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(54) Title: SUBSTITUTED PYRIDINE COMPOUNDS USEFUL FOR CONTROLLING CHEMICAL SYNAPTIC TRANSMISSION

(57) Abstract: The present invention is directed to a series of substituted pyridine compounds (I), a method for selectively controlling neurotransmitter release in mammals using these compounds, and pharmaceutical compositions containing these compounds. Preferred compounds are 3’-(5’- and/or 6’-substituted) pyridyl ethers. n = 1-4, R’-R” as in the claims.
SUBSTITUTED PYRIDINE COMPOUNDS USEFUL FOR CONTROLLING CHEMICAL SYNAPTIC TRANSMISSION

Field of the Invention

The present invention is directed to a series of substituted pyridine compounds, a method for selectively controlling neurotransmitter release in mammals using these compounds, and pharmaceutical compositions containing these compounds. Preferred compounds are 3′-(5′- and/or 6′-substituted) pyridyl ethers.

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.


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 an 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 Ca²⁺) 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 membrane 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 predict 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 the 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, which is incorporated herein by reference.

Existing acetylcholine agonists are therapeutically suboptimal 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, debecation 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*, F. Giacobini and R. Becker, ed.; Taylor & Francis: New York, 1988; pp 333-336).


Ethers which are useful as antagonists of specific 5-hydroxy tryptamine (5-HT) receptors are disclosed in GB 2 208 510A; U.S. Patent No. 4,929,625; U.S. Patent No. 5,082,843 and U.S. Patent No. 4,997,839. However, these references disclose a 2-pyridyl moiety linked by oxygen to a saturated azabicyclic ring such as quinuclidyl or tropanyl. Analgesic pyridine-2-ethers are also disclosed in U.S. Patent Nos. 4,946,836 and 4,643,995. In these references, a 2-pyridyl moiety is linked to a nitrogen-containing cycloaliphatic ring through an -O-(CH₂)ₙ- linkage.

3-Pyridyloxymethyl heterocyclic ether compounds useful in controlling chemical synaptic transmission are disclosed in U.S. Patent No. 5,629,325; wherein a 3-pyridyl moiety is linked to a nitrogen-containing cycloaliphatic ring through an -O-CH₂- linkage. PCT Patent Application WO 94/08992 discloses various 3-pyridyloxy-heterocyclic compounds that are either unsubstituted or mono-substituted on the pyridine rings with groups such as Br, Cl, F, hydroxyl, C₁₋C₃ alkyl or C₁₋C₃ alkoxy, such compounds also described as having utility in enhancing cognitive function.

1,3-disubstituted pyrrolidines which have pharmacological action on the central nervous system wherein the pyrrolidine nitrogen is substituted by an -(CH₂)ₙ-B group, and ether-linked to a substituted pyridyl, among others are disclosed in U.S. Patent No. 5,037,841.

Cyclic amine compounds effective against senile dementia wherein the ring is ether-linked to a substituted 3-pyridyl among others are disclosed in European Patent Application No. 0 673 927 A1.

Aza ring ether derivatives and their use as nicotinic ACH receptor modulators are disclosed in WO 99/24422.

U.S. Patent No. 4,206,117 discloses 3-pyridyl aminoalkyl ether derivatives.

U.S. Patent No. 5,852,041 discloses a class of pyridine compounds which are modulators of acetylcholine receptors.
However, there is still a need for improved compounds for controlling chemical synaptic transmission.

It is therefore an object of this invention to provide novel substituted pyridine compounds. It is a further object of this invention to provide such compounds which selectively control neurotransmitter release.

**Summary of the Invention**

The present invention is directed to a series of substituted pyridine compounds, a method for selectively controlling neurotransmitter release in mammals using these compounds, and pharmaceutical compositions including these compounds. More particularly, the present invention is directed to compounds of the formula I

![Formula I](image)

wherein \( n \) is an integer of 1 to 4;

\( R^1 \) and \( R^2 \) are independently selected from the group consisting of hydrogen, lower alkyl, alkenyl, alkynyl, aralkyl and cyanomethyl;

\( R^3 \), at each occurrence, is selected from the group consisting of hydrogen, haloalkyl and lower alkyl;

\( R^4 \), at each occurrence, is independently selected from the group consisting of hydrogen, hydroxyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, alkenoxy, alkynoxy, thioalkoxy, aliphatic acyl, -CF₃, nitro, cyano, -N(C₁₋₃)₃
alkyl)-C(O)(C₁₋C₃ alkyl), -C₁₋C₃ alkylamino, alkenylamino, alkynylamino, di(C₁₋C₃ alkyl)amino, amino, halogen,
-C(O)O-(C₁₋C₃ alkyl), -C(O)NH-(C₁₋C₃ alkyl), aliphatic acyl,
-CH=NOH, -PO₃H₂, -OPO₃H₂, heterocyclylalkyl,
-C(O)N(C₁₋C₃ alkyl)₂, haloalkyl, alkoxy carbonyl, alkoxyalkoxy, carboxaldehyde, carboxamide, cycloalkyl, cycloalkenyl,
cycloalkynyl, aryl, aroyl, arylamino, arylamino, biaryl, thiopyridyl, heterocyclyl, heterocyclyl, alkylaryl, aralkyl, aralkenyl,
aliphatic acyl, alkylheterocyclyl, sulfonyl, sulfonamido, carbamate, arkoxyalkyl,
carboxyl and -C(O)NH(benzyl);

R³ is selected from the group consisting of hydrogen, halogen, lower alkyl, nitro, lower alkylamino and lower alkoxy;

R⁶ is selected from the group consisting of hydrogen, halogen, hydroxyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, alkenoxy, alkynoxy,
thioalkoxy, aliphatic acyl, -CF₃, nitro, amino, cyano, -N(C₁₋C₃ alkyl)-
-C(O)(C₁₋C₃ alkyl), -C₁₋C₃ alkylamino, alkenylamino, alkynylamino, di(C₁₋C₃ alkyl)amino,
-CH=NOH, -C(O)O-(C₁₋C₃ alkyl), -C(O)NH-(C₁₋C₃ alkyl),
-C(O)N(C₁₋C₃ alkyl)₂, haloalkyl, alkoxy carbonyl, alkoxyalkoxy, carboxaldehyde, carboxamide, cycloalkyl, cycloalkenyl,
cycloalkynyl, aryl, aroyl, arylamino, arylamino, biaryl, thiopyridyl, heterocyclyl, heterocyclyl, alkylaryl, aralkyl, aralkenyl,
aliphatic acyl, alkylheterocyclyl, sulfonyl, sulfonamido, carbamate, aliphatic acyl,
-CH=NOH, -PO₃H₂, -OPO₃H₂, heterocyclylalkyl, arkoxyalkyl, carboxyl
and -C(O)NH(benzyl); and

A is selected from the group consisting of -O-, -S-, -N(R¹)-, -SO₂N(R¹)- and
-NR¹SO₂-;

wherein R¹, R², R³, R⁴, R⁵ and R⁶ are unsubstituted or substituted with at least one electron donating or electron withdrawing group;
and pharmaceutically acceptable salts thereof; with the proviso that when \( A = O \), at least one of \( R^3 \) or \( R^6 \) is halogen; and with the further proviso that when \( R^3 \) and \( R^4 \) are attached to a carbon which is alpha to a heteroatom, \( R^4 \) is not halogen, hydroxyl or amino.

Presently preferred compounds are of formula II shown below:

![Chemical structure diagram](image)

**Formula II**

wherein \( n \) is an integer of 1 to 4;

\( R^1 \) and \( R^2 \) are independently selected from the group consisting of hydrogen, lower alkyl, alkenyl, alkynyl, aralkyl and cyanomethyl;

\( R^3 \), at each occurrence, is selected from the group consisting of hydrogen, haloalkyl and lower alkyl;

\( R^4 \), at each occurrence, is independently selected from the group consisting of hydrogen, hydroxyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, alkenoxy, alkyloxy,

- thioalkoxy, aliphatic acyl, -CF\(_3\), nitro, cyano, -N(C\(_1\)-C\(_3\) alkyl)-C(O)(C\(_1\)-C\(_3\) alkyl), -C\(_1\)-C\(_3\) alkylamino, alkenylamino, alkynylamino, di(C\(_1\)-C\(_3\) alkyl)amino, amino, halogen,

- -C(O)O-(C\(_1\)-C\(_3\) alkyl), -C(O)NH-(C\(_1\)-C\(_3\) alkyl), aliphatic acyl,

- -CH=NOH, -PO\(_3\)H\(_2\), -PO\(_4\)H\(_2\), heterocyclylalkyl,

- -C(O)N(C\(_1\)-C\(_3\) alkyl), haloalkyl, alkoxy carbonyl, alkoxyalkoxy, carboxaldehyde, carboxamide, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, aroyl, aryloxy, arylamino, biaryl, thiaaryl, heterocyclyl, heterocycloyl, alkylaryl, aralkyl, aralkenyl,
alkylheterocyclyl, sulfonyl, sulfonamido, carbamate, aryloxyalkyl, 
carboxyl and 
\(-\text{C(O)NH(benzyl)}\);

\(R^5\) is selected from the group consisting of hydrogen, halogen, lower alkyl, 
nitro, lower alkylamino and lower alkoxy; and

\(R^6\) is selected from the group consisting of hydrogen, halogen, hydroxyl, lower 
alkyl, lower alkenyl, lower alkynyl, lower alkoxy, alkenoxy, alkynoxy, 
thioalkoxy, aliphatic acyl, \(-\text{CF}_3\), nitro, amino, cyano, \(-\text{N(C}_1\text{-C}_3\text{ alkyl)}\)- 
\(\text{C(O)(C}_1\text{-C}_3\text{ alkyl)}, \text{-C}_1\text{-C}_3\text{ alkylamino, alkenylamino, alkynylamino,}
\text{di(C}_1\text{-C}_3\text{ alkylamino,}
\text{-C(O)O-(C}_1\text{-C}_3\text{ alkyl), -C(O)NH-(C}_1\text{-C}_3\text{ alkyl), -CH=NOH,}
\text{-C(O)N(C}_1\text{-C}_3\text{ alkyl)}_2, \text{haloalkyl, alkoxy carbonyl, alkoxyalkoxy,}
carboxaldehyde, carboxamide, cycloalkyl, cycloalkenyl, 
cycloalkynyl, aryl, aroyl, aryloxy, arylamino, biaryl, thioaryl, 
heterocyclyl, heterocyclyl, alkylaryl, aralkyl, aralkenyl, 
alylheterocyclyl, sulfonyl, sulfonamido, carbamate, aliphatic acyl, -
\text{CH=NOH, -PO}_3\text{H}_2, -\text{OPO}_3\text{H}_2, \text{heterocyclylalkyl, aryloxyalkyl, carboxyl}
and \(-\text{C(O)NH(benzyl)}\);

wherein \(R^1, R^2, R^3, R^4, R^5\) and \(R^6\) are unsubstituted or substituted with at least 
one electron donating or electron withdrawing group;

and pharmaceutically acceptable salts thereof;

with the proviso that when \(R^3\) and \(R^4\) are attached to a carbon 
which is alpha to a heteroatom, \(R^4\) is not halogen, 
hydroxyl or amino;

and with the further proviso that at least one of \(R^5\) or \(R^6\) is halogen.

Presently preferred are compounds of formula II wherein \(n = 2\), \(R^5\) is halogen and \(R^6\) 
is selected from the group consisting of hydrogen, lower alkyl and halogen.

Presently most preferred compounds are of formula III shown below:
wherein n is an integer of 1 to 4;
R¹ and R² are independently selected from the group consisting of hydrogen and lower alkyl;
R³ is selected from the group consisting of hydrogen, haloalkyl and lower alkyl;
R⁵ is selected from the group consisting of hydrogen, halogen, lower alkyl, nitro, lower alkylamino and lower alkoxy; and
R⁵ is selected from the group consisting of hydrogen, halogen, hydroxyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, alkenoxy, alkynoxy, thioalkoxy, aliphatic acyl, -CF₃, nitro, amino, cyano, -N(C₁₋₃ alkyl)-C(O)(C₁₋₃ alkyl), -C₁₋₃ alkylamino, alkenylamino, alkynylamino, di(C₁₋₃ alkyl)amino, CH=NOH, -C(O)O-(C₁₋₃ alkyl), -C(O)NH-(C₁₋₃ alkyl), -C(O)N(C₁₋₃ alkyl)₂, haloalkyl, alkoxy carbonyl, alkoxyalkoxy, aliphatic acyl, -CH=NOH, -PO₃H₂, -OPO₃H₂, heterocyclylalkyl, carboxaldehyde, carboxamide, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, aroyl, aryloxy, alylamino, biaryl, thioaryl, heterocycl, heterocyclyl, alkylaryl, aralkyl, aralkenyl, alkylheterocycl, sulfonyl, sulfonamido, carbamate, aryloxyalkyl, carboxyl and -C(O)NH(benzyl);
wherein R₁, R², R³, R⁵ and R⁶ are unsubstituted or substituted with at least one
electron donating or electron withdrawing group;

and pharmaceutically acceptable salts thereof;

with the proviso that at least one of R² or R₆ is halogen.

Presently preferred compounds of formula III have R² and R₆ each
independently selected from the group consisting of lower alkyl, -F, -Cl and
-Br; n=1 or 2 and R³ as lower alkyl or haloalkyl.

Presently preferred compounds include 5-[(S)-2-amino-1-propoxy]-2-chloro
pyridine, 5-[(S)-2-methylamino-1-propoxy]-2-chloro pyridine, 5-[(S)-2-amino-1-
propoxy]-2-fluoro pyridine, 5-[(S)-2-methylamino-1-propoxy]-2-fluoro pyridine,
5-[(S)-2-methylamino-1-propoxy]-2-chloro-3-bromo pyridine, 5-[(S)-2-
methylamino-1-propoxy]-2-chloro-3-methyl pyridine and pharmaceutically
acceptable salts thereof including, but not limited to p-toluene sulfonic acid.

**Detailed Description of the Invention**

**Definitions of Terms**

The term “alkyl” as used herein alone or in combination refers to C₁-C₁₂
straight or branched, substituted or unsubstituted saturated chain radicals derived from
saturated hydrocarbons by the removal of one hydrogen atom, unless the term alkyl is
preceded by a C₅-C₆ designation. Representative examples of alkyl groups include
methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, and tert-butyl among
others.

The term “alkenyl”, alone or in combination, refers to a substituted or
unsubstituted straight-chain or substituted or unsubstituted branched-chain alkenyl
radical containing from 2 to 10 carbon atoms. Examples of such radicals include, but
are not limited to, ethenyl, E- and Z-pentenyl, decenyl and the like.

The term “alkynyl”, alone or in combination, refers to a substituted or
unsubstituted straight or substituted or unsubstituted branched chain alkynyl radical
containing from 2 to 10 carbon atoms. Examples of such radicals include, but are not
limited to ethynyl, propynyl, propargyl, butynyl, hexynyl, decynyl and the like.

The term “lower” modifying “alkyl”, “alkenyl”, “alkynyl” or “alkoxy” refers to
a C₁-C₆ unit for a particular functionality. For example lower alkyl means C₁-C₆ alkyl.

The term “aliphatic acyl” alone or in combination, refers to radicals of formula
alkyl-C(=O)-, alkenyl-C(=O)- and alkynyl-C(=O)- derived from an alkane-, alkene-
or
alkynicarboxylic acid, wherein the terms “alkyl”, “alkenyl” and “alkynyl” are as defined
above. Examples of such aliphatic acyl radicals include, but are not limited to, acetyl,
propionyl, butyryl, valeryl, 4-methylvaleryl, acryloyl, crotyl, propioly and
methylpropioly, among others.

The term “cycloalkyl” as used herein refers to an aliphatic ring system having 3
to 10 carbon atoms and 1 to 3 rings, including, but not limited to cyclopropyl,
cyclopentyl, cyclohexyl, norbornyl, and adamantyl among others. Cycloalkyl groups
can be unsubstituted or substituted with one, two or three substituents independently
selected from lower alkyl, haloalkyl, alkoxy, thioalkoxy, amino, alkylamino,
dialkylamino, hydroxy, halo, mercapto, nitro, carboxaldehyde, carboxy, alkoxycarbonyl
and carbamid.

“Cycloalkyl” includes cis or trans forms. Furthermore, the substituents may either be
in endo or exo positions in the bridged bicyclic systems.

The term “cycloalkenyl” as used herein alone or in combination refers to a
cyclic carbocycle containing from 4 to 8 carbon atoms and one or more double bonds.
Examples of such cycloalkenyl radicals include, but are not limited to, cyclopentenyl,
cyclohexenyl, cyclopentadienyl and the like.

The term “cycloalkylalkyl” as used herein refers to a cycloalkyl group appended
to a lower alkyl radical, including, but not limited to cyclohexylmethyl.

The term “halo” or “halogen” as used herein refers to I, Br, Cl or F.

