5-bromo-6-methyl-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine	5-carbamoyl-6-methyl-3-(2-(S)-azetidinylmethoxy)pyridine
146	5-bromo-6-methyl-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine	5-carbamoyl-6-methyl-3-(2-(R)-azetidinylmethoxy)pyridine
147	5-bromo-6-methyl-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine	5-carbamoyl-6-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine
148	5-bromo-6-methyl-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine	5-carbamoyl-6-methyl-3-(2-(R)-pyrrolidinylmethoxy)pyridine
149	5-bromo-6-methyl-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine	5-carbamoyl-6-methyl-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine

150	5-bromo-6-methyl-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine	5-carbamoyl-6-methyl-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine
151	5-bromo-6-methyl-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine	5-carbamoyl-6-methyl-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine
152	5-bromo-6-methyl-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine	5-carbamoyl-6-methyl-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine
153	5-bromo-6-fluoro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine	5-carbamoyl-6-fluoro-3-(2-(S)-azetidinylmethoxy)pyridine
154	5-bromo-6-fluoro-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine	5-carbamoyl-6-fluoro-3-(2-(R)-azetidinylmethoxy)pyridine
155	5-bromo-6-fluoro-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine	5-carbamoyl-6-fluoro-3-(2-(S)-pyrrolidinylmethoxy)pyridine
156	5-bromo-6-fluoro-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine	5-carbamoyl-6-fluoro-3-(2-(R)-pyrrolidinylmethoxy)pyridine
157	5-bromo-6-fluoro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine	5-carbamoyl-6-fluoro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine
158	5-bromo-6-fluoro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine	5-carbamoyl-6-fluoro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine
159	5-bromo-6-fluoro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine	5-carbamoyl-6-fluoro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine
160	5-bromo-6-fluoro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine	5-carbamoyl-6-fluoro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine
161	5-bromo-6-chloro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine	5-carbamoyl-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine
162	5-bromo-6-chloro-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine	5-carbamoyl-6-chloro-3-(2-(R)-azetidinylmethoxy)pyridine
163	5-bromo-6-chloro-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine	5-carbamoyl-6-chloro-3-(2-(S)-pyrrolidinylmethoxy)pyridine
164	5-bromo-6-chloro-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine	5-carbamoyl-6-chloro-3-(2-(R)-pyrrolidinylmethoxy)pyridine
165	5-bromo-6-chloro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine	5-carbamoyl-6-chloro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine
166	5-bromo-6-chloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine	5-carbamoyl-6-chloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine
167	5-bromo-6-chloro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine	5-carbamoyl-6-chloro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine

Examples 168-183

The starting material from Example 168-183above are treated with bromine in aqueous alkali under conditions of the Hofmann rearrangement (*cf.*, Allen and Wolf, *Org. Syn.*, 30: 3 (**1950**)) to replace the carbamoyl group with the amino group.

Table 10



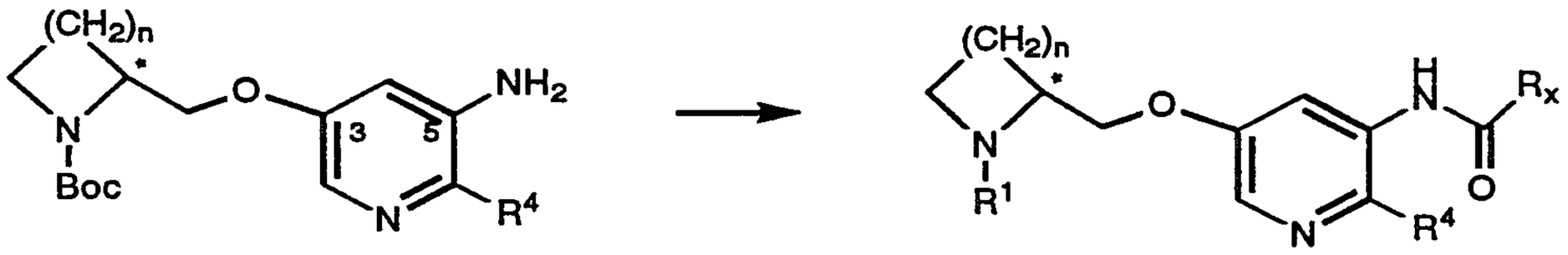
Ex. No.	Starting material	Product
168	5-carbamoyl-6-fluoro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine	5-amino-6-fluoro-3-(2-(S)-azetidinylmethoxy)pyridine
169	5-carbamoyl-6-fluoro-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine	5-amino-6-fluoro-3-(2-(R)-azetidinylmethoxy)pyridine
170	5-carbamoyl-6-fluoro-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine	5-amino-6-fluoro-3-(2-(S)-pyrrolidinylmethoxy)pyridine
171	5-carbamoyl-6-fluoro-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine	5-amino-6-fluoro-3-(2-(R)-pyrrolidinylmethoxy)pyridine
172	5-carbamoyl-6-fluoro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine	5-amino-6-fluoro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine
172	5-carbamoyl-6-fluoro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine	5-amino-6-fluoro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine
174	5-carbamoyl-6-fluoro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine	5-amino-6-fluoro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine
175	5-carbamoyl-6-fluoro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine	5-amino-6-fluoro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine
176	5-carbamoyl-6-chloro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine	5-amino-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine
177	5-carbamoyl-6-chloro-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine	5-amino-6-chloro-3-(2-(R)-azetidinylmethoxy)pyridine

178	5-carbamoyl-6-chloro-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine	5-amino-6-chloro-3-(2-(S)-pyrrolidinylmethoxy)pyridine
179	5-carbamoyl-6-chloro-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine	5-amino-6-chloro-3-(2-(R)-pyrrolidinylmethoxy)pyridine
180	5-carbamoyl-6-chloro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine	5-amino-6-chloro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine
181	5-carbamoyl-6-chloro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine	5-amino-6-chloro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine
182	5-carbamoyl-6-chloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine	5-amino-6-chloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine
183	5-carbamoyl-6-chloro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine	5-amino-6-chloro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine

Examples 184-215

The starting material compounds shown in the table below (some of which are BOC intermediates of Examples 168-183) are treated with 2,4-dinitrophenyl formate (for Examples 184-199) or acetic anhydride (for Examples 200-215). The product is subjected to BOC deprotection, isolation and salt formation as in Example 2 and 3.