The term “haloalkyl” as used herein refers to a lower alkyl radical, to which is
appended at least one halogen substituent, for example chloromethyl, fluoroethyl,
trifluoromethyl and pentafluoroethyl among others.
The term "alkoxy", alone or in combination, refers to an alkyl ether radical, wherein the term “alkyl” is as defined above. Examples of suitable alkyl ether radicals include, but are not limited to, methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy and the like.

The term “alkenoxo”, alone or in combination, refers to a radical of formula alkenyl-O-, provided that the radical is not an enol ether, wherein the term “alkenyl” is as defined above. Examples of suitable alkenoxy radicals include, but are not limited to, allyloxy, E- and Z- 3-methyl-2-propenoxo and the like.

The term “alkynoxy”, alone or in combination, refers to a radical of formula alkynyl-O-, provided that the radical is not an -ynol ether. Examples of suitable alkynoxy radicals include, but are not limited to, propargyloxy, 2-butylnyloxy and the like.

The term “carboxyl” as used herein refers to a carboxylic acid radical, -C(O)OH.

The term “thioalkoxy”, refers to a thioether radical of formula alkyl-S-, wherein “alkyl” is as defined above.

The term “carboxaldehyde” as used herein refers to -C(O)R wherein R is hydrogen.

The term “carboxamide” as used herein refers to -C(O)NR,R wherein R,a and R,b are each independently hydrogen, alkyl or any other suitable substituent.

The term "alkoxyalkoxy" as used herein refers to R_cO-R_dO- wherein R_c is lower alkyl as defined above and R_d is alkylene wherein alkylene is -(CH_2)_n- wherein n' is an integer from 1 to 6. Representative examples of alkoxyalkoxy groups include methoxymethoxy, ethoxymethoxy, t-butoxymethoxy among others.

The term "alkylamino" as used herein refers to R_eNH- wherein R_e is a lower alkyl group, for example, ethylamino, butylamino, among others.

The term “alkenylamino” alone or in combination, refers to a radical of formula alkenyl-NH-or (alkenyl)_2N-, wherein the term “alkenyl” is as defined
above, provided that the radical is not an enamine. An example of such
alkenylamino radical is the allylamino radical.

The term “alkynylamino”, alone or in combination, refers to a radical of
formula alkynyln-NH- or (alkynyln)_2N- wherein the term “alkynyln” is as defined
above, provided that the radical is not an amine. An example of such
alkynylamino radicals is the propargyl amino radical.

The term "dialkylamino" as used herein refers to R_tR_sN- wherein R_t and
R_s are independently selected from lower alkyl, for example diethylamino, and
methyl propylamino, among others.

The term "amino" as used herein refers to H_2N-.

The term "alkoxycarbonyl" as used herein refers to an alkoxyl group as
previously defined appended to the parent molecular moiety through a carbonyl
group. Examples of alkoxycarbonyl include methoxycarbonyl, ethoxycarbonyl,
and isopropoxycarbonyl among others.

The term “aryl” or “aromatic” as used herein alone or in combination
refers to a substituted or unsubstituted carbocyclic aromatic group having
about 6 to 12 carbon atoms such as phenyl, naphthyl, indenyl, indanyl, azulenyl,
fluorenyl and anthracenyl; or a heterocyclic aromatic group selected from the
group consisting of furyl, thiophenyl, pyridyl, pyrrolyl, oxazolyl, thiazolyl,
imidazolyl, pyrazolyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, 1,2,3-
oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyridazinyl, pyrimidinyl;
pyrazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, indolizinyl, indolyl, isoindolyl, 3H-
indolyl, indoliny, benzo[b]furanyl, 2,3-dihydrobenzofuranyl,
benzo[b]thiophenyl, 1H-indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-
quinolizinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl,
1,8-naphthridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl,
phenoxyazinyl, pyrazolo[1,5-c]triazinyl and the like. “Arylalkyl” and “alkylaryl”
employ the term “alkyl” as defined above. Rings may be multiply substituted.
The term “aralkyl”, alone or in combination, refers to an aryl substituted alkyl radical, wherein the terms “alkyl” and “aryl” are as defined above. Examples of suitable aralkyl radicals include, but are not limited to, phenylmethyl, phenethyl, phenylhexyl, diphenylmethyl, pyridylmethyl, tetrazolyl methyl, furylmethyl, imidazolyl methyl, indolylmethyl, thiarylpropyl and the like.

The term “aralkenyl”, alone or in combination, refers to an aryl substituted alkenyl radical, wherein the terms “aryl” and “alkenyl” are as defined above.

The term “arylamino”, alone or in combination, refers to a radical of formula aryl-NH-, wherein “aryl” is as defined above. Examples of arylamino radicals include, but are not limited to, phenylamino(anilido), naphthlamino, 2-, 3-, and 4- pyridylamino and the like.

The term “biaryl”, alone or in combination, refers to a radical of formula aryl-aryl, wherein the term “aryl” is as defined above.

The term “thioaryl”, alone or in combination, refers to a radical of formula aryl-S-, wherein the term “aryl” is as defined above. An example of a thioaryl radical is the thiophenyl radical.

The term “aryloyl”, alone or in combination, refers to a radical of formula aryl-CO-, wherein the term “aryl” is as defined above. Examples of suitable aromatic acyl radicals include, but are not limited to, benzoyle, 4-halobenzoyle, 4-carboxybenzoyle, naphthoyl, pyridylcarbonyl and the like.

The term “heterocyclyl”, alone or in combination, refers to a non-aromatic 3- to 10-membered ring containing at least one endocyclic N, O, or S atom. The heterocycle may be optionally aryl-fused. The heterocycle may also optionally be substituted with at least one substituent which is independently selected from the group consisting of hydrogen, halogen, hydroxyl, amino, nitro, trifluoromethyl, trifluoromethoxy, alkyl, aralkyl, alkenyl, alkyndyl, aryl, cyano, carboxy, carboxalkoxy, carboxyalkyl, oxo, arylsulfonyl and aralkylaminocarbonyl among others.
The term "alkylheterocycyl" as used herein refers to an alkyl group as previously defined appended to the parent molecular moiety through a heterocycyl group.

The term "heterocyclalkyl" as used herein refers to a heterocycyl group as previously defined appended to the parent molecular moiety through an alkyl group.

The term “aminal” as used herein refers to the structure $R_iC(NR_jR_k)(NR_kR_l)$ wherein $R_i$, $R_j$, $R_k$, and $R_l$ are each independently hydrogen, alkyl or any other suitable substituent.

Use of the above terms is meant to encompass substituted and unsubstituted moieties. Substitution may be by one or more groups such as alcohols, ethers, esters, amides, sulfones, sulfides, hydroxyl, nitro, cyano, carboxy, amines, heteroatoms, lower alkyl, lower alkoxy, lower alkoxy carbonyl, alkoxyalkoxy, acyloxy, halogens, trifluoromethoxy, trifluoromethyl, alkyl, aralkyl, alkenyl, alkynyl, aryl, cyano, carboxy, carboalkoxy, carboxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycyl, alkylheterocycyl, heterocyclalkyl, oxo, arylsulfonyl and aralkylaminocarbonyl or any of the substituents of the preceding paragraphs or any of those substituents either attached directly or by suitable linkers. The linkers are typically short chains of 1-3 atoms containing any combination of $-C-$, $-C(O)-$, $-NH-$, $-S-$, $-S(O)-$, $-O-$, $-C(O)O-$ or $-S(O)O-$. Rings may be substituted multiple times.

The terms “electron-withdrawing” or “electron-donating” refer to the
ability of a substituent to withdraw or donate electrons relative to that of hydrogen if hydrogen occupied the same position in the molecule. These terms are well-understood by one skilled in the art and are discussed in Advanced Organic Chemistry by J. March, 1985, pp. 16-18, incorporated herein by reference. Electron withdrawing groups include halo, nitro, carboxyl, lower alkenyl, lower alkynyl, carboxaldehyde, carboxyamido, aryl, quaternary ammonium, trifluoromethyl, and aryl lower alkanoyl among others. Electron donating groups include such groups as hydroxy, lower alkyl, amino, lower alkylamino, di(lower alkyl)amino, aryloxy, mercapto, lower alkylthio, lower alkylmercapto, and disulfide among others. One skilled in the art will appreciate that the aforesaid substituents may have electron donating or electron withdrawing properties under different chemical conditions. Moreover, the present invention contemplates any combination of substituents selected from the above-identified groups.

The most preferred electron donating or electron withdrawing substituents are halo, nitro, alkanoyl, carboxaldehyde, arylalkanoyl, aryloxy, carboxyl, carboxamide, cyano, sulfonyl, sulf oxide, heterocyclyl, guanidine, quaternary ammonium, lower alkenyl, lower alkynyl, sulfonium salts, hydroxy, lower alkoxy, lower alkyl, amino, lower alkylamino, di(lower alkyl)amino, amine lower alkyl mercapto, mercaptoalkyl, alkylthio and alkyl dithio.

As used herein, the term “composition” is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from a combination of the
specified ingredients in the specified amounts.

The term "heteroatom" as used herein encompasses nitrogen, sulfur and oxygen.

The term "alpha" as used herein indicates the position immediately adjacent to the position described.

Abbreviations

Abbreviations which have been used in the reaction schemes and the examples that follow have the following meanings: BOC for t-butyloxycarbonyl, Et₂O for diethyl ether, EtOAc for ethyl acetate, MeOH for methanol, EDC for ethylene dichloride, FMOC for 9-fluorenylmethoxy carbonyl, DMF for dimethylformamide, LAH for lithium aluminum hydride, DEAD for diethylazodicarboxylate and TFA for trifluoroacetic acid.

The compounds of the present invention can be used in the form of pharmaceutically acceptable salts derived from inorganic or organic acids. The phrase "pharmaceutically acceptable salts" means those salts which are, within the scope of sound medical judgement, 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, 1977, 66: p. 1 et seq. The salts can be prepared in situ during the final isolation and purification of the compounds of the invention or separately by reacting a free base function with a suitable organic acid.
Representative acid addition salts include, but are not limited to acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate (isothionate), lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmitoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, phosphate, glutamate, bicarbonate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; arylalkyl halides like benzyl and phenethyl bromides and others. Water or oil-soluble or dispersible products are thereby obtained. Examples of acids which can be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, hydrobromic acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid.

Basic addition salts can be prepared in situ during the final isolation and purification of compounds of this invention by reacting a carboxylic acid-containing moiety with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia or an organic primary, secondary or tertiary amine. Pharmaceutically acceptable
salts include, but are not limited to, cations based on alkali metals or alkaline earth metals such as lithium, sodium, potassium, calcium, magnesium and aluminum salts and the like and nontoxic quaternary ammonia and amine cations including ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine and the like. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, piperazine and the like.

Dosage forms for topical administration of a compound of this invention include powders, sprays, ointments and inhalants. The active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives, buffers or propellants which can be required. Ophthalmic formulations, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

Actual dosage levels of active ingredients in the pharmaceutical compositions of this invention can be varied so as to obtain an amount of the active compound(s) which is effective to achieve the desired therapeutic response for a particular patient, compositions and mode of administration. The selected dosage level will depend upon the activity of the particular compound, the route of administration, the severity of the condition being treated and the condition and prior medical history of the patient being treated. However, it is within the skill of the art to start doses of the compound at levels lower than required for to achieve the desired therapeutic effect and to gradually increase
the dosage until the desired effect is achieved.

When used in the above or other treatments, a therapeutically effective amount of one of the compounds of the present invention can be employed in pure form or, where such forms exist, in pharmaceutically acceptable salt, ester or prodrug form. Alternatively, the compound can be administered as a pharmaceutical composition containing the compound of interest in combination with one or more pharmaceutically acceptable excipients. The phrase "therapeutically effective amount" of the compound of the invention means a sufficient amount of the compound to treat disorders, 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 judgement. 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; 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. For example, it is well within the skill of the art to start doses of the compound at levels lower than required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.
The total daily dose of the compounds of this invention administered to a human or lower animal may range from about 0.0001 to about 1000 mg/kg/day. For purposes of oral administration, more preferable doses can be in the range of from about 0.001 to about 5 mg/kg/day. If desired, the effective daily dose can be divided into multiple doses for purposes of administration; consequently, single dose compositions may contain such amounts or submultiples thereof to make up the daily dose.

The present invention also provides pharmaceutical compositions that comprise compounds of the present invention formulated together with one or more non-toxic pharmaceutically acceptable carriers. The pharmaceutical compositions can be specially formulated for oral administration in solid or liquid form, for parenteral injection or for rectal administration.

The pharmaceutical compositions of this invention can be administered to humans and other mammals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments or drops), bucally or as an oral or nasal spray. The term "parenterally," as used herein, refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Pharmaceutical compositions of this invention for parenteral injection comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use.
Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol and the like), vegetable oils (such as olive oil), injectable organic esters (such as ethyl oleate) and suitable mixtures thereof. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms can be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of the drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This can 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.

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 just prior to use.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound may be 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 carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, 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 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 may also be of a composition such 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.

The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, 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, dimethyl formamide, 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 may also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, tragacanth and mixtures thereof.

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 room temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals which are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients and the like. The preferred lipids are natural and synthetic phospholipids and phosphatidyl cholines (lecithins) used
separately or together.


The term "pharmaceutically acceptable prodrugs" as used herein represents those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. Prodrugs of the present invention may be rapidly transformed in vivo to the parent compound of the above formula, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, “Pro-drugs as Novel Delivery Systems”, V. 14 of the *A.C.S. Symposium Series*, and in Edward B. Roche, ed., *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association and Pergamon Press (1987), hereby incorporated by reference.

The present invention contemplates both synthetic compounds of formulae I-III of the present invention, as well as compounds formed by *in vivo* conversion to compounds of the present invention.

Compounds of the present invention may exist as stereoisomers wherein asymmetric or chiral centers are present. These stereoisomers are "R" or "S" depending on the configuration of substituents around the chiral carbon atom.
The present invention contemplates various stereoisomers and mixtures thereof. Stereoisomers include enantiomers and diastereomers, and mixtures of enantiomers or diastereomers. Individual stereoisomers of compounds of the present invention may be prepared synthetically from commercially available starting materials which contain asymmetric or chiral centers or by preparation of racemic mixtures followed by resolution well-known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary or (2) direct separation of the mixture of optical enantiomers on chiral chromatographic columns.

The compounds of the invention can exist in unsolvated as well as solvated forms, including hydrated forms, such as hemi-hydrates. In general, the solvated forms, with pharmaceutically acceptable solvents such as water and ethanol among others are equivalent to the unsolvated forms for the purposes of the invention.

The present compounds may have activity against disorders which are mediated through the central nervous system. The following references describe various disorders affected by nicotinic acetylcholine receptors: 1) Williams, M.; Armeric, S. P.: “Beyond the Tobacco Debate: dissecting out the therapeutic potential of nicotine” Exp. Opin. Invest. Drugs (1996) 5 (8) pp. 1035-1045; 2) Armeric, S. P.; Sullivan, J. P.; Williams, W.: “Neuronal nicotinic acetylcholine receptors. Novel targets for central nervous system

Arneric, S. P.; Holladay, M. W.; Sullivan, J. P.: “Cholinergic channel modulators as a novel therapeutic strategy for Alzheimer’s disease.” Exp. Opin. Invest. Drugs (1996) 5 (1): 79-100; 4) Lindstrom, J.: “Nicotinic Acetylcholine Receptors in Health and Disease.” Molecular Neurobiology (1997) 15: pp. 193-222; and 5) Lloyd, G K; Menzaghi, F; Bontempi B; Suto, C; Siegel, R; Akong, M; Stauderman, K; Velicelebi, G; Johnson, E; Harpold, M M; Rao, T S; Sacaan, A I; Chavez-Noriega, L E; Washburn, M S; Vernier, J M; Cosford, N D P; McDonald, L A: “The potential of subtype-selective neuronal nicotinic acetylcholine receptor agonists as therapeutic agents.” Life Sciences (1998) 62 (17/18): pp. 1601-1606. These disorders include, but are not limited to the following: pain (references 1 and 2), Alzheimer’s disease (references 1-5), Parkinson’s disease (references 1, 4 and 5), memory dysfunction, Tourette’s syndrome (references 1, 2 and 4), sleep disorders (reference 1), attention deficit hyperactivity disorder (references 1 and 3), neurodegeneration, inflammation, neuroprotection (references 2 and 3), amyotrophic lateral sclerosis, anxiety (references 1, 2 and 3), depression (reference 2), mania, schizophrenia (references 1, 2 and 4), anorexia and other eating disorders, AIDS-induced dementia, epilepsy (references 1, 2 and 4), urinary incontinence (reference 1), Crohn’s disease, migraines, PMS, erectile dysfunction, substance abuse, smoking cessation (references 1 and 2) and inflammatory bowel syndrome (references 1 and 4) among others.
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 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. As indicated in Scheme 1, a suitably N-protected amino acid may be converted to the corresponding alcohol, by the action of one of several appropriate reducing agents, including for example BH₃-THF, BH₃-SMe₂, DiBAI-H, LiAlH₄, and the like. The t-butoxycarbonyl (Boc) group is illustrated, but other standard N-protecting groups can also be used, including for example benzylxycarbonyl, benzyl, toluenesulfonyl, FMOC, and phthalimido among others. The starting amino acids are chiral, and generally available from commercial sources in either R or S-configuration, as well as in the racemic modification. Since the reduction and subsequent transformations can be achieved while maintaining optical purity, the methods outlined below provide access to individual enantiomers, as well as racemates of the final compounds.