Table 11



Ex. No.	Starting material	Product
184	5-amino-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine	5-formamido-3-(2-(S)-azetidinylmethoxy)pyridine
185	5-amino-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine	5-formamido-3-(2-(R)-azetidinylmethoxy)pyridine
186	5-amino-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine	5-formamido-3-(2-(S)-pyrrolidinylmethoxy)pyridine
187	5-amino-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine	5-formamido-3-(2-(R)-pyrrolidinylmethoxy)pyridine

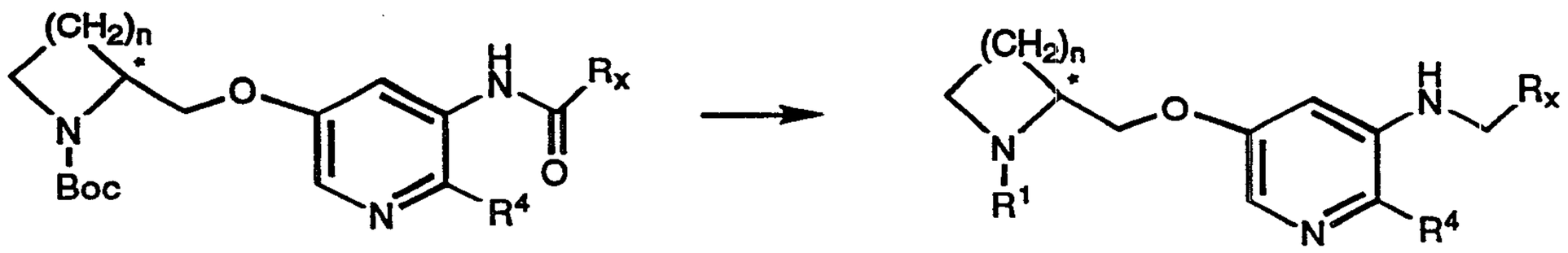
188	5-amino-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine	5-formamido-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine
189	5-amino-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine	5-formamido-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine
190	5-amino-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine	5-formamido-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine
191	5-amino-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine	5-formamido-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine
192	5-amino-6-methyl-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine	5-formamido-6-methyl-3-(2-(S)-azetidinylmethoxy)pyridine
193	5-amino-6-methyl-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine	5-formamido-6-methyl-3-(2-(R)-azetidinylmethoxy)pyridine
194	5-amino-6-methyl-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine	5-formamido-6-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine
195	5-amino-6-methyl-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine	5-formamido-6-methyl-3-(2-(R)-pyrrolidinylmethoxy)pyridine
196	5-amino-6-methyl-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine	5-formamido-6-methyl-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine
197	5-amino-6-methyl-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine	5-formamido-6-methyl-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine
198	5-amino-6-methyl-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine	5-formamido-6-methyl-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine
199	5-amino-6-methyl-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine	5-formamido-6-methyl-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine
200	5-bromo-6-fluoro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine	5-acetamido-6-fluoro-3-(2-(S)-azetidinylmethoxy)pyridine
201	5-amino-6-fluoro-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine	5-acetamido-6-fluoro-3-(2-(R)-azetidinylmethoxy)pyridine
202	5-amino-6-fluoro-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine	5-acetamido-6-fluoro-3-(2-(S)-pyrrolidinylmethoxy)pyridine
203	5-amino-6-fluoro-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine	5-acetamido-6-fluoro-3-(2-(R)-pyrrolidinylmethoxy)pyridine
204	5-amino-6-fluoro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine	5-acetamido-6-fluoro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine

205	5-amino-6-fluoro-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine	5-acetamido-6-fluoro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine
206	5-amino-6-fluoro-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine	5-acetamido-6-fluoro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine
207	5-amino-6-fluoro-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine	5-acetamido-6-fluoro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine
208	5-amino-6-chloro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine	5-acetamido-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine
209	5-amino-6-chloro-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine	5-acetamido-6-chloro-3-(2-(R)-azetidinylmethoxy)pyridine
210	5-amino-6-chloro-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine	5-acetamido-6-chloro-3-(2-(S)-pyrrolidinylmethoxy)pyridine
211	5-amino-6-chloro-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine	5-acetamido-6-chloro-3-(2-(R)-pyrrolidinylmethoxy)pyridine
212	5-amino-6-chloro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine	5-acetamido-6-chloro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine
213	5-amino-6-chloro-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine	5-acetamido-6-chloro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine
214	5-amino-6-chloro-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine	5-acetamido-6-chloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine
215	5-amino-6-chloro-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine	5-acetamido-6-chloro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine

Examples 216-247

The starting material compounds shown in the table below (some of which are BOC-intermediates from Examples 184-215 above) are treated with borane as in Ex 1d followed by deprotection and salt formation as in Example 2b to give the product compounds shown. For products with R^1= methyl, BOC-deprotection as in Example 2b and N-methylation precede the treatment with borane.

Table 12



Ex. No.	Starting material	Product
216	5-formamido-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine	5-methylamino-3-(2-(S)-azetidinylmethoxy)pyridine
217	5-formamido-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine	5-methylamino-3-(2-(R)-azetidinylmethoxy)pyridine
218	5-formamido-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine	5-methylamino-3-(2-(S)-pyrrolidinylmethoxy)pyridine
219	5-formamido-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine	5-methylamino-3-(2-(R)-pyrrolidinylmethoxy)pyridine
220	5-formamido-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine	5-methylamino-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine
221	5-formamido-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine	5-methylamino-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine
222	5-formamido-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine	5-methylamino-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine
223	5-formamido-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine	5-methylamino-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine
224	5-formamido-6-methyl-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine	5-methylamino-6-methyl-3-(2-(S)-azetidinylmethoxy)pyridine
225	5-formamido-6-methyl-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine	5-methylamino-6-methyl-3-(2-(R)-azetidinylmethoxy)pyridine