Scheme 1

![Scheme 1 Diagram](image-url)
Formation of the pyridyl ether may be accomplished in two distinct ways. One construct involves activation of the hydroxyl group of the amino alcohol and its subsequent displacement by a substituted hydroxypyridine. Thus, as illustrated in Scheme 1, conversion of the alcohol to a good leaving group, such as a sulfonate ester (tosylate, mesylate, etc.) or halides provides suitable activation so that reaction with an hydroxypyridine under basic conditions will produce the ether. Alternatively, activation of the alcohol with triphenylphosphine and a dialkyl azodicarboxylate allows ether formation under neutral conditions.

An alternate mode for pyridyl ether formation is illustrated in Scheme 2.

In this process, the alcohol is engaged in aromatic substitution of a substituted pyridine. Suitable leaving groups on the pyridine include halide, nitro, and trifluoromethanesulfonate. In favorable cases, substitution can be achieved by reaction of the alkoxide, formed from the alcohol by action of sodium or potassium hydride, directly with the substituted pyridine. For less-reactive pyridines, a suitable transition metal catalyst (e.g., palladium or copper...
complexes) may be used to facilitate the displacement.

Scheme 3 illustrates that deprotection of the amine may be accomplished in conjunction with alkylation to provide a primary, secondary, or tertiary amine, as desired. Thus, alkylation of the Boc-protected amine with a suitable alkyl halide provides for introduction of one alkyl group. Removal of the protecting group under acidic conditions provides the secondary amine, which can be alkylated again with the same or a different alkyl group. Other standard manipulations of the amine also apply, so that amine alkylations can be accomplished via condensation with an aldehyde or ketone with reduction by NaBH₃CN, NaBH₄, or H₂ (reductive amination), or acylation with, e.g., an acyl halide followed by reduction with LiAlH₄.

In this manner, the range of nitrogen substituents represented in the invention may be introduced.
Further elaboration of the pyridine substituents may be accomplished after ether formation as illustrated in Scheme 4. A halide substituent may be activated by palladium catalysis to C-C bond formation with aryl, vinyl and alkynyl tin of boronate derivatives. Likewise, alkenes can be added via the Heck reaction, and a similar process allows incorporation of a nitrile. The products of these initial transformations may be further elaborated according to standard, well-known methods of organic synthesis to provide further compounds of the invention. Another useful method involves lithiation of the halopyridine with trapping of the organolithium intermediate by a suitable electrophile, for example N,N-dimethylformamide for introduction of the formyl group. This can in turn be elaborated in a variety of ways familiar to one skilled in the art, including reduction and addition of suitable organometallic reagents.
The following examples are presented to describe the preferred embodiments and utilities of the invention, and are not meant to limit the invention unless otherwise stated in the claims appended hereto.

Example 1

5-{(S)-2-amino-1-propyloxy}-2-chloro pyridine p-toluenesulfonic acid 1 was prepared as follows.

First, 2-{(S)-N-BOC}-propanol 1A was prepared in the following manner. A solution of N-(tert-butoxycarbonyl)-L-alanine (25 g, 132 mmol) in anhydrous THF (150 mL) at 0°C was treated with borane (1M solution in THF, 200 mL) over a period of 45 minutes. The ice bath was then removed and the reaction mixture was stirred at room temperature for 3 hours. Saturated NaHCO₃ solution was added slowly to quench the reaction. The resultant solution was then stirred overnight. Next, solvent was removed under reduced pressure. The remaining water phase was extracted 4X with ethyl ether.
combined ether extract was washed with brine, dried (MgSO₄), filtered, and concentrated. The residue was flash chromatographed on silica gel with 30% ethyl acetate/hexanes to provide a clear oil 1A (69%, 15.9 g). MS (Cl/NH₃) m/e 176 (M+H)⁺, 193 (M+NH₄)!; ¹H NMR (CDCl₃, 300 MHz) δ: 1.15 (d, J=7 Hz, 3H), 1.45 (s, 9H), 3.51 (q, J=5 Hz, 1H), 3.65 (dd, J=4, 11 Hz, 1H), 3.78 (bs, 1H).

2-[(S)-N-BOC]-propanol tosylate 1B was prepared next in the following manner. A solution of the product 1A (7.30 g, 41.7 mmol) in CH₂Cl₂ (100 mL) at room temperature was treated with triethylamine (9.3 mL, 66.7 mmol) and p-toluenesulfonyl chloride (9.54 g, 50.1 mmol), stirred overnight. The reaction mixture was diluted with CH₂Cl₂ to 300 mL, washed with water, 5% NaHCO₃, and brine. It was then dried (MgSO₄), filtered and concentrated. The residue was flash chromatographed on silica gel with 30% ethyl acetate/hexanes to provide a white solid 1B (61%, 8.40 g). MS (Cl/NH₃) m/e 330 (M+H)⁺, 347 (M+NH₄)⁺; ¹H NMR (CDCl₃, 300 MHz) δ: 1.16 (d, J=7 Hz, 3H), 1.40 (s, 9H), 2.45 (s, 3H), 3.92-4.07 (m, 3H), 4.57 (bs, 1H), 7.35 (d, J=8 Hz, 2H), 7.79 (d, J=6 Hz, 2H).

5-[(S)-2-N-BOC-amino-1-propoxy]-2-chloro pyridine 1C was prepared next in the following manner. A solution of the product 1B (2.35 g, 7.14 mmol) in DMF (47 mL) was treated with potassium hydroxide (1.00 g, 17.9 mmol) and 2-chloro-5-hydroxyl pyridine (1.16 g, 8.93 mmol), stirred at 85°C overnight. DMF was removed under reduced pressure at 60°C. The residue was dissolved in a mixture of H₂O and CH₂Cl₂. The organic layer was
washed with water, and brine. It was then dried (MgSO₄), filtered and concentrated. The residue was flash chromatographed on silica gel with 20% ethyl acetate/hexanes to provide a light yellow solid 1C (53%, 1.07 g). MS (Cl/NH₃) m/e 287 (M+H)⁺, 304 (M+NH₃)⁺; ¹H NMR (CDCl₃, 300 MHz) δ: 1.30 (d, J=7 Hz, 3H), 1.45 (s, 9H), 3.92-4.14 (m, 3H), 4.68 (bs, 1H), 7.22-7.25 (m, 2H), 8.07 (m, 1H).

5-[(S)-2-amino-1-propyloxy]-2-chloro pyridine p-toluenesulfonic acid 1 was next prepared as follows. A solution of the product 1C (198 mg, 0.691 mmol) in CH₂Cl₂ (5 mL) was treated with p-toluenesulfonic acid monohydrate (138 mg, 0.726 mmol) and refluxed at 60°C overnight. Solvent was removed by bubbling nitrogen into the solution. Ethyl ether (30 mL) was added next and stirred for 5 minutes. The ether was then decanted and the procedure was repeated. The residue was then dried under vacuum to provide a white solid 1. mp 110-112°C; MS (APCI⁺) m/e 187 (M+H)⁺; ¹H NMR (D₂O, 500 MHz) δ: 1.42 (d, J=5 Hz, 3H), 2.38 (s, 3H), 3.83 (bs, 1H), 4.11 (t, J=8 Hz, 1H), 4.29 (dd, J=5, 10 Hz, 1H), 7.33 (d, J=5 Hz, 2H), 7.40-7.50 (m, 2H), 7.67 (d, J=10 Hz, 2H), 8.05 (s, 1H); Analysis calculated for C₁₀H₁₂ClN₂O•1.2C₇H₈O₃S•0.4H₂O: C, 49.18; H, 5.39; N, 6.99; Found: C, 49.13; H, 5.55; N, 6.74; [α]D²⁵⁺ = +6.1° (c=1.4, MeOH).

Example 2

5-[(S)-2-dimethylamino-1-propyloxy]-2-chloro pyridine p-toluenesulfonic acid 2 was synthesized as follows.
5-[(S)-2-dimethylamino-1-propyloxy]-2-chloro-pyridine 2A was
prepared as follows. A solution of the product from Example 1C (220 mg,
0.768 mmol) in a mixture of formaldehyde (37 wt. % in water, 8 mL) and
formic acid (6 mL) was stirred at 65°C overnight. The excess reagents were
removed under reduced pressure at 45°C. Aqueous NaOH solution (1N) was
added to the residue and extracted 3X with CH₂Cl₂. The combined CH₂Cl₂
extract was washed with brine, dried (MgSO₄), filtered, and concentrated. The
residue was flash chromatographed on silica gel with 95/5/0.5
CH₂Cl₂/MeOH/NH₄OH to provide the title compound (65%, 113 mg). MS
(Cl/NH₄) m/e 215 (M+H)+.

5-[(S)-2-dimethylamino-1-propyloxy]-2-chloro pyridine p-
toluenesulfonic acid 2 was prepared next as follows.

A solution of the product 2A (100 mg, 0.466 mmol) in ethyl acetate (1
mL) at room temperature was treated with p-toluenesulfonic acid monohydrate
(93 mg, 0.489 mmol) and stirred for 5 minutes. Ethyl ether (30 mL) was added
next and stirred for additional 5 minutes. The ether was decanted and the
procedure was repeated. The residue was then dried under vacuum to provide 2
as a white hygroscopic solid. mp 54-56°C; MS (APCI⁺) m/e 215 (M+H)+; ¹H
NMR (D₂O, 500 MHz) δ: 1.42 (d, J=5 Hz, 3H), 2.38 (s, 3H), 2.85 (s, 3H), 2.95
(s, 3H), 3.84 (m, 1H), 4.25 (m, 1H), 4.35-4.41 (m, 1H), 7.35 (d, J=5 Hz, 2H),
7.44-7.68 (m, 2H), 7.68 (d, J=15 Hz, 2H), 8.08 (m, 1H); Analysis calculated
for C₁₉H₁₅N₂ClO·1.2C₂H₅O₂S·0.4H₂O: C, 51.57; H, 5.97; N, 6.54; Found: C,
51.31; H, 5.99; N, 6.55; [α]D²⁵=+2.9° (c=2.5, MeOH).
Example 3

5-[(S)-2-methylamino-1-propyloxy]-2-chloro pyridine p-toluenesulfonic acid 3 was synthesized as follows.

First, 5-[(S)-2-N-BOC-methylamino-1-propyloxy]-2-chloro pyridine 3A was prepared according to the following procedure.

A solution of the product 1C (190 mg, 0.663 mmol) in THF (10 mL) at room temperature was treated with sodium hydride (60% dispersion in mineral oil, 80 mg, 1.99 mmol) and stirred for 20 minutes. Iodomethane (0.33 mL, 5.31 mmol) was added and stirred at room temperature overnight. The reaction was quenched by adding saturated ammonium chloride solution (6 mL). Saturated sodium carbonate (10 mL) was also added. THF and the excess iodomethane were removed under reduced pressure. Next, the water phase was extracted 3X with CH₂Cl₂. The combined CH₂Cl₂ extract was washed with brine, dried (MgSO₄), filtered and concentrated. The residue was flash chromatographed on silica gel with 20% ethyl acetate/hexane to provide a light yellow oil as the title compound (80%, 160 mg). MS (Cl/NH₃) m/e 301 (M+H)⁺, 318 (M+NH₄)⁺; ¹H NMR (CDCl₃, 300 MHz) δ: 1.25 (d, J=7 Hz, 3H), 1.46 (s, 9H), 2.80 (s, 3H), 3.93 (bs, 1H), 4.01 (m, 1H), 4.56 (bs, 1H), 7.21 (m, 2H), 8.05 (d, J=3 Hz, 1H).

5-[(S)-2-methylamino-1-propyloxy]-2-chloro pyridine p-toluenesulfonic acid 3 was prepared next.

A solution of the product from Example 3A (160 mg, 0.532 mmol) in CH₂Cl₂ (5 mL) was treated with p-toluenesulfonic acid monohydrate (121 mg, 0.639 mmol) and refluxed at 60°C overnight. Solvent was removed by bubbling
nitrigen into the solution. Ethyl ether (30 mL) was added next and stirred for 5 minutes. The ether was decanted and the procedure was repeated. The residue was then dried under vacuum to provide 3 as a white solid. mp 56-58°C; MS (CI/NH₃) m/e 201 (M+H)⁺; ¹H NMR (D₂O, 500 MHz) δ: 1.44 (d, J=7 Hz, 3H), 2.37 (s, 3H), 2.77 (s, 3H), 3.72 (m, 1H), 4.17 (m, 1H), 4.34 (m, 1H), 7.33 (d, J=8 Hz, 2H), 7.40-7.47 (m, 2H), 7.67 (d, J=8 Hz, 2H), 8.05 (d, J=3 Hz, 1H); Analysis calculated for C₉H₁₃N₃ClO•1.4C₇H₄O₃S•0.4H₂O: C, 50.30; H, 5.61; N, 6.24; Found: C, 50.49; H, 5.90; N, 6.09; [α]²³D = +6.6° (c=1.1, MeOH).

Example 4

5-[(S)-2-amino-1-propyloxy]-2-fluoro pyridine p-toluenesulfonic acid 4 was synthesized according to the following procedure.

5-[(S)-2-N-BOC-amino-1-propyloxy]-2-fluoro pyridine 4A was first prepared as follows.

A solution of the product 1B (2.25 g, 6.84 mmol) in DMF (40 mL) was treated with potassium hydroxide (960 mg, 17.1 mmol) and 2-fluoro-5-hydroxyl pyridine (970 mg, 8.55 mmol), and stirred at 85°C overnight. DMF was removed under reduced pressure at 60°C. Next, the residue was dissolved in a mixture of H₂O and CH₃Cl₂. The organic layer was washed with water, and brine, then dried (MgSO₄), filtered and concentrated. The residue was flash chromatographed on silica gel with 20% ethyl acetate/hexane to provide a white solid 4A (27%, 500 mg). MS (CI/NH₃) m/e 271 (M+H)⁺, 288 (M+NH₃)⁺; ¹H
NMR (CDCl₃, 300 MHz) δ: 1.31 (d, J=7 Hz, 3H), 1.46 (s, 9H), 3.97-4.23 (m, 3H), 4.68 (bs, 1H), 6.76 (m, 1H), 7.35 (m, 1H), 7.86 (s, 1H).

5-[(S)-2-amino-1-propyloxy]-2-fluoro pyridine 4B was prepared next. A solution of the product 4A (500 mg, 1.85 mmol) in CH₂Cl₂ (15 mL) was treated with trifluoroacetic acid (5 mL) and stirred at room temperature overnight. Solvent and excess reagent were removed under reduced pressure. The residue was then dissolved in saturated sodium carbonate solution and extracted 3X with CH₂Cl₂. The combined CH₂Cl₂ extract was dried (MgSO₄), filtered and concentrated. The residue was flash chromatographed on silica gel with 95/5/0.5 CH₂Cl₂/CH₃OH/NH₂OH to provide a light yellow oil 4B (270 mg, 86%). MS (Cl/ NH₃) m/e 171 (M+H)⁺, 188 (M+NH₃)⁺; ¹H NMR (CDCl₃, 300 MHz) δ: 1.20 (d, J=7 Hz, 3H), 3.38 (m, 1H), 3.73 (dd, J=7, 8 Hz, 1H), 3.91 (dd, J=4, 9 Hz, 1H), 6.85 (dd, J=3, 9 Hz, 1H), 7.34 (m, 1H), 7.83 (m, 1H).

5-[(S)-2-amino-1-propyloxy]-2-fluoro pyridine p-toluenesulfonic acid 4 was prepared as follows.

A solution of 4B (87 mg, 0.512 mmol) in ethyl acetate (1 mL) was treated with p-toluenesulfonic acid monohydrate (102 mg, 0.537 mmol) and stirred for 5 minutes. Ethyl ether (30 ml) was added and stirred for an additional 5 minutes. The ether was decanted and the procedure was repeated. The residue was then dried under vacuum to provide 4 as a white solid. mp 139-141°C; MS (Cl/ NH₃) m/e 171 (M+H)⁺, 188 (M+NH₃)⁺; ¹H NMR (D₂O, 300 MHz) δ: 1.43 (d, J=7 Hz, 3H), 2.41 (s, 3H), 3.84 (m, 1H), 4.12 (dd, J=7, 11 Hz, 1H), 4.32 (dd, J=4, 11 Hz, 1H), 7.09 (dd, J=3, 9 Hz, 1H), 7.38 (d, J=8
Hz, 2H), 7.64 (m, 1H), 7.70 (d, J=8 Hz, 2H), 7.89 (m, 1H). Analysis calculated for C₈H₁₇N₂FO·C₇H₅O₃S: C, 52.62; H, 5.59; N, 8.81; Found: C, 52.61; H, 5.79; N, 8.01; [α]D⁰+7.0° (c=1.3, MeOH).

Example 5

5-[(S)-2-dimethylamino-1-propyloxy]-2-fluoro pyridine p-toluenesulfonic acid 5 was synthesized according to the following procedure.

First, 5-[(S)-2-dimethylamino-1-propyloxy]-2-fluoro pyridine 5A was prepared as follows. A solution of the product 4A (180 mg, 1.06 mmol) in the mixture of formaldehyde (37 wt. % in water, 7 mL) and formic acid (4 mL) was stirred at 65°C overnight. The excess reagents were removed under reduced pressure at 45°C. Aqueous NaOH solution (1N) was added to the residue and extracted 3X with CH₂Cl₂. The combined CH₂Cl₂ extract was washed with brine, dried (MgSO₄), filtered, and concentrated. The residue was flash chromatographed on silica gel with 95/5/0.5 CH₂Cl₂/MeOH/NH₄OH to provide a light yellow oil 5A (42%, 88 mg). MS (Cl/NH₂) m/e 199 (M+H)+.

5-[(S)-2-dimethylamino-1-propyloxy]-2-fluoro pyridine p-toluenesulfonic acid 5 was made next as follows.

A solution of 5A (88mg, 0.444 mmol) in ethyl acetate (1 mL) was treated with p-toluenesulfonic acid monohydrate (89 mg, 0.467 mmol) and stirred for 5 minutes. Ethyl ether (30 mL) was added and stirred for an additional 5 minutes. The ether was decanted and the procedure was repeated. It was then dried under vacuum to provide 5 as a white solid. mp 81-83°C;
MS (Cl/NH₃) m/e 199 (M+H)⁺; ¹H NMR (D₂O, 500 MHz) δ: 1.43 (d, J=7 Hz, 3H), 2.40 (s, 3H), 2.91 (s, 6H), 3.90 (m, 1H), 4.26 (dd, J=8, 11 Hz, 1H), 4.49 (dd, J=4, 11 Hz, 1H), 7.10 (dd, J=2, 9 Hz, 1H), 7.38 (d, J=8 Hz, 2H), 7.65 (m, 1H), 7.70 (d, J=9 Hz, 2H), 8.90 (dd, J=1, 3 Hz, 1H); Analysis calculated for C₁₀H₁₃N₂FO•1.1C₇H₈O₃S: C, 54.84; H, 6.19; N, 7.23; Found: C, 54.48; H, 6.35; N, 7.20; [α]D₂⁺5.1° (c=0.85, MeOH).

Example 6

5-[(S)-2-methylamino-1-propyloxy]-2-fluoro pyridine p-toluenesulfonic acid 6 was synthesized according to the following procedure. First 5-[(S)-2-N-BOC-methylamino-1-propyloxy]-2-fluoro pyridine 6A was first prepared as follows. A solution of the product 4A (510 mg, 1.89 mmol) in THF (15 mL) was treated with sodium hydride (60% dispersion in mineral oil, 227 mg, 5.67 mmol) and stirred for 20 minutes. Iodomethane (0.94 mL, 15.1 mmol) was added and stirred at room temperature for overnight. The reaction was quenched by adding saturated ammonium chloride solution (6 mL). Saturated sodium carbonate (10 mL) was also added. THF and the excess iodomethane were removed under reduced pressure. The water phase was extracted 3X with CH₂Cl₂. The combined CH₂Cl₂ extract was washed with brine, dried (MgSO₄), filtered and concentrated. The residue was flash chromatographed on silica gel with 10% ethyl acetate/hexane to provide a light yellow oil as the title compound (80%, 320 mg). MS (Cl/NH₃) m/e 285 (M+H)⁺, 302 (M+NH₄)⁺; ¹H NMR (CDCl₃, 300 MHz) δ: 1.25 (d, J=7 Hz, 3H), 1.46 (s, 9H), 2.80 (s, 3H),
3.98 (bs, 2H), 4.53 (bs, 1H), 6.86 (dd, J=3, 9 Hz, 1H), 7.32 (m, 1H), 7.82 (s, 1H).

Next, 5-[(S)-2-methylamino-1-propyloxy]-2-fluoro pyridine p-toluenesulfonic acid 6 was prepared in the following manner.

A solution of the product 6A (320 mg, 1.13 mmol) in CH₂Cl₂ (5 mL) was treated with p-toluenesulfonic acid monohydrate (236 mg, 1.24 mmol) and refluxed at 60°C overnight. Then solvent was removed by bubbling nitrogen into the solution. Ethyl ether (30 mL) was added and stirred for 5 minutes. The ether was decanted and the procedure was repeated. The residue was then dried under vacuum to provide 6 as a white solid. mp 85-87°C; MS (Cl/NH₃) m/e 185 (M+H)⁺, 202 (M+NH₄)⁺; ¹H NMR (D₂O, 500 MHz) δ: 1.45 (d, J=7 Hz, 3H), 2.39 (s, 3H), 2.78 (s, 3H), 3.73 (m, 1H), 4.18 (dd, J=7, 11 Hz, 1H), 4.35 (dd, J=3, 7 Hz, 1H), 7.08 (dd, J=3, 9 Hz, 1H), 7.35 (d, J=8 Hz, 2H), 7.62 (m, 1H), 7.69 (d, J=8 Hz, 2H), 7.87 (dd, J=1, 3 Hz, 1H); Analysis calculated for C₆H₄N₂FO•C₂H₅O₂S: C, 53.92; H, 5.94; N, 7.86; Found: C, 53.82; H, 5.79; N, 7.63; [α]²⁵D = +8.2° (c=3.5, MeOH).

Example 7

5-[(S)-2-amino-1-propyloxy]-2-chloro-3-bromo pyridine p-toluenesulfonic acid 7 was prepared according to the following procedure.

First, 5-[(S)-2-N-BOC-amino-1-propyloxy]-2-chloro-3-bromo pyridine 7A was made as follows. A solution of the product 1B (2.40 g, 7.30 mmol) in DMF (30 mL) was treated with potassium hydroxide (1.02 g, 18.3 mmol) and
2-chloro-3-bromo-5-hydroxyl pyridine (1.90 g, 9.13 mmol) and stirred at 85°C overnight. DMF was removed under reduced pressure at 60°C. The residue was then dissolved in a mixture of H₂O and CH₂Cl₂. The organic layer was washed 2X with water, and 1X with brine, dried (MgSO₄), filtered, and concentrated. It was flash chromatographed on silica gel with 15% ethyl acetate/hexane to provide a white solid 7A (59%, 1.58 g). MS (CI/NH₃) m/e 365 (M+H)⁺, 382 (M+NH₄)⁺; ¹H NMR (CDCl₃, 300 MHz) δ: 1.30 (dd, J=3, 7 Hz, 3H), 1.45 (s, 9H), 3.96-4.11 (m, 2H), 4.55 (bs, 1H), 7.53(d, J=3 Hz, 1H), 8.06 (m, 1H).

Then 5-[(S)-2-amino-1-propyloxy]-2-chloro-3-bromo pyridine p-toluenesulfonic acid 7 was prepared as follows.

A solution of the product 7A (140 mg, 0.421 mmol) in CH₂Cl₂ (5 mL) was treated with p-toluenesulfonic acid monohydrate (121 mg, 0.639 mmol) and refluxed at 60°C overnight. Next, solvent was removed by bubbling nitrogen into the solution. Ethyl ether (30 mL) was then added and stirred for 5 minutes. The ether was decanted and the procedure was repeated. It was then dried under vacuum to provide 7 as a white solid. mp 156-158°C; MS (Cl/NH₃) m/e 265 (M+H)⁺, 282 (M+NH₄)⁺; ¹H NMR (D₂O, 500 MHz) δ: 1.44 (d, J=7 Hz, 3H), 2.39 (s, 3H), 3.85 (m, 1H), 4.14 (dd, J=7, 10 Hz, 1H), 4.32 (dd, J=4, 10 Hz, 1H), 7.36 (d, J=8 Hz, 2H), 7.68 (d, J=8 Hz, 2H), 7.84 (d, J=3 Hz, 1H), 8.09 (d, J=3 Hz, 1H); Analysis calculated for C₄H₁₆N₂BrClO•C₇H₅O₂S: C, 41.16; H, 4.14; N, 6.40; Found: C, 41.15; H, 4.29; N, 6.30; [α]D²⁰=+6.9° (c=1.4, MeOH).
Example 8

5-[(S)-2-dimethylamino-1-propyloxy]-2-chloro-3-bromo pyridine p-toluenesulfonic acid 8 was prepared according to the following procedure.

First, 5-[(S)-2-dimethylamino-1-propyloxy]-2-chloro-3-bromo pyridine 8A was prepared as follows. A solution of the product 7A (270 mg, 0.739 mmol) in a mixture of formaldehyde (37 wt. % in water, 7 mL) and formic acid (4 mL) was stirred at 65°C overnight. The excess reagents were removed under reduced pressure at 45°C. Aqueous NaOH solution (1N) was added to the residue and extracted 3X with CH₂Cl₂. The combined CH₂Cl₂ extract was washed with brine, dried (MgSO₄), filtered, and concentrated. The residue was flash chromatographed on silica gel with 95/5/0.5 CH₂Cl₂/MeOH/NH₄OH to provide 7A as a light yellow oil (61%, 133 mg). MS (Cl/NH₄) m/e 293 (M+H)⁺.

Then 5-[(S)-2-dimethylamino-1-propyloxy]-2-chloro-3-bromo pyridine p-toluenesulfonic acid 8 was made as follows.

A solution of 8A (130 mg, 0.442 mmol) in ethyl acetate (1 mL) at room temperature was treated with p-toluenesulfonic acid monohydrate (95 mg, 0.499 mmol) and stirred for 5 minutes. Next, diethyl ether (30 mL) was added and stirred for an additional 5 minutes. The ether was decanted and the procedure was repeated. The residue was then dried under vacuum to provide 8 as a white hygroscopic solid. MS (Cl/NH₄) m/e 293 (M+H)⁺; ¹H NMR (D₂O, 500 MHz) δ: 1.44 (d, J=7 Hz, 3H), 2.39 (s, 3H), 2.92 (s, 6H), 3.91 (m, 1H),
4.27 (dd, J=8, 11 Hz, 1H), 4.40 (dd, J=4, 11 Hz, 1H), 7.36 (d, J=8 Hz, 2H), 7.68 (d, J=8 Hz, 2H), 7.86 (d, J=3 Hz, 1H), 8.10 (d, J=3, 1H); Analysis calculated for C_{19}H_{14}N_{2}BrClO\cdot C_{3}H_{4}O_{5}S: C, 43.84; H, 4.76; N, 6.01; Found: C, 43.93; H, 4.81; N, 5.76; [α]^{25}_{D} = +2.5° (c=0.60, MeOH).

Example 9

5-[(S)-2-methylamino-1-propyloxy]-2-chloro-3-bromo pyridine p-toluenesulfonic acid 9 was prepared according to the following procedure.

First, 5-[(S)-2-N-BOC-methylamino-1-propyloxy]-2-chloro-3-bromo pyridine 9A was made as follows.

A solution of the product 7A (270 mg, 0.739 mmol) in THF (10 mL) at room temperature was treated with sodium hydride (60% dispersion in mineral oil, 89 mg, 2.22 mmol) and stirred for 20 minutes. Iodomethane (0.37 mL, 5.95 mmol) was then added and stirred at room temperature overnight. The reaction was quenched by adding saturated ammonium chloride solution (6 mL). Saturated sodium carbonate (10 mL) was also added. THF and the excess iodomethane were removed under reduced pressure. The water phase was extracted 3X with CH₂Cl₂. The combined CH₂Cl₂ extract was washed with brine, dried (MgSO₄), filtered and concentrated. The residue was flash chromatographed on silica gel with 10% ethyl acetate/hexane to provide a light yellow oil 9A (67%, 187 mg). MS (Cl/NH₃) m/e 379 (M+H)^+, 396 (M+NH₄)^+.

Then 5-[(S)-2-methylamino-1-propyloxy]-2-chloro-3-bromo pyridine p-toluenesulfonic acid 9 was made as follows.
A solution of the product 9A (187 mg, 0.493 mmol) in CH₂Cl₂ (5 mL) was treated with p-toluenesulfonic acid monohydrate (103 mg, 0.542 mmol) and refluxed at 60°C overnight. Solvent was removed by bubbling nitrogen into the solution. Next, ethyl ether (30 mL) was added and stirred for 5 minutes. The ether was decanted and the procedure was repeated. The residue was then dried under vacuum to provide 9 as a hygroscopic white solid. mp 48-50°C; MS (Cl/NH₃) m/e 279 (M+H)⁺, 296 (M+NH₄)⁺; ¹H NMR (D₂O, 500 MHz) δ: 1.45 (d, J=7 Hz, 3H), 2.36 (s, 3H), 2.78 (s, 3H), 3.73 (m, 1H), 4.16 (dd, J=7, 11 Hz, 1H), 4.33 (dd, J=3, 11 Hz, 1H), 7.30 (d, J=8 Hz, 2H), 7.65 (d, J=8 Hz, 2H), 7.76 (d, J=3 Hz, 1H), 8.02 (d, J=3 Hz, 1H); Analysis calculated for C₉H₁₂N₂BrClO•C₇H₅O₂S: C, 42.54; H, 4.46; N, 6.20; Found: C, 42.27; H, 4.51; N, 5.95; [α]D⁺=+4.8° (c=4.8, MeOH).

Example 10

5-[(S)-2-amino-1-propyloxy]-2-chloro-3-methyl pyridine p-toluenesulfonic acid 10 was synthesized according to the following procedure.

First, 5-[(S)-2-N-BOC-amino-1-propyloxy]-2-chloro-3-methyl pyridine 10A was prepared as follows.

A solution of the product 1B (1.35 g, 4.10 mmol) in DMF (30 mL) was treated with potassium hydroxide (570 mg, 10.2 mmol) and 2-chloro-3-methyl-5-hydroxyl pyridine (730 mg, 5.09 mmol), then stirred at 85°C overnight. Next, DMF was removed under reduced pressure at 60°C. The residue was dissolved in a mixture of H₂O and CH₂Cl₂. The organic layer was washed with water, and
brine. It was then dried (MgSO₄), filtered and concentrated. The residue was flash chromatographed on silica gel with 20% ethyl acetate/hexane to provide a white solid 10A (24%, 300 mg). MS (Cl/ NH₃) m/e 301 (M+H)+; ¹H NMR (CDCl₃, 300 MHz) δ: 1.29 (d, J=7 Hz, 3H), 1.45 (s, 9H), 2.35 (s, 3H), 3.95 (d, J=4 Hz, 2H), 4.02 (bs, 1H), 4.68 (bs, 1H), 7.13 (d, J=3 Hz, 1H), 7.92 (d, J=3 Hz, 1H).

5-[(S)-2-amino-1-propyloxy]-2-chloro-3-methyl pyridine p-toluenesulfonic acid 10 was then made as follows. A solution of the product 10A (53 mg, 0.177 mmol) in CH₂Cl₂ (5 mL) was treated with p-toluenesulfonic acid monohydrate (37 mg, 0.195 mmol) and refluxed at 60°C overnight. Solvent was removed by bubbling nitrogen into the solution. Ethyl ether (30 mL) was added and stirred for 5 minutes. The ether was decanted and the procedure was repeated. It was then dried under vacuum to provide a white solid 10. mp 181-183°C; MS (Cl/NH₃) m/e 201 (M+H)+; ¹H NMR (D₂O, 500 MHz) δ: 1.44 (d, J=7 Hz, 3H), 2.36 (s, 3H), 2.40 (s, 3H), 3.84 (m, 1H), 4.12 (dd, J=7, 11 Hz, 1H), 4.31 (dd, J=3, 11 Hz, 1H), 7.37 (d, J=8 Hz, 2H), 7.44 (d, J=3 Hz, 1H), 7.69 (d, J=8 Hz, 2H), 7.93 (d, J=3 Hz, 1H); Analysis calculated for C₈H₁₃N₂ClO•C₇H₈O₃S: C, 51.54; H, 5.68; N, 7.51; Found: C, 51.53; H, 5.57; N, 7.33; [α]D²⁵=-7.0° (c=0.32, MeOH).

Example 11

5-[(S)-2-dimethylamino-1-propyloxy]-2-chloro-3-methyl pyridine p-toluenesulfonic acid 11 was synthesized according to the following procedure.
First, 5-[(S)-2-dimethylamino-1-propyloxy]-2-chloro-3-methyl pyridine 11A was made as follows.

A solution of the product 10A (115 mg, 0.383 mmol) in a mixture of formaldehyde (37 wt. % in water, 7 mL) and formic acid (4 mL) was stirred at 65°C overnight. The excess reagents were removed under reduced pressure at 45°C. Aqueous NaOH solution (1N) was then added to the residue and extracted 3X with CH₂Cl₂. The combined CH₂Cl₂ extract was washed with brine, dried (MgSO₄), filtered, and concentrated. The residue was flash chromatographed on silica gel with 95/5/0.5 CH₂Cl₂/MeOH/NH₄OH to provide 11A as a light yellow oil (41%, 36 mg). MS (Cl/NH₃) m/z 229 (M+H)⁺.