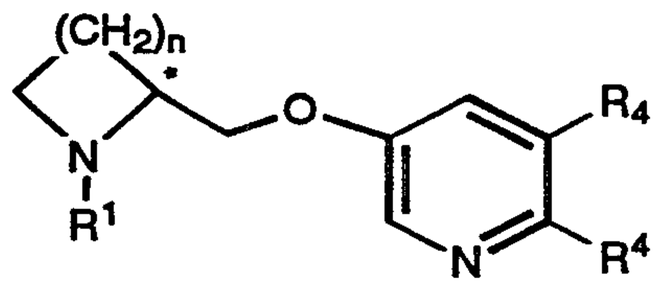
226	5-formamido-6-methyl-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine	5-methylamino-6-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine
227	5-formamido-6-methyl-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine	5-methylamino-6-methyl-3-(2-(R)-pyrrolidinylmethoxy)pyridine
228	5-formamido-6-methyl-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine	5-methylamino-6-methyl-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine
229	5-formamido-6-methyl-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine	5-methylamino-6-methyl-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine
230	5-formamido-6-methyl-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine	5-methylamino-6-methyl-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine
231	5-formamido-6-methyl-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine	5-methylamino-6-methyl-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine
232	5-acetamido-6-fluoro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine	5-ethylamino-6-fluoro-3-(2-(S)-azetidinylmethoxy)pyridine
233	5-acetamido-6-fluoro-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine	5-ethylamino-6-fluoro-3-(2-(R)-azetidinylmethoxy)pyridine
234	5-acetamido-6-fluoro-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine	5-ethylamino-6-fluoro-3-(2-(S)-pyrrolidinylmethoxy)pyridine
235	5-acetamido-6-fluoro-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine	5-ethylamino-6-fluoro-3-(2-(R)-pyrrolidinylmethoxy)pyridine
236	5-acetamido-6-fluoro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine	5-ethylamino-6-fluoro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine
237	5-acetamido-6-fluoro-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine	5-ethylamino-6-fluoro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine
238	5-acetamido-6-fluoro-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine	5-ethylamino-6-fluoro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine
239	5-acetamido-6-fluoro-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine	5-ethylamino-6-fluoro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine
240	5-acetamido-6-chloro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine	5-ethylamino-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine
241	5-acetamido-6-chloro-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine	5-ethylamino-6-chloro-3-(2-(R)-azetidinylmethoxy)pyridine
242	5-acetamido-6-chloro-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine	5-ethylamino-6-chloro-3-(2-(S)-pyrrolidinylmethoxy)pyridine

243	5-acetamido-6-chloro-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine	5-ethylamino-6-chloro-3-(2-(R)-pyrrolidinylmethoxy)pyridine
244	5-acetamido-6-chloro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine	5-ethylamino-6-chloro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine
245	5-acetamido-6-chloro-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine	5-ethylamino-6-chloro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine
246	5-acetamido-6-chloro-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine	5-ethylamino-6-chloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine
247	5-acetamido-6-chloro-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine	5-ethylamino-6-chloro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine

Examples 248-271

The starting material compounds shown in the table below (some of which are BOC-protected intermediates of Examples 88-94 above) are treated as in Example 45 (for examples 248-263 wherein R^4 = ethyl). In Examples 264-271, wherein R^4 = propyl, the intermediates are treated as in Example 45 except substituting allyl tri-n-propyltin for the vinyl tri-n-butyltin therein.

Table 13



Ex. No.	Starting Material	Product
248	5-bromo-6-methyl-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine	5-ethyl-6-methyl-3-(2-(S)-azetidinylmethoxy)pyridine
249	5-bromo-6-methyl-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine	5-ethyl-6-methyl-3-(2-(R)-azetidinylmethoxy)pyridine
250	5-bromo-6-methyl-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine	5-ethyl-6-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine
251	5-bromo-6-methyl-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine	5-ethyl-6-methyl-3-(2-(R)-pyrrolidinylmethoxy)pyridine
252	5-bromo-6-methyl-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine	5-ethyl-6-methyl-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine

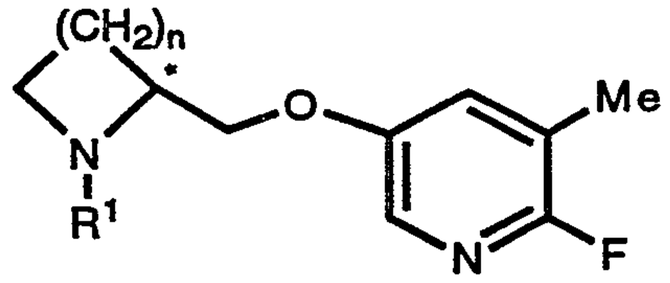
253	5-bromo-6-methyl-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine	5-ethyl-6-methyl-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine
254	5-bromo-6-methyl-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine	5-ethyl-6-methyl-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine
255	5-bromo-6-methyl-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine	5-ethyl-6-methyl-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine
256	5-bromo-6-fluoro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine	5-ethyl-6-fluoro-3-(2-(S)-azetidinylmethoxy)pyridine
257	5-bromo-6-fluoro-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine	5-ethyl-6-fluoro-3-(2-(R)-azetidinylmethoxy)pyridine
258	5-bromo-6-fluoro-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine	5-ethyl-6-fluoro-3-(2-(S)-pyrrolidinylmethoxy)pyridine
259	5-bromo-6-fluoro-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine	5-ethyl-6-fluoro-3-(2-(R)-pyrrolidinylmethoxy)pyridine
260	5-bromo-6-fluoro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine	5-ethyl-6-fluoro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine
261	5-bromo-6-fluoro-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine	5-ethyl-6-fluoro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine
262	5-bromo-6-fluoro-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine	5-ethyl-6-fluoro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine
263	5-bromo-6-fluoro-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine	5-ethyl-6-fluoro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine
264	5-bromo-6-chloro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine	5-propyl-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine
265	5-bromo-6-chloro-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine	5-propyl-6-chloro-3-(2-(R)-azetidinylmethoxy)pyridine
266	5-bromo-6-chloro-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine	5-propyl-6-chloro-3-(2-(S)-pyrrolidinylmethoxy)pyridine
267	5-bromo-6-chloro-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine	5-propyl-6-chloro-3-(2-(R)-pyrrolidinylmethoxy)pyridine
268	5-bromo-6-chloro-3-(1-BOC-2-(S)-azetidinylmethoxy)pyridine	5-propyl-6-chloro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine
269	5-bromo-6-chloro-3-(1-BOC-2-(R)-azetidinylmethoxy)pyridine	5-propyl-6-chloro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine

270	5-bromo-6-chloro-3-(1-BOC-2-(S)-pyrrolidinylmethoxy)pyridine	5-propyl-6-chloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine
271	5-bromo-6-chloro-3-(1-BOC-2-(R)-pyrrolidinylmethoxy)pyridine	5-propyl-6-chloro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine

Examples 272-278

Following the procedures of Example 55c-f, substituting the starting material shown in the table below for the 1-BOC-2-(S)-azetidinemethanol thereof, the product compounds of Examples 272-274 are prepared. Following the procedures of Example 55c-d, substituting the starting material shown in the table below for the 1-BOC-2-(S)-azetidinemethanol thereof, then reacting the product thereof with paraformaldehyde and sodium cyanoborohydride according to the procedure of Example 3, the product compounds of Examples 275-278 are prepared.

Table 14



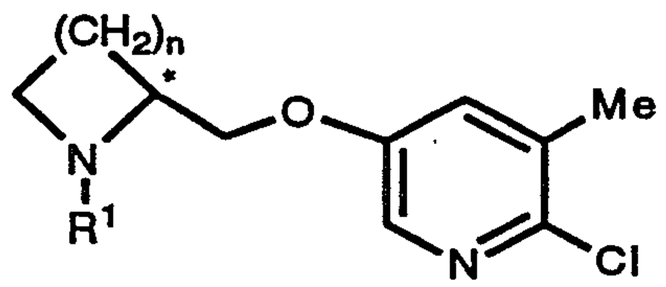
Ex. No.	Starting Material	Product
272	1-CBZ-2-(R)-azetidinemethanol	5-methyl-6-fluoro-3-(2-(R)-azetidinylmethoxy)pyridine
273	1-CBZ-2-(S)-pyrrolidinemethanol	5-methyl-6-fluoro-3-(2-(S)-pyrrolidinylmethoxy)pyridine
274	1-CBZ-2-(R)-pyrrolidinemethanol	5-methyl-6-fluoro-3-(2-(R)-pyrrolidinylmethoxy)pyridine
274	1-CBZ-2-(S)-azetidinemethanol	5-methyl-6-fluoro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine
276	1-CBZ-2-(R)-azetidinemethanol	5-methyl-6-fluoro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine
277	1-CBZ-(S)-pyrrolidinemethanol	5-methyl-6-fluoro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine

278	1-CBZ-(R)-pyrrolidinemethanol	5-methyl-6-fluoro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine

Examples 279-285

Following the procedures of Example 56a-b, substituting the starting material shown in the table below for the 1-BOC-2-(S)-azetidinemethanol thereof, the product compounds of Examples 279-281 are prepared. Following the procedures of Example 56c-d, substituting the starting material shown in the table below for the 1-BOC-2-(S)-azetidinemethanol thereof, then reacting the product thereof with paraformaldehyde and sodium cyanoborohydride according to the procedure of Example 3, the product compounds of Examples 272-285 are prepared.

Table 15

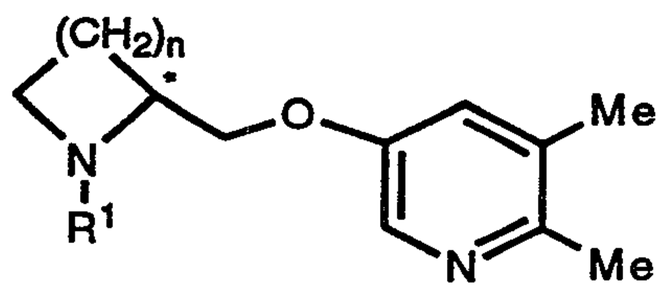


Ex. No.	Starting Material	Product
279	1-BOC-2-(R)-azetidinemethanol	5-methyl-6-chloro-3-(2-(R)-azetidinylmethoxy)pyridine
280	1-BOC-2-(S)-pyrrolidinemethanol	5-methyl-6-chloro-3-(2-(S)-pyrrolidinylmethoxy)pyridine
281	1-BOC-2-(R)-pyrrolidinemethanol	5-methyl-6-chloro-3-(2-(R)-pyrrolidinylmethoxy)pyridine
282	1-BOC-2-(S)-azetidinemethanol	5-methyl-6-chloro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine
283	1-BOC-2-(R)-azetidinemethanol	5-methyl-6-chloro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine
284	1-BOC-(S)-pyrrolidinemethanol	5-methyl-6-chloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine
285	1-BOC-(R)-pyrrolidinemethanol	5-methyl-6-chloro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine

Examples 286-292

Following the procedures of Example 61a-b, substituting the starting material shown in the table below for the 1-BOC-2-(S)-azetidinemethanol thereof, the product compounds of Examples 286-288 are prepared. Following the procedures of Example 61a-b, substituting the starting material shown in the table below for the 1-BOC-2-(S)-azetidinemethanol thereof, then reacting the product thereof with paraformaldehyde and sodium cyanoborohydride according to the procedure of Example 3, the product compounds of Examples 289-292 are prepared.

Table 16

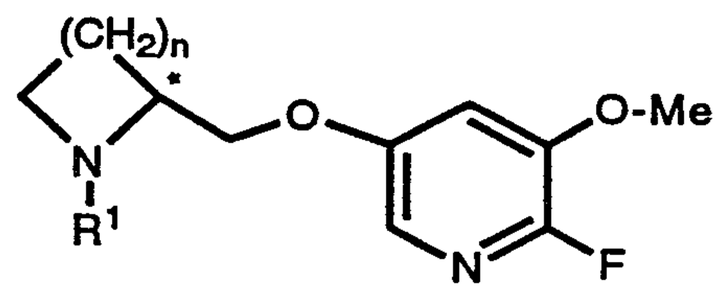


Ex. No.	Starting Material	Product
286	1-BOC-2-(R)-azetidinemethanol	5,6-dimethyl-3-(2-(R)-azetidinylmethoxy)pyridine
287	1-BOC-2-(S)-pyrrolidinemethanol	5,6-dimethyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine
288	1-BOC-2-(R)-pyrrolidinemethanol	5,6-dimethyl-3-(2-(R)-pyrrolidinylmethoxy)pyridine
289	1-BOC-2-(S)-azetidinemethanol	5,6-dimethyl-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine
290	1-BOC-2-(R)-azetidinemethanol	5,6-dimethyl-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine
291	1-BOC-(S)-pyrrolidinemethanol	5,6-dimethyl-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine
292	1-BOC-(R)-pyrrolidinemethanol	5,6-dimethyl-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine

Examples 293-300

Following the procedures of Example 58, substituting the starting material shown in the table below for the 1-BOC-2-(S)-azetidinemethanol thereof and replacing step 58e with the procedure and reagents of Example 57c, the product compounds of Examples 293-296 are prepared. Following the procedures of Example 58, substituting the starting material shown in the table below for the 1-BOC-2-(S)-azetidinemethanol thereof and replacing step 58e with the procedure and reagents of Example 57c, then reacting the product thereof with paraformaldehyde and sodium cyanoborohydride according to the procedure of Example 3, the product compounds of Examples 297-292 are prepared.

Table 17



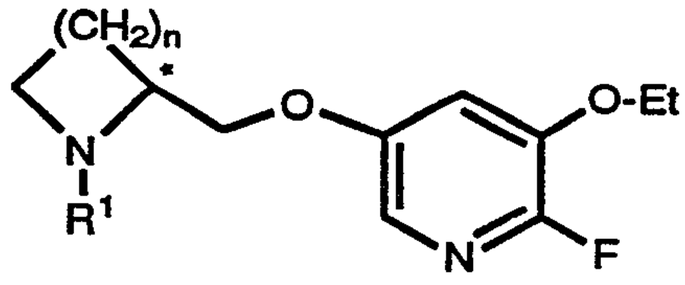
Ex. No.	Starting Material	Product
293	1-BOC-2-(S)-azetidinemethanol	6-fluoro-5-methoxy-3-(2-(S)-azetidinylmethoxy)pyridine
294	1-BOC-2-(R)-azetidinemethanol	6-fluoro-5-methoxy-3-(2-(R)-azetidinylmethoxy)pyridine
295	1-BOC-2-(S)-pyrrolidinemethanol	6-fluoro-5-methoxy-3-(2-(S)-pyrrolidinylmethoxy)pyridine
296	1-BOC-2-(R)-pyrrolidinemethanol	6-fluoro-5-methoxy-3-(2-(R)-pyrrolidinylmethoxy)pyridine
297	1-BOC-2-(S)-azetidinemethanol	6-fluoro-5-methoxy-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine
298	1-BOC-2-(R)-azetidinemethanol	6-fluoro-5-methoxy-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine
299	1-BOC-(S)-pyrrolidinemethanol	6-fluoro-5-methoxy-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine
300	1-BOC-(R)-pyrrolidinemethanol	6-fluoro-5-methoxy-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine

Examples 301-308

Following the procedures of Example 58, substituting ethanol for the methanol reagent in Example 58a, substituting the starting material shown in the table below for the 1-BOC-2-(S)-azetidinemethanol in step 58a and replacing step 58e with the procedure and reagents of Example 57c, the product compounds of Examples 301-304 are prepared.

Following the procedures of Example 58, substituting the starting material shown in the table below for the 1-BOC-2-(S)-azetidinemethanol thereof and replacing step 58e with the procedure and reagents of Example 57c, then reacting the product thereof with paraformaldehyde and sodium cyanoborohydride according to the procedure of Example 3, the product compounds of Examples 305-308 are prepared.

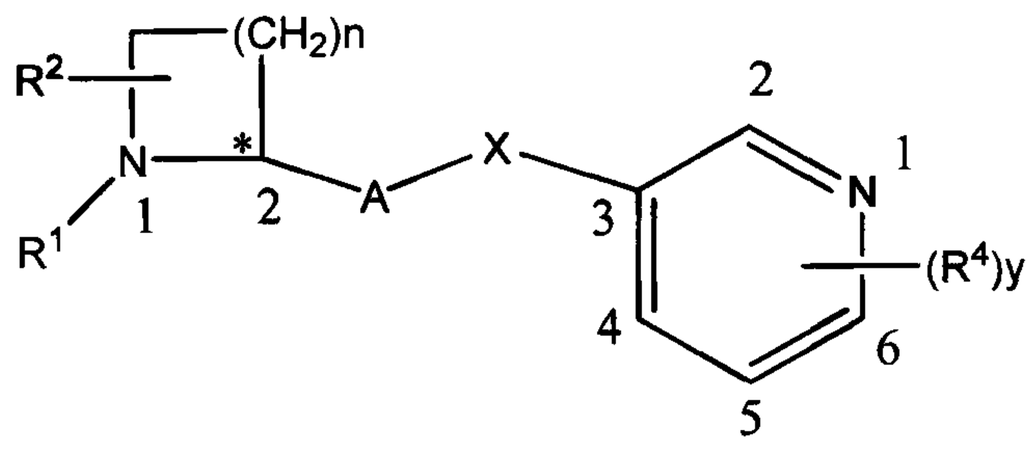
Table 18



Ex. No.	Starting Material	Product
301	1-BOC-2-(S)-azetidinemethanol	6-fluoro-5-ethoxy-3-(2-(S)-azetidinylmethoxy)pyridine
302	1-BOC-2-(R)-azetidinemethanol	6-fluoro-5-ethoxy-3-(2-(R)-azetidinylmethoxy)pyridine
303	1-BOC-2-(S)-pyrrolidinemethanol	6-fluoro-5-ethoxy-3-(2-(S)-pyrrolidinylmethoxy)pyridine
304	1-BOC-2-(R)-pyrrolidinemethanol	6-fluoro-5-ethoxy-3-(2-(R)-pyrrolidinylmethoxy)pyridine
305	1-BOC-2-(S)-azetidinemethanol	6-fluoro-5-ethoxy-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine
306	1-BOC-2-(R)-azetidinemethanol	6-fluoro-5-ethoxy-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine
307	1-BOC-(S)-pyrrolidinemethanol	6-fluoro-5-ethoxy-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine
308	1-BOC-(R)-pyrrolidinemethanol	6-fluoro-5-ethoxy-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine

CLAIMS:

1. A compound or pharmaceutically acceptable salt thereof, wherein said compound has the structure:



wherein:

* represents a chiral center;

n is 1, 2, or 3;

X is oxygen or sulfur;

R^1 is selected from the group consisting of H, allyl, and C_1-C_6-alkyl;

R^2 is hydrogen when n is 1 or 3; and when n is 2, R^2 is hydrogen or a single substituent selected from the group consisting of:

-CH_2OH,

-CH_2F,

-CH_2CN,

-CH_2OCH_3,

-Br,

-Cl,

-F,

-OH,

-CN,

-C_1-C_3-alkoxy,

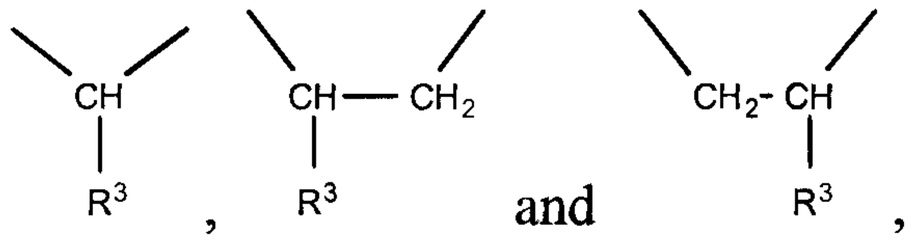
-O-C(O)-CH_3,

-O-methanesulfonyl;

3-C_1-C_3-alkyl, and

5-C_1-C_3-alkyl,

A is selected from the group consisting of :



wherein:

R^3 is H or C_1-C_6-alkyl;

y is 2; and

R^4 is a substituent at the 2,5-, 2,6-, or 5,6- positions of the pyridine ring wherein the 2-position substituent is selected from the group consisting of:

-Br,
-Cl,
-F,
-OH,
-C_1-C_4-alkyl, and
-C_1-C_3-alkoxy; and

the substituents at the 5- and 6-position of the pyridine ring are selected from the group consisting of:

-Br,
-Cl,
-F,
-OH,
-C_1-C_4-alkyl,
-CN,
-CF_3,
-NO_2,
-CH_2OH,
-CH_2CN,
-C_1-C_3-alkoxy,
-NH_2,
-NH-CHO,
-NH-C(O)-(C_1-C_3-alkyl),
-N(C_1-C_3-alkyl)-C(O)-(C_1-C_3-alkyl),

-N(C_1-C_3-alkyl)$_2$,
-NH-(C_1-C_3-alkyl),
-C(O)-OH,
-C(O)-O-C_1-C_3-alkyl,
-C(O)-NH_2,
-C(O)-NH-C_1-C_3-alkyl,
-C(O)-NH-CH_2-benzyl, and
-O-C(O)-(C_1-C_3-alkyl).

2. The compound as defined by Claim 1, or a pharmaceutically acceptable salt thereof wherein n=1.

3. The compound as defined by Claim 1, or a pharmaceutically acceptable salt thereof wherein n=2.

4. The compound as defined by Claim 1, or a pharmaceutically acceptable salt thereof wherein n=3.

5. The compound as defined by any one of Claims 1 to 4, or a pharmaceutically acceptable salt thereof wherein X is oxygen.

6. The compound as defined by any one of Claims 1 to 4, or a pharmaceutically acceptable salt thereof wherein X is sulfur.

7. The compound as defined by Claim 2, which is selected from the group consisting of:
5-bromo-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine;
5-bromo-6-chloro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5,6-dichloro-3-(2-(S)-azetidinylmethoxy)pyridine;
5,6-dichloro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5,6-dichloro-3-(2-(R)-azetidinylmethoxy)pyridine;
5,6-dichloro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-ethyl-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine;
5-cyano-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine;

5-cyano-6-chloro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;

5-carbamoyl-6-chloro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
6-fluoro-5-methyl-3-(2-(S)-azetidinylmethoxy)pyridine;
6-chloro-5-methyl-3-(2-(S)-azetidinylmethoxy)pyridine;
5-bromo-6-fluoro-3-(2-(S)-azetidinylmethoxy)pyridine;
5-methoxy-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine;
5-ethoxy-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine;
5,6-dimethyl-3-(2-(S)-azetidinylmethoxy)pyridine;
5-nitro-6-methyl-3-(2-(S)-azetidinylmethoxy)pyridine;
5-nitro-6-methyl-3-(2-(R)-azetidinylmethoxy)pyridine;
5-nitro-6-methyl-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-nitro-6-methyl-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-amino-6-methyl-3-(2-(R)-azetidinylmethoxy)pyridine;
5-amino-6-methyl-3-(2-(S)-azetidinylmethoxy)pyridine;
5-amino-6-methyl-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-amino-6-methyl-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-bromo-6-methyl-3-(2-(S)-azetidinylmethoxy)pyridine;
5-bromo-6-methyl 3-(2-(R)-azetidinylmethoxy)pyridine;
5-bromo-6-methyl-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-bromo-6-fluoro-3-(2-(R)-azetidinylmethoxy)pyridine;
5-bromo-6-fluoro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-bromo-6-fluoro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-bromo-6-chloro-3-(2-(R)-azetidinylmethoxy)pyridine;
5-bromo-6-chloro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-cyano-6-methyl-3-(2-(S)-azetidinylmethoxy)pyridine;
5-cyano-6-methyl-3-(2-(R)-azetidinylmethoxy)pyridine;
5-cyano-6-methyl-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-cyano-6-methyl-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-cyano-6-fluoro-3-(2-(S)-azetidinylmethoxy)pyridine;
5-cyano-6-fluoro-3-(2-(R)-azetidinylmethoxy)pyridine;
5-cyano-6-fluoro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-cyano-6-fluoro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-cyano-6-chloro-3-(2-(R)-azetidinylmethoxy)pyridine;
5-cyano-6-chloro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;