5-[(S)-2-dimethylamino-1-propyloxy]-2-chloro-3-methyl pyridine p-toluenesulfonic acid 11 was then prepared as follows.

A solution of the product 11A (36 mg, 0.158 mmol) in ethyl acetate (1 mL) at room temperature was treated with p-toluenesulfonic acid monohydrate (33 mg, 0.173 mmol) and stirred for 5 minutes. Next, ethyl ether (30 mL) was added and stirred for an additional 5 minutes. The ether was decanted and the procedure was repeated. It was then dried under vacuum to provide 11 as a white hygroscopic solid. mp 58-60°C; MS (Cl/NH₃) m/z 229 (M+H)⁺; ¹H NMR (D₂O, 300 MHz) δ: 1.43 (d, J=7 Hz, 3H), 2.37 (s, 3H), 2.40 (s, 3H), 2.88 (bs, 3H), 2.95 (bs, 3H), 3.87 (m, 1H), 4.25 (m, 1H), 4.41 (m, 1H), 7.38 (d, J=8 Hz, 2H), 7.47 (d, J=3 Hz, 1H), 7.70 (d, J=8 Hz, 2H), 7.95 (d, J=3 Hz, 1H);

Analysis calculated for C₁₁H₁₇N₂ClO•1.45C₂H₅O₂S•0.40H₂O: C, 52.31; H, 6.10; N, 5.77; Found: C, 52.00; H, 6.12; N, 6.06; [α]D²⁵ =+3.8° (c=0.21, MeOH).
Example 12

5-[(S)-2-methylamino-1-propyloxy]-2-chloro-3-methyl pyridine p-toluenesulfonic acid 12 was synthesized according to the following procedure.

First, 5-[(S)-2-N-BOC-methylamino-1-propyloxy]-2-chloro-3-methyl pyridine 12A was prepared as follows.

A solution of the product 10A (127 mg, 0.423 mmol) in THF (8 mL) at room temperature was treated with sodium hydride (60% dispersion in mineral oil, 51 mg, 1.27 mmol) and stirred for 20 minutes. Iodomethane (0.21 mL, 3.38 mmol) was added and then the solution was stirred at room temperature overnight. The reaction was quenched by adding saturated ammonium chloride solution (6 mL). Saturated sodium carbonate (10 mL) was also added. THF and the excess iodomethane were removed under reduced pressure. The water phase was extracted 3X with CH₂Cl₂. The combined CH₂Cl₂ extract was washed with brine, dried (MgSO₄), filtered and concentrated. The residue was flash chromatographed on silica gel with 20% ethyl acetate/hexane to provide a light yellow oil 12A (72%, 96 mg). MS (Cl/CH₃) m/e 315 (M+H)⁺, 332 (M+NH₄)⁺; ¹H NMR (CDCl₃, 300 MHz) δ: 1.25 (d, J=7 Hz, 3H), 1.46 (s, 9H), 2.35 (s, 3H), 2.80 (s, 3H), 3.89-4.03 (m, 2H), 4.56 (m, 1H), 7.10 (bs, 1H), 7.89 (d, J=3 Hz, 1H).

Next, 5-[(S)-2-methylamino-1-propyloxy]-2-chloro-3-methyl pyridine p-toluenesulfonic acid 12 was prepared as follows.

A solution of the product 12A (96 mg, 0.305 mmol) in CH₂Cl₂ (5 mL) was treated with p-toluenesulfonic acid monohydrate (64 mg, 0.336 mmol) and
then refluxed at 60°C overnight. Solvent was removed by bubbling nitrogen into the solution. Next, ethyl ether (30 mL) was added and stirred for 5 minutes. The ether was decanted and the procedure was repeated. The residue was then dried under vacuum to provide 12 as a hygroscopic white solid. mp 62-64°C; MS (Cl/NH₃) m/e 215 (M+H)+; ¹H NMR (D₂O, 500 MHz) δ: 1.44 (d, J=7 Hz, 3H), 2.37 (s, 3H), 2.41 (s, 3H), 2.77 (s, 3H), 3.72 (m, 1H), 4.19 (dd, J=7, 11 Hz, 1H), 4.37 (dd, J=3, 10 Hz, 1H), 7.33 (d, J=8 Hz, 2H), 7.45 (d, J=3 Hz, 1H), 7.67 (d, J=8 Hz, 2H), 7.94 (d, J=3 Hz, 1H); Analysis calculated for C₁₀H₁₂N₂ClO•1.25C₂H₄O₃S•0.3H₂O: C, 51.73; H, 5.93; N, 6.43; Found: C, 51.77; H, 5.68; N, 6.32; [α]²⁵D=+6.9° (c=2.2, MeOH).

Example 13

5-[(S)-2-amino-1-propyloxy]-2-chloro-3-(4-vinylpyridinyl) pyridine p-toluenesulfonic acid 13 was synthesized according to the following procedure.

First, 5-[(S)-2-N-BOC-amino-1-propyloxy]-2-chloro-3-(4-vinylpyridinyl) pyridine 13A was prepared as follows.

A solution of the product 7A (620 mg, 1.70 mmol), 4-vinyl pyridine (0.23 mL, 2.12 mmol), palladium (II) acetate (16 mg, 0.071 mmol), tri-o-tolylphosphine (44 mg, 0.145 mmol), and triethylamine (0.85 mL, 6.12 mmol) in acetonitrile (10 mL) was refluxed at 100°C overnight. The reaction mixture was diluted with ethyl acetate, washed with saturated sodium carbonate, brine, dried (MgSO₄), filtered and concentrated. Then residue was flash
chromatographed with 30% ethyl acetate/hexane to provide 13A as a white solid (73%, 480 mg); MS (Cl/\text{NH}_2) \text{ m/e 390 (M+H)}^+.

Next, 5-[(S)-2-amino-1-propyloxy]-2-chloro-3-(4-vinylpyridinyl) pyridine 13B was prepared as follows.

A solution of the product 13A (120 mg, 0.308 mmol) in CH_2Cl_2 (4 mL) was treated with trifluoroacetic acid (1 mL) and then stirred at room temperature overnight. Solvent and the excess reagent were removed under reduced pressure. The residue was dissolved in saturated sodium carbonate solution and extracted 3X with CH_2Cl_2. The combined CH_2Cl_2 extract was dried (MgSO_4), filtered and concentrated. The residue was flash chromatographed on silica gel with 95/5/0.5 CH_2Cl_2/CH_3OH/NH_4OH to provide a light yellow oil 13B (79%, 70 mg). MS (Cl/\text{NH}_3) \text{ m/e 290 (M+H)}^+.

Then 5-[(S)-2-amino-1-propyloxy]-2-chloro-3-(4-vinylpyridinyl) pyridine p-toluenesulfonylic acid 13 was prepared as follows. A solution of the product 13B (70 mg, 0.242 mmol) in ethyl acetate (1 mL) was treated with p-toluenesulfonylic acid monohydrate (51 mg, 0.266 mmol) and stirred for 5 minutes. Next, ethyl ether (30 mL) was added and stirred for an additional 5 minutes. The ether was decanted and the procedure was repeated. It was then dried under vacuum to provide 13 as a light yellow solid. mp 69-71°C; MS (Cl/\text{NH}_3) \text{ m/e 290 (M+H)}^+; \text{^1H NMR (D}_2\text{O, 500 MHz)} \delta: 1.48 (d, J=7 Hz, 3H), 2.35 (s, 3H), 3.87 (m, 1H), 4.14 (m, 1H), 4.31 (dd, J=4, 10 Hz, 1H), 7.10 (d, J=6 Hz, 2H), 7.29 (d, J=8 Hz, 2H), 7.45 (d, J=16 Hz, 2H), 7.64 (d, J=8 Hz, 2H), 7.68 (d, J=3 Hz, 1H), 7.93 (d, J=3 Hz, 1H), 8.45 (d, J=6 Hz, 2H);
Analysis calculated for C_{18}H_{18}N_{3}ClO\cdot1.65C_{7}H_{8}O_{2}S\cdot1.15H_{2}O: C, 53.63; H, 5.34; N, 7.07; Found: C, 53.83; H, 5.25; N, 6.77; \([\alpha]^{25}_D=+1.3^\circ\) (c=0.75, MeOH).

Example 14

5-[(S)-2-N-dimethylamino-1-propyloxy]-2-chloro-3-(4-vinylpyridinyl) pyridine p-toluenesulfonic acid 14 was prepared according to the following procedure.

First, 5-[(S)-2-N-dimethylamino-1-propyloxy]-2-chloro-3-(4-vinylpyridinyl) pyridine 14A was made as follows.

A solution of the product 13A (220 mg, 0.564 mmol) in a mixture of formaldehyde (37 wt. % in water, 7 mL) and formic acid (4 mL) was stirred at 65°C overnight. The excess reagents were removed under reduced pressure at 45°C. Aqueous NaOH solution (1N) was added to the residue and extracted 3X with CH$_2$Cl$_2$. The combined CH$_2$Cl$_2$ extract was washed with brine, dried (MgSO$_4$), filtered, and concentrated. The residue was flash chromatographed on silica gel with 95/5/0.5 CH$_2$Cl$_2$/MeOH/NH$_3$OH to provide 14A as a light yellow oil (99%, 163 mg). MS (Cl/Na$_3$) m/e 318 (M+H)$^+$. 

5-[(S)-2-N-dimethylamino-1-propyloxy]-2-chloro-3-(4-vinylpyridinyl) pyridine p-toluenesulfonic acid 14 was then made as follows.
A solution of the product 14A (133 mg, 0.420 mmol) in ethyl acetate (1 mL) at room temperature was treated with p-toluenesulfonic acid monohydrate (88 mg, 0.462 mmol) and stirred for 5 minutes. Ethyl ether (30 mL) was added and stirred for an additional 5 minutes. The ether was decanted and the procedure was repeated. The residue was then dried under vacuum to provide 14 as a light yellow solid. mp 79-81°C; MS (Cl/NH₃) m/e 318 (M+H)⁺; ¹H NMR (D₂O, 500 MHz) δ: 1.46 (d, J=7 Hz, 3H), 2.33 (s, 3H), 2.90 (s, 3H), 2.98 (s, 3Hz, 6H) 3.93 (m, 1H), 4.30 (dd, J=8, 11 Hz, 1H), 4.42 (m, 1H), 7.23 (s, 1H), 7.27 (d, J=8 Hz, 2H), 7.62 (d, J=8, 2H), 7.69 (d, J=16 Hz, 1H), 7.75 (d, J=2 Hz, 1H), 7.96 (d, J=7 Hz, 2H), 8.08 (d, J=3 Hz, 1H), 8.59 (d, J=6 Hz, 2H); Analysis calculated for C₁₇H₂₆N₃ClO·1.5C₇H₈O₃S·0.75H₂O: C, 56.02; H, 5.73; N, 7.13; Found: C, 56.23; H, 5.72; N, 6.83; [α]²⁵D=+0.80° (c=1.0, MeOH).

Example 15

5-[(S)-2-amino-1-butylloxy]-2-chloro pyridine p-toluenesulfonic acid 15 was synthesized according to the following procedure.

First, 2-[(S)-N-BOC]-butanol 15A was prepared as follows. A solution of N-(tert-butoxycarbonyl-L-α-aminobutyric acid (15 g, 73.8 mmol) in anhydrous THF (100 mL) at 0°C was treated with borane (1M solution in THF, 200 mL) over a period of 45 minutes. The ice bath was then removed and the reaction mixture was stirred at room temperature for 3 hours. Saturated NaHCO₃ solution was added slowly to quench the reaction. The resultant solution was then stirred overnight. Next, solvent was removed under reduced
pressure. The remaining water phase was extracted 4X with ethyl ether. The combined ether extract was washed with brine, dried (MgSO₄), filtered, and concentrated. The residue was flash chromatographed on silica gel with 30% ethyl acetate/hexane to provide a clear oil 15A (55%, 7.73 g). MS (Cl/NH₃) m/e 190 (M+H)+, 207 (M+NH₄)+; ¹H NMR (CDCl₃, 300 MHz) δ: 0.96 (t, J=7 Hz, 3H), 1.45 (s, 9H), 1.39-1.67 (m, 2H), 3.52-3.59 (m, 2H), 3.69 (m, 1H), 4.61 (bs, 1H).

Next, 2-[(S)-N-BOC]-butanol tosylate 15B was prepared as follows.

A solution of the product 15A (7.60 g, 40.2 mmol) in CH₂Cl₂ (150 mL) at room temperature was treated with triethylamine (8.9 mL, 66.3 mmol) and p-toluensulfonyl chloride (9.58 g, 50.3 mmol), and then stirred overnight. The reaction mixture was diluted with CH₂Cl₂ to 300 mL, washed with water, 5% NaHCO₃, and brine. It was then dried (MgSO₄), filtered and concentrated. The residue was flash chromatographed on silica gel with 15% ethyl acetate/hexane to provide 15B (58%, 8.01 g). MS (Cl/NH₃) m/e 344 (M+H)+, 361 (M+NH₄)+; ¹H NMR (CDCl₃, 300 MHz) δ: 0.88 (t, J=8 Hz, 3H), 1.41 (s, 9H), 1.45-1.55 (m, 2H), 2.45 (s, 3H), 3.65 (bs, 1H), 3.97-4.07 (m, 2H), 4.56 (m, 1H), 7.36 (d, J=8 Hz, 2H), 7.79 (d, J=6 Hz, 2H).

Then 5-[(S)-2-N-BOC-amino-1-butyloxy]-2-chloro pyridine 15C was prepared as follows.

A solution of the product from Example 15B (1.38 g, 4.02 mmol) in DMF (20 mL) was treated with potassium hydroxide (338 mg, 6.03 mmol) and 2-chloro-5-hydroxyl pyridine (651 mg, 5.03 mmol), and then stirred at 85°C
overnight. DMF was removed under reduced pressure at 60°C. The residue was dissolved in a mixture of H₂O and CH₂Cl₂. The organic layer was washed with water, and brine. It was then dried (MgSO₄), filtered and concentrated. The residue was flash chromatographed on silica gel with 20% ethyl acetate/hexane to provide a light yellow solid 15C (11%, 130 mg). MS (Cl/NH₃) m/e 301 (M+H)^+, 318 (M+NH₄)^+; ¹H NMR (CDCl₃, 300 MHz) δ: 0.99 (t, J=7 Hz, 3H), 1.45 (s, 9H), 1.59-1.75 (m, 2H), 3.85 (m, 1H), 4.00 (d, J=4 Hz, 2H), 4.67 (bs, 1H), 7.22 (s, 2H), 8.06 (d, J=2 Hz, 1H).

Then, 5-[(S)-2-amino-1-butyl oxy]-2-chloro pyridine p-toluenesulfonic acid 15 was prepared as follows.

A solution of the product 15C (127 mg, 0.423 mmol) in CH₂Cl₂ (5 mL) was treated with p-toluenesulfonic acid monohydrate (88 mg, 0.463 mmol) and refluxed at 60°C overnight. Then, solvent was removed by bubbling nitrogen into the solution. Next, ethyl ether (30 mL) was added and stirred for 5 minutes. The ether was decanted and the procedure was repeated. The residue was then dried under vacuum to provide a light yellow solid 15. mp145-147 °C; MS (Cl/NH₃) m/e 201 (M+H)^+, 218 (M+NH₄)^+; ¹H NMR (D₂O, 500 MHz) δ: 1.06 (t, J=7 Hz, 3H), 1.78-1.90 (m, 2H), 2.39 (s, 3H), 3.67 (m, 1H), 4.20 (dd, J=7, 11 Hz, 1H), 4.35 (dd, J=3, 12 Hz, 1H), 7.36 (d, J=8 Hz, 2H), 7.44 (d, J=8 Hz, 1H), 7.49 (dd, J=3, 9 Hz, 1H), 7.70 (d, J=8 Hz, 2H), 8.09 (d, J=3 Hz, 1H); Analysis calculated for C₉H₁₃N₂ClO•1.25C₇H₄O₃S: C, 51.26; H, 5.57; N, 6.74; Found: C, 51.15; H, 5.29; N, 6.67; [α]²⁵D =+11.7° (c=0.60, MeOH).
Example 16

5-[(S)-2-amino-1-butyloxy]-2-fluoro pyridine p-toluenesulfonic acid 16 was synthesized according to the following procedure.

First, 5-[(S)-2-N-BOC-amino-1-butyloxy]-2-fluoro pyridine 16A was prepared as follows.

A solution of the product from Example 15B (1.41 g, 4.11 mmol) in DMF (30 mL) was treated with potassium hydroxide (575 mg, 10.3 mmol) and 2-fluoro-5-hydroxyl pyridine (581 mg, 5.14 mmol), stirred at 85°C for overnight. DMF was removed under reduced pressure at 60°C. The residue was dissolved in a mixture of H₂O and CH₂Cl₂. The organic layer was washed with water, and brine. It was then dried (MgSO₄), filtered and concentrated. The residue was flash chromatographed on silica gel with 20% ethyl acetate/hexane to provide a light yellow solid 16A (13%, 152 mg). MS (Cl/NH₃) m/e 285 (M+H)⁺, 302 (M+NH₄)⁺. ¹H NMR (CDCl₃, 300 MHz) δ:

0.99 (t, J=8 Hz, 3H), 1.45 (s, 9H), 1.59-1.78 (m, 2H), 3.85 (m, 1H), 4.00 (d, J=4 Hz, 2H), 4.67 (bs, 1H), 6.86 (dd, J=3, 8 Hz, 1H), 7.39 (m, 1H), 7.82 (s, 1H).

5-[(S)-2-amino-1-butyloxy]-2-fluoro pyridine p-toluenesulfonic acid 16 was then prepared as follows.

A solution of the product 16A (75 mg, 0.264 mmol) in CH₂Cl₂ (5 mL) was treated with p-toluenesulfonic acid monohydrate (55 mg, 0.289 mmol) and then refluxed at 60°C overnight. Next, solvent was removed by bubbling nitrogen into the solution. Ethyl ether (30 mL) was added and stirred for 5
minutes. The ether was decanted and the procedure was repeated. The residue was then dried under vacuum to provide a white solid 16. mp 140-142 °C; MS (Cl/\text{NH}_3) m/e 185 (M+H)^+, 202 (M+\text{NH}_3)^+; ^1\text{H} NMR (D_2O, 500 MHz) δ: 1.06 (t, J=7 Hz, 3H), 1.78-1.90 (m, 2H), 2.40 (s, 3H), 3.65 (m, 1H), 4.18 (dd, J=7, 8 Hz, 1H), 4.35 (m, J=3 Hz, 1H), 7.08 (m, 1H), 7.37 (d, J=8 Hz, 2H), 7.62 (bs, 1H), 7.79 (d, J=8 Hz, 2H), 7.88 (d, J=1 Hz, 1H); Analysis calculated for C_9H_12N_2FO•C_7H_6O_2S: C, 53.92; H, 5.94; N, 7.86; Found: C, 53.72; H, 5.96; N, 7.65; [\alpha]^{25D} = +8.8° (c=0.60, MeOH).

Example 17

5-[(S)-2-methylamino-1-butyloxy]-2-fluoro pyridine p-toluenesulfonic acid 17 was synthesized according to the following procedure.

First, 5-[(S)-2-\text{N-BOC-methylamino-1-butyloxy}]-2-fluoro pyridine 17A was prepared as follows.

A solution of the product 16A (170 mg, 0.493 mmol) in THF (10 mL) at room temperature was treated with sodium hydride (60% dispersion in mineral oil, 59 mg, 1.48 mmol) and stirred for 20 minutes. Then iodomethane (0.25 mL, 3.94 mmol) was added and stirred at room temperature overnight. The reaction was quenched by adding saturated ammonium chloride solution (6 mL). Saturated sodium carbonate (10 mL) was also added. THF and the excess iodomethane were removed under reduced pressure. The water phase was extracted 3X with CH_2Cl_2. The combined CH_2Cl_2 extract was washed with brine, dried (MgSO_4), filtered and concentrated. The residue was flash
chromatographed on silica gel with 15% ethyl acetate/hexane to provide a light yellow oil 17A (79%, 116 mg). MS (Cl/NH$_3$) m/e 299 (M+H)$^+$, 316 (M+NH$_3$)$^+$.

Then 5-[(S)-2-methylamino-1-butyloxy]-2-fluoro pyridine p-toluenesulfonic acid 17 was made as follows.

A solution of the product 17A (116 mg, 0.389 mmol) in CH$_2$Cl$_2$ (5 mL) was treated with p-toluenesulfonic acid monohydrate (81 mg, 0.426 mmol) and refluxed at 60°C overnight. Then solvent was removed by bubbling nitrogen into the solution. Next, ethyl ether (30 mL) was added and stirred for 5 minutes. The ether was decanted and the procedure was repeated. It was then dried under vacuum to provide 17. MS (Cl/NH$_3$) m/e 199 (M+H)$^+$, 216 (M+NH$_3$)$^+$; $^1$H NMR (D$_2$O, 500 MHz) δ: 1.04 (t, J=7 Hz, 3H), 1.80-1.94 (m, 2H), 2.37 (s, 3H), 2.79 (s, 3H), 3.52 (m, 1H), 4.25 (dd, J=6, 11 Hz, 1H), 4.37 (dd, J=3, 11 Hz, 1H), 7.06 (dd, J=3, 9 Hz, 1H), 7.34 (d, J=8 Hz, 2H), 7.60 (m, 1H), 7.67 (d, J=8 Hz, 2H), 7.86 (dd, J=1, 3 Hz, 1H); Analysis calculated for C$_{10}$H$_{15}$N$_2$FO•C$_3$H$_8$O$_2$S: C, 55.12; H, 6.26; N, 7.56; Found: C, 54.73; H, 6.07; N, 7.20; [α]$^{25}$D=+8.9° (c=1.2, MeOH).

Example 18

5-[(S)-2-amino-1-butyloxy]-2-chloro-3-bromo pyridine p-toluenesulfonic acid 18 was synthesized according to the following procedure.

First, 5-[(S)-2-N-BOC-amino-1-butyloxy]-2-chloro-3-bromo pyridine 18A was prepared as follows.
A solution of the product 15B (3.16 g, 9.21 mmol) in DMF (40 mL) was treated with potassium hydroxide (1.29 g, 23.0 mmol) and 2-chloro-3-bromo-5-hydroxyl pyridine (2.40 g, 11.5 mmol), stirred at 85°C overnight. Then DMF was removed under reduced pressure at 60°C. The residue was dissolved in a mixture of H₂O and CH₂Cl₂. The organic layer was washed with water, and brine. It was then dried (MgSO₄), filtered and concentrated. The residue was flash chromatographed on silica gel with 15% ethyl acetate/hexane to provide a light yellow solid 18A (10%, 345 mg). MS (Cl/NH₃) m/e 379 (M+H)⁺; ¹H NMR (CDCl₃, 300 MHz) δ: 0.99 (t, J=7 Hz, 3H), 1.45 (s, 9H), 1.59-1.78 (m, 2H), 3.85 (m, 1H), 4.01 (d, J=4 Hz, 2H), 4.67 (bs, 1H), 7.52 (d, J=3 Hz, 1H), 8.05 (d, J=3 Hz, 1H).

5-[(S)-2-amino-1-butyloxy]-2-chloro-3-bromo pyridine p-toluenesulfonic acid 18 was then prepared as follows.

A solution of the product 18A (52 mg, 0.137 mmol) in CH₂Cl₂ (5 mL) was treated with p-toluenesulfonic acid monohydrate (29 mg, 0.153 mmol) and refluxed at 60°C overnight. Then solvent was removed by bubbling nitrogen into the solution. Ethyl ether (30 mL) was added and stirred for 5 minutes. The ether was decanted and the procedure was repeated. The residue was then dried under vacuum to provide a white solid 18. mp141-143 °C; MS (Cl/NH₃) m/e 279 (M+H)⁺; ¹H NMR (D₂O, 400 MHz) δ: 1.06 (t, J=8 Hz, 3H), 1.80-1.90 (m, 2H), 2.40 (s, 3H), 3.65 (m, 1H), 4.21 (dd, J=7, 11 Hz, 1H), 4.35 (dd, J=3, 10 Hz, 1H), 7.36 (d, J=8 Hz, 2H), 7.68 (d, J=8 Hz, 2H), 7.85 (d, J=3 Hz, 1H), 8.11 (d, J=3 Hz, 1H); Analysis calculated for C₁₀H₁₂N₂BrClO•C₇H₄O₃S: C,
42.54; H, 4.46; N, 6.20; Found: C, 42.62; H, 4.52; N, 6.14; [α]D^25 = +12.7°
(c=0.30, MeOH).

Example 19

5-[(S)-2-amino-1-butoxy]-2-chloro-3-(4-vinylpyridinyl) pyridine
di-p-toluenesulfonic acid 19 was synthesized as follows.

First, 5-[(S)-2-N-BOC-amino-1-butoxy]-2-chloro-3-(4-vinylpyridinyl)-
pyridine 19A was made as follows.

A solution of the product 18A (285 mg, 0.751 mmol), 4-vinyl pyridine
(0.12 mL, 1.13 mmol), palladium (II) acetate (17 mg, 0.075 mmol), tri-o-
tolylyphosphine (46 mg, 0.15 mmol), and triethylamine (0.37 mL, 2.70 mmol) in
acetonitrile (10 mL) was refluxed at 100°C overnight. The reaction mixture
was then diluted with ethyl acetate, washed with saturated sodium carbonate,
brine, dried (MgSO₄), filtered and concentrated. The residue was flash
chromatographed with 30% ethyl acetate/hexane to provide 19A as a white
solid (89%, 271 mg); MS (Cl/Na₃) m/e 404 (M+H)^+.

Then 5-[(S)-2-amino-1-butoxy]-2-chloro-3-(4-vinylpyridinyl) pyridine
di-p-toluenesulfonic acid 19 was prepared as follows.

A solution of the product 19A (111 mg, 0.273 mmol) in ethyl acetate (1
mL) was treated with p-toluenesulfonic acid monohydrate (110 mg, 0.579
mmol) and stirred for 5 minutes. Next, ethyl ether (30 mL) was added and
stirred for an additional 5 minutes. The ether was decanted and the procedure
was repeated. The residue was then dried under vacuum to provide 19 as a light
yellow solid. mp 101-103°C; MS (Cl/ NH₃) m/e 304 (M+H)⁺; ¹H NMR
(D₂O, 400 MHz) δ: 1.08 (t, J=7 Hz, 3H), 1.82-1.91 (m, 2H), 2.33 (s, 3H), 3.68 (m, 1H), 4.24-4.27 (dd, J=7, 11 Hz, 1H), 4.39 (dd, J=3, 11 Hz, 1H), 7.23-7.31 (m, 4H), 7.61 (d, J=8 Hz, 4H), 7.72-7.78 (m, 2H), 8.05 (d, J=8 Hz, 4H), 8.63 (d, J=7 Hz, 2H); Analysis calculated for C₁₅H₁₈N₃ClO₂•2.2O₂C₂H₄O₂S•1.40H₂O:
C, 53.28; H, 5.47; N, 5.94; Found: C, 53.29; H, 5.37; N, 5.81; [α]D²⁺=+3.3°
(c=1.3, MeOH).

Example 20

5-{[(S)-2-N-dimethylamino-1-butyloxy]-2-chloro-3-(4-vinylpyridinyl)} pyridine di-p-toluenesulfonic acid 20 was synthesized as follows.

First, 5-{[(S)-2-N-dimethylamino-1-butyloxy]-2-chloro-3-(4-vinylpyridinyl)} pyridine 20A was made as follows.

A solution of the product 19A (160 mg, 0.397 mmol) in a mixture of formaldehyde (37 wt. % in water, 7 mL) and formic acid (4 mL) was stirred at 65°C overnight. The excess reagents were removed under reduced pressure at 45°C. Aqueous NaOH solution (1N) was added to the residue and extracted 3X with CH₂Cl₂. The combined CH₂Cl₂ extract was washed with brine, dried (MgSO₄), filtered, and concentrated. The residue was flash chromatographed on silica gel with 95/5 CH₂Cl₂/MeOH to provide 20A as a light yellow oil (63%, 83 mg). MS (Cl/NH₃) m/e 332 (M+H)⁺.

Then 5-{[(S)-2-N-dimethylamino-1-butyloxy]-2-chloro-3-(4-vinylpyridinyl)} pyridine di-p-toluenesulfonic acid 20 was made as follows.
A solution of the product 20A (39 mg, 0.118 mmol) in ethyl acetate (1 mL) at room temperature was treated with p-toluenesulfonic acid monohydrate (47 mg, 0.247 mmol) and stirred for 5 minutes. Then ethyl ether (30 mL) was added and stirred for an additional 5 minutes. The ether was decanted and the procedure was repeated. The residue was then dried under vacuum to provide 20 as a light yellow solid. mp 73-75°C; MS (ESI+) m/e 332 (M+H)+; 1H NMR (D2O, 400 MHz) δ: 1.09 (t, J=8 Hz, 3H), 1.80-2.00 (m, 2H), 2.34 (s, 3H), 2.93 (s, 3H), 2.99 (s, 3H), 3.68 (m, 1H), 4.39 (dd, J=7, 11 Hz, 1H), 4.52 (dd, J=3, 11 Hz, 1H), 7.27 (d, J=8 Hz, 4H), 7.31 (s, 1H), 7.62 (d, J=18 Hz, 4H), 7.76 (d, J=2 Hz, 1H), 7.79 (d, J=3 Hz, 2H), 8.08-8.10 (m, 2H), 8.65 (d, J=6 Hz, 2H); Analysis calculated for C18H22N3ClO•2.30C5H9O3S•2.50H2O: C, 52.99; H, 5.92; N, 5.44; Found: C, 53.38; H, 5.89; N, 5.04; [α]25D=+0.6.4° (c=1.1, MeOH).

Example 21

5-[(S)-2-amino-3-phenyl-1-propyloxy]-2-chloro-3-bromo pyridine p-toluenesulfonic acid 21 was synthesized according to the following procedure.

First, 2-[(S)-N-BOC]-3-phenyl-butanol 21A was made as follows.

A solution of N-(tert-butoxycarbonyl)-L-phenylalanine (25.3 g, 95.5 mmol) in anhydrous THF (120 mL) at 0°C was treated with borane (1M solution in THF, 143 mL) over a period of 45 minutes. The ice bath was then removed and the reaction mixture was stirred at room temperature for 3 hours. Then saturated NaHCO3 solution was added slowly to quench the reaction, and
the resultant solution was stirred overnight. Next, solvent was removed under reduced pressure. The remaining water phase was extracted 4X with ethyl ether. The combined ether extract was washed with brine, dried (MgSO₄), filtered, and concentrated. The residue was flash chromatographed on silica gel with 30% ethyl acetate/hexane to provide a white solid 21A (43%, 9.80 g). MS (Cl/NH₃) m/e 252 (M+H)⁺, 269 (M+NH₄)⁺; ¹H NMR (CDCl₃, 300 MHz) δ: 1.42 (s, 9H), 2.85 (d, J=7 Hz, 2H), 3.56 (dd, J=5, 11 Hz, 1H), 3.68 (dd, J=4, 11 Hz, 1H), 3.86 (bs, 1H), 4.72 (bs, 1H), 7.16-7.33 (m, 5H).

Then 2-[(S)-N-BOC]-3-phenyl-propanol tosylate 21B was prepared as follows.

A solution of the product from Example 21A (9.80 g, 39.0 mmol) in CH₂Cl₂ (200 mL) at room temperature was treated with triethylamine (8.66 mL, 62.4 mmol) and p-toluenesulfonyl chloride (9.30 g, 48.8 mmol), and then stirred overnight. The reaction mixture was diluted with CH₂Cl₂ to 300 mL, washed with water, 5% NaHCO₃, and brine. It was then dried (MgSO₄), filtered and concentrated. The residue was flash chromatographed on silica gel with 20% ethyl acetate/hexane to provide a white solid 21B (63%, 10.0 g). MS (Cl/NH₃) m/e 423 (M+NH₄)⁺; ¹H NMR (CDCl₃, 300 MHz) δ: 1.39 (s, 9H), 2.46 (s, 3H), 2.72-2.90 (bs, 2H), 3.84-4.05 (m, 3H), 4.72 (bs, 1H), 7.03-7.09 (m, 2H), 7.21-7.26 (m, 3H), 7.30 (d, J=8 Hz, 2H), 7.79 (d, J=7 Hz, 2H).

Next, 5-[(S)-2-N-BOC-amino-3-phenyl-1-propyloxy]-2-chloro-3-bromo pyridine 21C was prepared as follows.
A solution of the product 21B (3.53 g, 8.63 mmol) in DMF (40 mL) was treated with potassium hydroxide (1.21 g, 21.6 mmol) and 2-chloro-3-bromo-5-hydroxyl pyridine (2.25 g, 10.8 mmol), and then stirred at 85°C overnight. DMF was removed under reduced pressure at 60°C. The residue was dissolved in a mixture of H₂O and CH₂Cl₂. The organic layer was washed with water, and brine. It was then dried (MgSO₄), filtered and concentrated. The residue was flash chromatographed on silica gel with 15% ethyl acetate/hexane to provide a white solid 21C (46%, 1.75 g). MS (Cl/NH₃) m/e 441 (M+H)⁺; ¹H NMR (CDCl₃, 300 MHz) δ: 1.43 (s, 9H), 2.90-3.04 (m, 2H), 3.87-3.98 (m, 2H), 4.18 (bs, 1H), 4.82 (bs, 1H), 7.05-7.33 (m, 5H), 7.48 (d, J=3 Hz, 1H), 8.04 (d, J=3 Hz, 1H).