5-carbamoyl-6-methyl-3-(2-(S)-azetidinylmethoxy)pyridine;
5-carbamoyl-6-methyl-3-(2-(R)-azetidinylmethoxy)pyridine;
5-carbamoyl-6-methyl-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-carbamoyl-6-methyl-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-carbamoyl-6-fluoro-3-(2-(S)-azetidinylmethoxy)pyridine;
5-carbamoyl-6-fluoro-3-(2-(R)-azetidinylmethoxy)pyridine;
5-carbamoyl-6-fluoro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-carbamoyl-6-fluoro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-carbamoyl-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine;
5-carbamoyl-6-chloro-3-(2-(R)-azetidinylmethoxy)pyridine;
5-carbamoyl-6-chloro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-amino-6-fluoro-3-(2-(S)-azetidinylmethoxy)pyridine;
5-amino-6-fluoro-3-(2-(R)-azetidinylmethoxy)pyridine;
5-amino-6-fluoro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-amino-6-fluoro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-amino-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine;
5-amino-6-chloro-3-(2-(R)-azetidinylmethoxy)pyridine;
5-amino-6-chloro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-amino-6-chloro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-formamido-6-methyl-3-(2-(S)-azetidinylmethoxy)pyridine;
5-formamido-6-methyl-3-(2-(R)-azetidinylmethoxy)pyridine;
5-formamido-6-methyl-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-formamido-6-methyl-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-acetamido-6-fluoro-3-(2-(S)-azetidinylmethoxy)pyridine;
5-acetamido-6-fluoro-3-(2-(R)-azetidinylmethoxy)pyridine;
5-acetamido-6-fluoro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-acetamido-6-fluoro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-acetamido-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine;
5-acetamido-6-chloro-3-(2-(R)-azetidinylmethoxy)pyridine;
5-acetamido-6-chloro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-acetamido-6-chloro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-methylamino-6-methyl-3-(2-(S)-azetidinylmethoxy)pyridine;
5-methylamino-6-methyl-3-(2-(R)-azetidinylmethoxy)pyridine;
5-methylamino-6-methyl-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-methylamino-6-methyl-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;

5-ethylamino-6-fluoro-3-(2-(S)-azetidinylmethoxy)pyridine;
5-ethylamino-6-fluoro-3-(2-(R)-azetidinylmethoxy)pyridine;
5-ethylamino-6-fluoro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-ethylamino-6-fluoro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-ethylamino-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine;
5-ethylamino-6-chloro-3-(2-(R)-azetidinylmethoxy)pyridine;
5-ethylamino-6-chloro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-ethylamino-6-chloro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-ethyl-6-methyl-3-(2-(S)-azetidinylmethoxy)pyridine;
5-ethyl-6-methyl-3-(2-(R)-azetidinylmethoxy)pyridine;
5-ethyl-6-methyl-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-ethyl-6-methyl-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-ethyl-6-fluoro-3-(2-(S)-azetidinylmethoxy)pyridine;
5-ethyl-6-fluoro-3-(2-R)-azetidinylmethoxy)pyridine;
5-ethyl-6-fluoro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-ethyl-6-fluoro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-propyl-6-chloro-3-(2-(R)-azetidinylmethoxy)pyridine;
5-propyl-6-chloro-3-(2-(S)-azetidinylmethoxy)pyridine;
5-propyl-6-chloro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-propyl-6-chloro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-methyl-6-fluoro-3-(2-(R)-azetidinylmethoxy)pyridine;
5-methyl-6-fluoro-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5-methyl-6-fluoro-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
5-methyl-6-chloro-3-(2-(R)-azetidinylmethoxy)pyridine;
5-methyl-6-chloro-3-(1-methyl-2-(*S*)-azetidinylmethoxy)pyridine;
5-methyl-6-chloro-3-(1-methyl-2-(*R*)-azetidinylmethoxy)pyridine;
5,6-dimethyl-3-(2-(R)-azetidinylmethoxy)pyridine;
5,6-dimethyl-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
5,6-dimethyl-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
6-fluoro-5-methoxy-3-(2-(S)-azetidinylmethoxy)pyridine;
6-fluoro-5-methoxy-3-(2-(R)-azetidinylmethoxy)pyridine;

6-fluoro-5-methoxy-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
6-fluoro-5-methoxy-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine;
6-fluoro-5-ethoxy-3-(2-(S)-azetidinylmethoxy)pyridine;
6-fluoro-5-ethoxy-3-(2-(R)-azetidinylmethoxy)pyridine;
6-fluoro-5-ethoxy-3-(1-methyl-2-(S)-azetidinylmethoxy)pyridine;
6-fluoro-5-ethoxy-3-(1-methyl-2-(R)-azetidinylmethoxy)pyridine; and
pharmaceutically acceptable salts thereof.

8. A compound as defined by Claim 3 selected from the group consisting of:
5-bromo-6-chloro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-bromo-6-chloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-bromo-6-chloro-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-bromo-6-chloro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5,6-dichloro-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5,6-dichloro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5,6-dichloro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5,6-dichloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-ethyl-6-chloro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-nitro-6-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-nitro-6-methyl-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-nitro-6-methyl-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-nitro-6-methyl-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-amino-6-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-amino-6-methyl-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-amino-6-methyl-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-amino-6-methyl-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-bromo-6-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-bromo-6-methyl-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-bromo-6-methyl-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-bromo-6-methyl-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5- bromo -6- fluoro -3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5- bromo -6- fluoro l-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5- bromo -6- fluoro -3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;

5- bromo -6- fluoro -3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-cyano-6-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-cyano-6-methyl-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-cyano-6-methyl-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-cyano-6-methyl-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-cyano-6-fluoro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-cyano-6-fluoro-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-cyano-6-fluoro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-cyano-6-fluoro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-cyano-6-chloro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-cyano-6-chloro-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-cyano-6-chloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-cyano-6-chloro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-carbamoyl-6-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-carbamoyl-6-methyl-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-carbamoyl-6-methyl-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-carbamoyl-6-methyl-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-carbamoyl-6-fluoro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-carbamoyl-6-fluoro-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-carbamoyl-6-fluoro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-carbamoyl-6-fluoro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-carbamoyl-6-chloro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-carbamoyl-6-chloro-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-carbamoyl-6-chloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-carbamoyl-6-chloro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-amino-6-fluoro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-amino-6-fluoro-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-amino-6-fluoro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-amino-6-fluoro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-amino-6-chloro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-amino-6-chloro-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-amino-6-chloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-amino-6-chloro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-formamido-6-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine;