5-[(S)-2-amino-3-phenyl-1-propyloxy]-2-chloro-3-bromo pyridine p-toluensulfonic acid 21 was then prepared as follows.

A solution of the product from Example 21C (137 mg, 0.310 mmol) in CH₂Cl₂ (5 mL) was treated with p-toluensulfonic acid monohydrate (65 mg, 0.342 mmol) and refluxed at 60°C overnight. Next, solvent was removed by bubbling nitrogen into the solution. Ethyl ether (30 mL) was added and stirred for 5 minutes. The ether was decanted and the procedure was repeated. It was then dried under vacuum to provide a white solid as 21. mp162-164 °C; MS (ESI⁺) m/e 341 (M+H)⁺; ¹H NMR (D₂O, 400 MHz) δ: 2.40 (s, 3H), 3.16 (d, J=8 Hz, 2H), 3.99 (m, 1H), 4.14 (dd, J=6, 11 Hz, 1H), 4.30 (dd, J=3, 12 Hz, 1H), 7.32-7.46 (m, 7H), 7.68-7.80 (m, 2H), 7.81 (d, J=3 Hz, 1H), 8.08 (d, J=3
Hz, 1H); Analysis calculated for C$_{14}$H$_{14}$N$_2$BrClO•C$_7$H$_4$O$_4$S: C, 49.09; H, 4.32; N, 5.45; Found: C, 49.10; H, 4.31; N, 5.35; $\{\alpha\}^{25}$D=+30° (c=0.45, MeOH).

Example 22

5-[(S)-2-dimethylamino-3-phenyl-1-propyloxy]-2-chloro-3-bromo pyridine p-toluenesulfonic acid 22 was synthesized as follows.

First, 5-[(S)-2-dimethylamino-3-phenyl-1-propyloxy]-2-chloro-3-bromo pyridine 22A was made as follows.

A solution of the product 21C (242 mg, 0.548 mmol) in a mixture of formaldehyde (37 wt. % in water, 7 mL) and formic acid (4 mL) was stirred at 65°C overnight. The excess reagents were removed under reduced pressure at 45°C. Aqueous NaOH solution (1N) was added to the residue and extracted 3X with CH$_2$Cl$_2$. The combined CH$_2$Cl$_2$ extract was washed with brine, dried (MgSO$_4$), filtered, and concentrated. The residue was flash chromatographed on silica gel with 95/5 CH$_2$Cl$_2$/MeOH to provide 22A as a light yellow oil (84%, 170 mg). MS (Cl/NH$_3$) m/e 369 (M+H)$^+$. Then 5-[(S)-2-dimethylamino-3-phenyl-1-propyloxy]-2-chloro-3-bromo pyridine p-toluenesulfonic acid 22B was prepared as follows.

A solution of the product 22A (170 mg, 0.459 mmol) in ethyl acetate (1 mL) at room temperature was treated with p-toluenesulfonic acid monohydrate (96 mg, 0.505 mmol) and stirred for 5 minutes. Then ethyl ether (30 mL) was added and stirred for an additional 5 minutes. The ether was decanted and the procedure was repeated. The residue was then dried under vacuum to provide
22 as a white hygroscopic solid. mp 45-47°C; MS (ESI+) m/e 369 (M+H)+;
1H NMR (D2O, 300 MHz) δ: 2.39 (s, 3H), 3.06 (s, 6H), 3.13 (m, 1H), 3.37 (dd, J=5, 14 Hz, 1H), 4.02 (m, 1H), 4.18 (dd, J=6, 12 Hz, 1H), 4.30 (dd, J=3, 12 Hz, 1H), 7.30-7.43 (m, 7H), 7.68 (d, J=8 Hz, 2H), 7.71 (d, J=3 Hz, 1H), 8.01 (d, J=3 Hz, 1H); Analysis calculated for
C18H18N2BrClO•1.15C7H5O2S•0.60H2O: C, 49.93; H, 4.95; N, 4.84; Found: C, 49.82; H, 4.88; N, 4.72; [α]25D=+58° (c=3.0, MeOH).

Example 23

5-[(S)-2-amino-3-phenyl-1-propyloxy]-2-chloro-3-(4-vinylpyridinyl) pyridine di-p-toluenesulfonic acid 23 was synthesized as follows.

First, 5-[(S)-2-N-BOC-amino-3-phenyl-1-propyloxy]-2-chloro-3-(4-vinylpyridinyl) pyridine 23A was prepared as follows.

A solution of the product 21A (670 mg, 1.52 mmol), 4-vinyl pyridine (0.25 mL, 2.28 mmol), palladium (II) acetate (34 mg, 0.152 mmol), tri-o-tolylphosphine (92 mg, 0.304 mmol), and triethylamine (0.76 mL, 5.47 mmol) in acetonitrile (20 mL) was refluxed at 100°C overnight. The reaction mixture was diluted with ethyl acetate, washed with saturated sodium carbonate, brine, dried (MgSO4), filtered and concentrated. The residue was flash chromatographed with 30% ethyl acetate/hexane to provide 23A as a light yellow solid (80%, 565 mg); MS (Cl/NH3) m/e 466 (M+H)+.

5-[(S)-2-amino-3-phenyl-1-propyloxy]-2-chloro-3-(4-vinylpyridinyl) pyridine di-p-toluenesulfonic acid 23 was then prepared as follows.
A solution of the product 23A (151 mg, 0.325 mmol) in ethyl acetate (1 mL) was treated with p-toluenesulfonic acid monohydrate (130 mg, 0.684 mmol) and stirred for 5 minutes. Next, ethyl ether (30 mL) was added and stirred for an additional 5 minutes. The ether was decanted and the procedure was repeated. The residue was then dried under vacuum to provide 23 as a light yellow solid. mp 229-231°C; MS (ESI) m/e 366 (M+H)+; 1H NMR (D2O, 400 MHz) δ: 2.35 (s, 6H), 3.18 (d, J=8 Hz, 2H), 4.03 (m, 1H), 4.20 (dd, J=6, 10 Hz, 1H), 4.35 (dd, J=3, 11 Hz, 1H), 7.23-7.46 (m, 9H), 7.64 (d, J=8 Hz, 4H), 7.76 (m, 2H), 8.06 (t, J=3 Hz, 4H), 8.65 (d, J=7 Hz, 2H); Analysis calculated for C21H20N3ClO2C7H8O3S: C, 59.19; H, 5.11; N, 5.92; Found: C, 58.98; H, 4.96; N, 5.85; [α]25D=+18° (c=0.80, MeOH).

Example 24

5-[(S)-2-N-dimethyl-amino-3-phenyl-1-propyloxy]-2-chloro-3-(4-vinylpyridinyl) pyridine 24A was synthesized according to the following procedure.

First, 5-[(S)-2-N-dimethyl-amino-3-phenyl-1-propyloxy]-2-chloro-3-(4-vinylpyridinyl) pyridine 24A was prepared as follows.

A solution of the product 23A (400 mg, 0.860 mmol) in a mixture of formaldehyde (37 wt. % in water, 14 mL) and formic acid (8 mL) was stirred at 65°C overnight. Then the excess reagents were removed under reduced pressure at 45°C. Aqueous NaOH solution (1N) was added to the residue and extracted 3X with CH2Cl2. The combined CH2Cl2 extract was washed with
brine, dried (MgSO\(_4\)), filtered, and concentrated. The residue was flash chromatographed on silica gel with 95/5 CH\(_2\)Cl\(_2\)/MeOH to provide 24A as a light yellow oil (67%, 226 mg). MS (Cl/\(\text{NH}_3\)) m/e 394 (M+H\(^+\)).

Then 5-[(S)-2-N-dimethyl-amino-3-phenyl-1-propyloxy]-2-chloro-3-(4-vinylpyridinyl) pyridine di-p-toluenesulfonic acid 24 was made as follows.

A solution of the product 24A (220 mg, 0.559 mmol) in ethyl acetate (1 mL) at room temperature was treated with p-toluenesulfonic acid monohydrate (224 mg, 1.18 mmol) and stirred for 5 minutes. Then ethyl ether (30 mL) was added and stirred for an additional 5 minutes. The ether was decanted and the procedure was repeated. The residue was then dried under vacuum to provide 24 as a light yellow solid. mp 81-83°C; MS (ESI\(^+\)) m/e 394 (M+H\(^+\)); \(^1\)H NMR (D\(_2\)O, 300 MHz) \(\delta\): 2.31 (s, 6H), 3.07 (s, 3H), 3.10 (s, 3H), 3.35 (m, 2H), 4.02-4.37 (m, 3H), 7.12-7.40 (m, 10H), 7.6 (d, J=8 Hz, 4H), 7.70 (m, 1H), 7.98 (s, 1H), 8.04-8.06 (m, 3H), 8.64 (d, J=6 Hz, 2H); Analysis calculated for C\(_{23}\)H\(_{24}\)N\(_2\)ClO\(_2\)·2.20C\(_2\)H\(_6\)O\(_3\)S·1.45H\(_2\)O: C, 57.73; H, 5.61; N, 5.26; Found: C, 57.42; H, 5.64; N, 4.95; \([\alpha]^{25}\)D=+42° (c=1.8, MeOH).

Example 25

5-[(S)-2-methylamino-3-phenyl-1-propyloxy]-2-chloro-3-(4-vinylpyridinyl) pyridine di-p-toluenesulfonic acid 25 was synthesized according to the following procedure.

First, 5-[(S)-2-N-BOC-methylamino-3-phenyl-1-propyloxy]-2-chloro-3-bromo pyridine 25A was made as follows.
A solution of the product 21C (670 mg, 1.52 mmol) in THF (20 mL) at room temperature was treated with sodium hydride (60% dispersion in mineral oil, 109 mg, 4.55 mmol) and stirred for 20 minutes. Iodomethane (0.76 mL, 12.2 mmol) was then added and stirred at room temperature overnight. The reaction was quenched by adding saturated ammonium chloride solution (6 mL). Saturated sodium carbonate (10 mL) was also added. THF and the excess iodomethane were removed under reduced pressure. The water phase was extracted 3X with CH₂Cl₂. The combined CH₂Cl₂ extract was washed with brine, dried (MgSO₄), filtered and concentrated. The residue was flash chromatographed on silica gel with 10% ethyl acetate/hexane to provide a light yellow oil 25A (97%, 670 mg). MS (Cl/NH₃) m/e 455 (M+H)⁺, 472 (M+NH₃)⁺.

Next, 5-[(S)-2-N-BOC-methylamino-3-phenyl-1-propyloxy]-2-chloro-3-(4-vinylpyridinyl) pyridine 25B was prepared as follows.

A solution of the product 25A (560 mg, 1.23 mmol), 4-vinyl pyridine (0.20 mL, 1.84 mmol), palladium (II) acetate (27 mg, 0.12 mmol), tri-o-tolyphosphine (75 mg, 0.24 mmol), and triethylamine (0.62 mL, 4.43 mmol) in acetonitrile (20 mL) was refluxed at 100°C overnight. Next, the reaction mixture was diluted with ethyl acetate, washed with saturated sodium carbonate, brine, dried (MgSO₄), filtered and concentrated. The residue was flash chromatographed with 30% ethyl acetate/hexane to provide 25B (24%, 141 mg); MS (Cl/NH₃) m/e 480 (M+H)⁺.
Next, 5-[(S)-2-methy lamino-3-phenyl-1-propylo xy]-2-chloro-3-(4-vinylpyridinyl) pyridine di-p-tolu enesulfonic acid 25 was made as follows.

A solution of the product from 25B (138 mg, 0.288 mmol) in ethyl acetate (1 mL) was treated with p-tolu enesulfonic acid monohydrate (115 mg, 0.605 mmol) and stirred for 5 minutes. Next, ethyl ether (30 mL) was added and stirred for an additional 5 minutes. The ether was decanted and the procedure was repeated. The residue was then dried under vacuum to 25 as a light yellow solid. mp 81-83°C; MS (ESI⁺) m/e 380 (M+H)⁺; ¹H NMR (D₂O, 400 MHz) δ: 2.32 (s, 6H), 2.87 (s, 3H), 3.07-3.13 (m, 2H), 3.91 (m, 1H), 4.16 (dd, J=4, 11 Hz, 1H), 4.36 (d, J=11 Hz, 1H), 7.22-7.42 (m, 10H), 7.60-7.78 (m, 5H), 8.04 (d, J=7 Hz, 4H), 8.64 (d, J=7 Hz, 2H); Analysis calculated for C₂₂H₂₂N₂ClO⁻•2.1C₇H₄O₃S•1.3H₂O: C, 57.63; H, 5.46; N, 5.49; Found: C, 57.61; H, 5.63; N, 5.32; [α]₂₃°=+28° (c=1.4, MeOH).

Example 26

5-[(S)-2-amino-1-propylo xy]-2-chloro pyridine p-tolu enesulfonic acid 26 was synthesized according to the following procedure.

First, 2-[(S)-N-BOC]-propanol 26A was prepared as follows. A solution of N-(tert-butoxycarbonyl-D-alanine (25 g, 132 mmol) in anhydrous THF (150 mL) at 0°C was treated with borane (1M solution in THF, 200 mL) over a period of 45 minutes. The ice bath was then removed and the reaction mixture was stirred at room temperature for 3 hours. Saturated NaHCO₃ solution was added slowly to quench the reaction. The resultant solution was
then stirred overnight. Next, solvent was removed under reduced pressure.

The remaining water phase was extracted 4X with ethyl ether. The combined ether extract was washed with brine, dried (MgSO$_4$), filtered, and concentrated. The residue was flash chromatographed on silica gel with 30% ethyl acetate/hexane to provide a white solid 26A (62%, 14.3 g). MS (Cl/NH$_3$) m/e 176 (M+H)$^+$, 193 (M+NH$_4$)$^+$; $^1$H NMR (CDCl$_3$, 300 MHz) δ: 1.16 (d, J=6 Hz, 3H), 1.46 (s, 9H), 3.59 (bs, 1H), 3.70 (bs, 1H), 3.80 (bs, 1H).

Then 2-[(S)-N-BOC]-propanol tosylate 26B was made as follows.

A solution of the product from Example 26A (14.2 g, 81.1 mmol) in CH$_2$Cl$_2$ (300 mL) at room temperature was treated with triethylamine (18.0 mL, 130 mmol) and p-toluenesulfonyl chloride (19.3 g, 101 mmol), and then stirred overnight. The reaction mixture was diluted with CH$_2$Cl$_2$ to 300 mL, washed with water, 5% NaHCO$_3$, and brine. The residue was then dried (MgSO$_4$), filtered and concentrated. The residue was flash chromatographed on silica gel with 30% ethyl acetate/hexane to provide a white solid 26B (72%, 19.3 g). MS (Cl/NH$_3$) m/e 347 (M+NH$_4$)$^+$; $^1$H NMR (CDCl$_3$, 300 MHz) δ: 1.16 (d, J=7 Hz, 3H), 1.41 (s, 9H), 2.45 (s, 3H), 3.85-4.07 (m, 3H), 4.57 (bs, 1H), 7.35 (d, J=8 Hz, 2H), 7.79 (d, J=8 Hz, 2H).

Next, 5-[(S)-2-N-BOC-amino-1-propyloxy]-2-chloro pyridine 26C was prepared as follows.

A solution of the product 26B (700 mg, 2.13 mmol) in DMF (10 mL) was treated with potassium hydroxide (298 mg, 5.32 mmol) and 2-chloro-5-hydroxyl pyridine (344 mg, 2.66 mmol), and then stirred at 85°C overnight.
Next, DMF was removed under reduced pressure at 60°C. The residue was dissolved in a mixture of H₂O and CH₂Cl₂. The organic layer was washed with water, and brine; then dried (MgSO₄), filtered and concentrated. The residue was flash chromatographed on silica gel with 20% ethyl acetate/hexane to provide a light yellow solid 26C (23%, 143 mg). MS (Cl/NH₃) m/e 287 (M+H)⁺, 304 (M+NH₄)⁺; ¹H NMR (CDCl₃, 300 MHz) δ: 1.30 (d, J=7 Hz, 3H), 1.45 (s, 9H), 3.93-4.08 (m, 3H), 4.68 (bs, 1H), 7.23 (d, J=2 Hz, 2H), 8.07 (m, 1H).

Then 5-[(S)-2-amino-1-propyloxy]-2-chloro pyridine 26D was prepared as follows.

A solution of the product 26C (730 mg, 2.55 mmol) in CH₂Cl₂ (10 mL) was treated with trifluoroacetic acid (4 mL) and stirred at room temperature overnight. Then solvent and excess reagent were removed under reduced pressure. The residue was dissolved in saturated sodium carbonate solution and extracted 3X with CH₂Cl₂; and the combined CH₂Cl₂ extract was dried (MgSO₄), filtered and concentrated. The residue was flash chromatographed on silica gel with 95/5/0.5 CH₂Cl₂/CH₃OH/NH₄OH to provide a light yellow oil 26D (72%, 340mg). MS (Cl/ NH₃) m/e 187 (M+H)⁺.