5-formamido-6-methyl-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-formamido-6-methyl-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-formamido-6-methyl-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-acetamido-6-fluoro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-acetamido-6-fluoro-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-acetamido-6-fluoro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-acetamido-6-fluoro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-acetamido-6-chloro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-acetamido-6-chloro-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-acetamido-6-chloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-acetamido-6-chloro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-methylamino-6-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-methylamino-6-methyl-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-methylamino-6-methyl-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-methylamino-6-methyl-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-ethylamino-6-fluoro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-ethylamino-6-fluoro-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-ethylamino-6-fluoro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-ethylamino-6-fluoro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-ethylamino-6-chloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-ethylamino-6-chloro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-ethylamino-6-chloro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-ethylamino-6-chloro-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-ethyl-6-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-ethyl-6-methyl-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-ethyl-6-methyl-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-ethyl-6-methyl-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-ethyl-6-fluoro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-ethyl-6-fluoro-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-ethyl-6-fluoro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-ethyl-6-fluoro-3-(1-methyl-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-propyl-6-chloro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-propyl-6-chloro-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-propyl-6-chloro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;

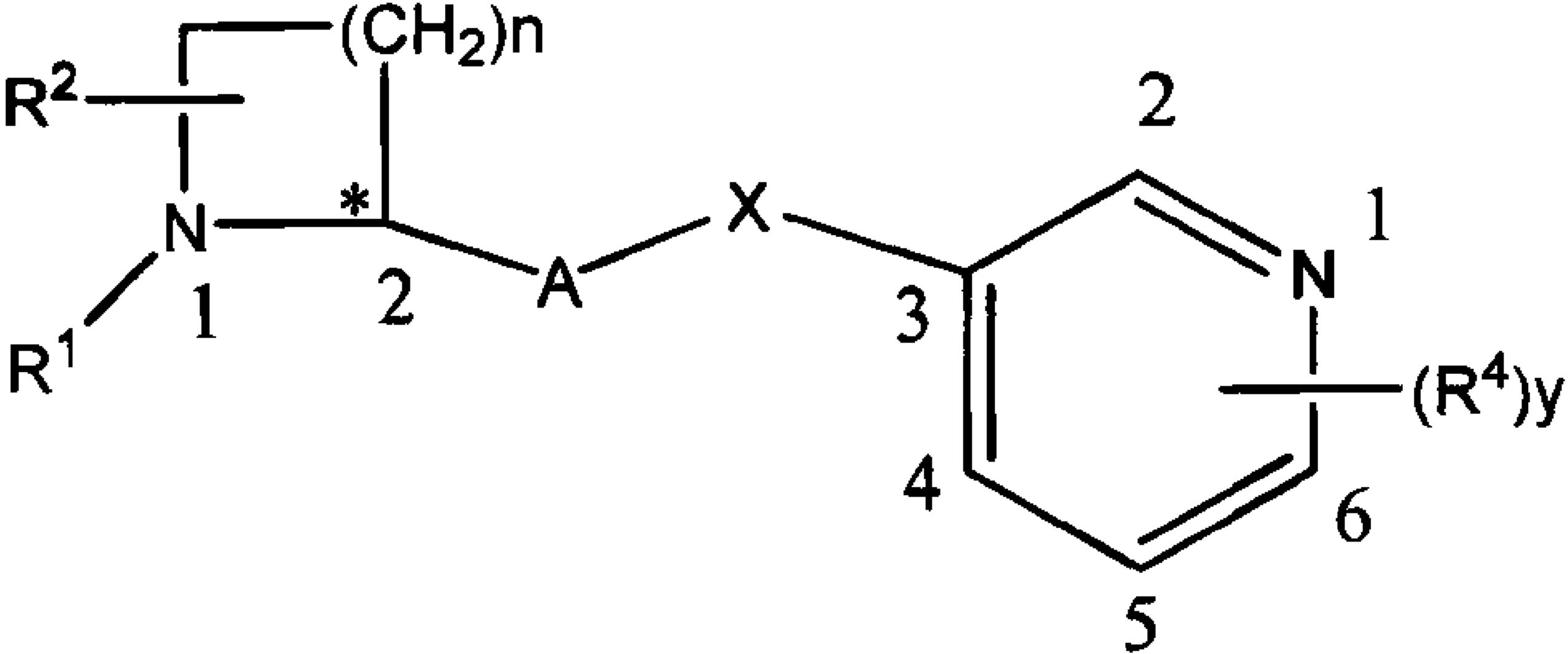
5-propyl-6-chloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-methyl-6-fluoro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-methyl-6-fluoro -3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5-methyl-6-fluoro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-methyl-6-fluoro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5-methyl-6-chloro-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5-methyl-6-chloro-3-(2-(*R)*-pyrrolidinylmethoxy)pyridine;
5-methyl-6-chloro-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5-methyl-6-chloro-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
5,6-dimethyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
5,6-dimethyl-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
5,6-dimethyl-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
5,6-dimethyl-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
6-fluoro-5-methoxy-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
6-fluoro-5-methoxy-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
6-fluoro-5-methoxy-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
6-fluoro-5-methoxy-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine;
6-fluoro-5-ethoxy-3-(2-(S)-pyrrolidinylmethoxy)pyridine;
6-fluoro-5-ethoxy-3-(2-(R)-pyrrolidinylmethoxy)pyridine;
6-fluoro-5-ethoxy-3-(1-methyl-2-(S)-pyrrolidinylmethoxy)pyridine;
6-fluoro-5-ethoxy-3-(1-methyl-2-(R)-pyrrolidinylmethoxy)pyridine; and
pharmaceutically acceptable salts thereof.

9. A pharmaceutical composition comprising a compound or salt as defined by any one of Claims 1 to 8, and a pharmaceutically acceptable carrier.

10. Use of a compound or salt as defined by any one of Claims 1 to 8, in the manufacture of a medicament for preventing or treating cognitive, neurological, and mental disorders characterized by decreased cholinergic function.

11. A compound or salt as defined by any one of Claims 1 to 8, for use in preventing or treating cognitive, neurological, and mental disorders characterized by decreased cholinergic function.

12. A pharmaceutical composition for preventing or treating cognitive, neurological, and mental disorders characterized by decreased cholinergic function, comprising a compound or salt as defined by any of Claims 1 to 8, and a pharmaceutically acceptable carrier.



(CH2)n
R2
N
*
X
A
R1
1
2
3
2
1
N
(R4)y
4
6
5