5-[(S)-2-amino-1-propyloxy]-2-chloro pyridine p-toluenesulfonic acid 26 was then made as follows.

A solution of the product 26D (80 mg, 0.429 mmol) in ethyl acetate (1 mL) was treated with p-toluenesulfonic acid monohydrate (86 mg, 0.452 mmol) and stirred for 5 minutes. Then ethyl ether (30 ml) was added and stirred
for an additional 5 minutes. The ether was decanted and the procedure was repeated. The residue was then dried under vacuum to provide 26 as a white solid. mp 177-179°C; MS (Cl/\text{NH}_3) m/e 187 (M+H)^{+}; ^1H NMR (D_2O, 300 MHz) δ: 1.24 (d, J=7 Hz, 3H), 2.21 (s, 3H), 3.66 (m, 1H), 3.94 (dd, J=7, 10 Hz, 1H), 4.14 (dd, J=4, 11 Hz, 1H), 7.18 (d, J=8 Hz, 2H), 7.25-7.35 (m, 2H), 7.50 (d, J=8 Hz, 2H), 7.91 (d, J=3 Hz, 1H). Analysis calculated for C_8H_{17}N_2ClO\cdotC_7H_6O_3S: C, 50.20; H, 5.33; N, 7.80; Found: C, 50.01; H, 5.23; N, 7.49; [α]^{25}D=−2.8° (c=0.82, MeOH).

Example 27

5-[(S)-2-dimethylamino-1-propyloxy]-2-chloro pyridine p-toluensulfonic acid 27 was synthesized according to the following procedure.

First, 5-[(S)-2-dimethylamino-1-propyloxy]-2-chloro pyridine 27A was made as follows.

A solution of the product 26D (260 mg, 1.39 mmol) in a mixture of formaldehyde (37 wt. % in water, 8 mL) and formic acid (4.2 mL) was stirred at 65°C overnight. The excess reagents were removed under reduced pressure at 45°C. Aqueous NaOH solution (1N) was added to the residue and extracted 3X with CH_2Cl_2. The combined CH_2Cl_2 extract was washed with brine, dried (MgSO_4), filtered, and concentrated. The residue was flash chromatographed on silica gel with 90/10/1 CH_2Cl_2/MeOH/NH_4OH to provide 27A (46%, 155 mg). MS (Cl/\text{NH}_3) m/e 215 (M+H)^{+}.
Next, 5-[(S)-2-dimethylamino-1-propyloxy]-2-chloro-pyridine p-toluenesulfonic acid 27 was made as follows.

A solution of the product 27A (150 mg, 0.701 mmol) in ethyl acetate (1 mL) at room temperature was treated with p-toluenesulfonic acid monohydrate (140 mg, 0.736 mmol) and stirred for 5 minutes. Next, ethyl ether (30 mL) was added and stirred for an additional 5 minutes. The ether was decanted and the procedure was repeated. The residue was then dried under vacuum to provide 27 as a white hygroscopic solid. mp 80-82°C; MS (Cl/NH3) m/e 215 (M+H)+; 1H NMR (D2O, 300 MHz) δ: 1.42 (d, J=7 Hz, 3H), 2.39 (s, 3H), 2.91 (d, J=1 Hz, 6H), 3.91 (m, 1H), 4.28 (dd, J=6, 11 Hz, 1H), 4.40 (dd, J=4, 12 Hz, 1H), 7.37 (d, J=8 Hz, 2H), 7.44-7.53 (m, 2H), 7.69 (d, J=8 Hz, 2H), 8.11 (d, J=3 Hz, 1H); Analysis calculated for C16H13N2ClO•1.03C7H4O3S•0.08H2O: C, 52.53; H, 5.99; N, 7.11; Found: C, 52.93; H, 5.88; N, 6.71; [α]25D=−3.3° (c=1.3, MeOH).

Example 28

5-[(R)-2-methylamino-1-propyloxy]-2-chloropyridine p-toluenesulfonic acid 28 was synthesized in the following manner.

First, 5-[(R)-2-N-BOC-methylamino-1-propyloxy]-2-chloro pyridine 28A was prepared as follows.

A solution of the product 26C (180 mg, 0.628 mmol) in THF (8 mL) at room temperature was treated with sodium hydride (60% dispersion in mineral oil, 75 mg, 1.88 mmol) and stirred for 20 minutes. Iodomethane (0.31 mL, 5.02
mmol) was then added and stirred at room temperature overnight. The reaction was quenched by adding saturated ammonium chloride solution (6 mL). Saturated sodium carbonate (10 mL) was also added. THF and the excess iodomethane were removed under reduced pressure. The water phase was extracted 3X with CH₂Cl₂. The combined CH₂Cl₂ extract was washed with brine, dried (MgSO₄), filtered and concentrated. The residue was flash chromatographed on silica gel with 15% ethyl acetate/hexane to provide a light yellow oil 28A (80%, 160 mg). MS (Cl/NH₃) m/e 301 (M+H)+, 318 (M+NH₄)+; ¹H NMR (CDCl₃, 300 MHz) δ: 1.25 (d, J=7 Hz, 3H), 1.46 (s, 9H), 2.80 (s, 3H), 3.89-4.03 (m, 2H), 4.56 (bs, 1H), 7.16-7.26 (m, 2H), 8.05 (d, J=3 Hz, 1H).

Then 5-[(R)-2-methylamino-1-propyloxy]-2-chloro pyridine p-toluenesulfonic acid 28 was prepared as follows.

A solution of the product from Example 28A (147 mg, 0.489 mmol) in CH₂Cl₂ (8 mL) was treated with p-toluenesulfonic acid monohydrate (102 mg, 0.536 mmol) and refluxed at 60°C overnight. Next, solvent was removed by bubbling nitrogen into the solution. Ethyl ether (30 mL) was added and stirred for 5 minutes. The ether was decanted and the procedure was repeated. The residue was then dried under vacuum to provide 28 as a light yellow solid. mp 65-67°C; MS (Cl/NH₃) m/e 201 (M+H)+; ¹H NMR (D₂O, 500 MHz) δ: 1.45 (d, J=7 Hz, 3H), 2.39 (s, 3H), 2.78 (s, 3H), 3.74 (m, 1H), 4.20 (dd, J=7, 11 Hz, 1H), 4.37 (dd, J=3, 10 Hz, 1H), 7.36 (d, J=8 Hz, 2H), 7.44 (d, J=9 Hz, 1H), 7.50 (dd, J=3, 9 Hz, 1H), 7.69 (d, J=8, 2H), 8.09 (d, J=3 Hz, 1H); Analysis
calculated for \( \text{C}_9\text{H}_{13}\text{N}_2\text{ClO}\cdot 1.2\text{C}_7\text{H}_8\text{O}_2\text{S} \cdot 0.2\text{H}_2\text{O} \): C, 50.86; H, 5.64; N, 6.82;
Found: C, 50.79; H, 5.37; N, 6.67; \([\alpha]_D^{25} = -7.4^\circ \) (c=1.4, MeOH).

Example 29

5-\([(\text{R})-2\text{-amino-1-propyloxy}]\)-2-fluoro pyridine p-toluenesulfonic acid 29 was synthesized in the following manner.

First, 5-\([(\text{R})-2\text{-N-BOC-amino-1-propyloxy}]\)-2-fluoro pyridine 29A was prepared as follows.

A solution of the product 26B (605 mg, 1.84 mmol) in DMF (10 mL) 10
was treated with potassium hydroxide (258 mg, 4.60 mmol) and 2-fluoro-5-
hydroxyl pyridine (260 mg, 2.30 mmol), and stirred at 85°C overnight. Then
DMF was removed under reduced pressure at 60°C. The residue was dissolved
in a mixture of \( \text{H}_2\text{O} \) and \( \text{CH}_2\text{Cl}_2 \). The organic layer was washed with water, and
brine. It was then dried (\( \text{MgSO}_4 \)), filtered and concentrated. The residue was
flash chromatographed on silica gel with 20% ethyl acetate/hexane to provide a
light yellow oil 26A (67%, 330 mg). MS (CI/NH\(_3\)) m/e 271 (M+H)\(^+\), 288
(M+NH\(_4\))\(^+\); \(^1\text{H NMR (CDCl}_3\), 300 MHz\) \(\delta\): 1.31 (d, J=7 Hz, 3H), 1.46 (s, 9H),
3.97-4.23 (m, 3H), 4.68 (bs, 1H), 6.76 (m, 1H), 7.35 (m, 1H), 7.86 (s, 1H).

Next, 5-\([(\text{R})-2\text{-amino-1-propyloxy}]\)-2-fluoro pyridine 29B was prepared 15
as follows.

A solution of the product from Example 29A (366 mg, 1.36 mmol) in
\( \text{CH}_2\text{Cl}_2 \) (4 mL) was treated with trifluoroacetic acid (2 mL) and stirred at room
temperature overnight. Next, solvent and excess reagent were removed under

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reduced pressure. The residue was dissolved in saturated sodium carbonate solution and extracted 3X with CH₂Cl₂. The combined CH₂Cl₂ extract was dried (MgSO₄), filtered and concentrated. The residue was flash chromatographed on silica gel with 95/5/0.5 CH₂Cl₂/CH₃OH/NH₄OH to provide a yellow oil 29B (72%, 166mg). MS (Cl/ NH₃) m/e 171 (M+H)⁺, 188 (M+NH₄)⁺.

Then 5-[(R)-2-amino-1-propyloxy]-2-fluoro pyridine p-toluenesulfonic acid 29 was prepared as follows.

A solution of the product 29B (160 mg, 0.976 mmol) in ethyl acetate (1 mL) was treated with p-toluenesulfonic acid monohydrate (195 mg, 1.03 mmol) and stirred for 5 minutes. Then ethyl ether (30 ml) was added and stirred for an additional 5 minutes. The ether was decanted and the procedure was repeated. The residue was then dried under vacuum to provide 29 as a white solid. mp 159-161°C; MS (Cl/ NH₃) m/e 171 (M+H)⁺, 188 (M+NH₄)⁺; ¹H NMR (D₂O, 300 MHz) δ: 1.43 (d, J=7 Hz, 3H), 2.41 (s, 3H), 3.84 (m, 1H), 4.13 (dd, J=7, 10 Hz, 1H), 4.32 (dd, J=3, 10 Hz, 1H), 7.09 (dd, J=3, 9 Hz, 1H), 7.38 (d, J=8 Hz, 2H), 7.64 (m, 1H), 7.70 (d, J=8 Hz, 2H), 7.89 (m, 1H). Analysis calculated for C₇H₁₁N₂FO•1.1C₇H₈O₃S: C, 52.44; H, 5.55; N, 7.79; Found: C, 52.09; H, 5.48; N, 8.09; [α]D²⁰=−3.9° (c=0.73, MeOH).

Example 30

5-[(R)-2-dimethylamino-1-propyloxy]-2-fluoro pyridine p-toluenesulfonic acid 30 was synthesized according to the following procedure.
First, 5-[(R)-2-dimethylamino-1-propyloxy]-2-fluoro pyridine 30A was synthesized as follows.

A solution of the product 29A (108 mg, 0.635 mmol) in the mixture of formaldehyde (37 wt. % in water, 4 mL) and formic acid (2.6 mL) was stirred at 65°C overnight. The excess reagents were removed under reduced pressure at 45°C. Aqueous NaOH solution (1N) was added to the residue and extracted 3X with CH₂Cl₂. The combined CH₂Cl₂ extract was washed with brine, dried (MgSO₄), filtered, and concentrated. The residue was flash chromatographed on silica gel with 95/5/0.5 CH₂Cl₂/MeOH/NH₄OH to provide a light yellow oil 30A (53%, 67 mg). MS (Cl/NH₃) m/e 199 (M+H)⁺.

5-[(R)-2-dimethylamino-1-propyloxy]-2-fluoro pyridine p-toluenesulfonic acid 30 was then prepared as follows.

A solution of the product 30A (60 mg, 0.303 mmol) in ethyl acetate (1 mL) was treated with p-toluenesulfonic acid monohydrate (60 mg, 0.318 mmol) and stirred for 5 minutes. Then ethyl ether (30 mL) was added and stirred for an additional 5 minutes. The ether was decanted and the procedure was repeated. The residue was then dried under vacuum to provide 30 as a white solid. mp 107-109°C; MS (APCI⁺) m/e 199 (M+H)⁺; ¹H NMR (D₂O, 500 MHz) δ: 1.43 (d, J=7 Hz, 3H), 2.40 (s, 3H), 2.92 (s, 6H), 3.90 (m, 1H), 4.27 (dd, J=8, 11 Hz, 1H), 4.40 (dd, J=4, 12 Hz, 1H), 7.10 (m, 1H), 7.36-7.39 (m, 2H), 7.65 (m, 1H), 7.68-7.72 (m, 2H), 7.90 (dd, J=1, 3 Hz, 1H); Analysis calculated for C₁₀H₁₅N₂FO·C₇H₈O₃S: C, 55.12; H, 6.25; N, 7.56; Found: C, 54.88; H, 6.17; N, 7.29; [α]D²⁵=-10° (c=0.30, MeOH).
Example 31

5-[(R)-2-methylamino-1-propyloxy]-2-fluoro pyridine p-toluenesulfonic acid 31 was synthesized according to the following procedure.

First, 5-[(R)-2-N-BOC-methylamino-1-propyloxy]-2-fluoro-pyridine 31A was made as follows.

A solution of the product 29A (320 mg, 1.19 mmol) in THF (15 mL) was treated with sodium hydride (60% dispersion in mineral oil, 142 mg, 3.56 mmol) and stirred for 20 minutes. Then, iodomethane (0.59 mL, 11.3 mmol) was added and stirred at room temperature overnight. The reaction was quenched by adding saturated ammonium chloride solution (6 mL). Saturated sodium carbonate (10 mL) was also added. THF and the excess iodomethane were removed under reduced pressure. The water phase was extracted 3X with CH$_2$Cl$_2$. The combined CH$_2$Cl$_2$ extract was washed with brine, dried (MgSO$_4$), filtered and concentrated. The residue was flash chromatographed on silica gel with 15% ethyl acetate/hexane to provide a clear oil 31A (66%, 230 mg). MS (Cl/NH$_3$) m/e 285 (M+H)$^+$, 302 (M+NH$_4$)$^+$; $^1$H NMR (CDCl$_3$, 300 MHz) δ: 1.25 (d, J=7 Hz, 3H), 1.46 (s, 9H), 2.80 (s, 3H), 3.90-4.03 (m, 2H), 4.53 (br, 1H), 6.85 (dd, J=3, 9 Hz, 1H), 7.31 (m, 1H), 7.81 (s, 1H).

Then 5-[(R)-2-methylamino-1-propyloxy]-2-fluoro pyridine p-toluenesulfonic acid 31 was prepared as follows.

A solution of the product 31A (223 mg, 0.785 mmol) in CH$_2$Cl$_2$ (8 mL) was treated with p-toluenesulfonic acid monohydrate (164 mg, 0.863 mmol) and refluxed at 60°C overnight. Next solvent was removed by bubbling
nitrogen into the solution. Ethyl ether (30 mL) was added and stirred for 5 minutes. The ether was decanted and the procedure was repeated. The residue was then dried under vacuum to provide 31 as a white solid. mp 87-89°C; MS (Cl/NH₃) m/e 185 (M+H)⁺, 202 (M+NH₄)⁺; ¹H NMR (D₂O, 500 MHz) δ: 1.45 (d, J=7 Hz, 3H), 2.39 (s, 3H), 2.78 (s, 3H), 3.73 (m, 1H), 4.18 (dd, J=6, 10 Hz, 1H), 4.35 (dd, J=3, 10 Hz, 1H), 7.08 (dd, J=3, 9 Hz, 1H), 7.35 (d, J=8 Hz, 2H), 7.61 (m, 1H), 7.68 (d, J=8 Hz, 2H), 7.86 (d, J=2 Hz, 1H); Analysis calculated for C₉H₁₃N₂FO•C₇H₉O₃S: C, 53.92; H, 5.94; N, 7.86; Found: C, 53.69; H, 5.96; N, 7.72; [α]²⁵D=−8.6° (c=1.0, MeOH).

Example 32

5-[(R)-2-amino-1-propyloxy]-2-chloro-3-bromo pyridine p-toluenesulfonic acid 32 was synthesized according to the following procedure.

First, 5-[(R)-2-N-BOC-amino-1-propyloxy]-2-chloro-3-bromo pyridine 32A was prepared as follows.

A solution of the product 26B (3.14 g, 9.54 mmol) in DMF (40 mL) was treated with potassium hydroxide (1.33 g, 23.8 mmol) and 2-chloro-3-bromo-5-hydroxy xyl pyridine (2.49 g, 11.9 mmol) and then stirred at 85°C overnight. DMF was removed under reduced pressure at 60°C. The residue was dissolved in a mixture of H₂O and CH₂Cl₂. The organic layer was washed 2X with water, and 1X with brine, dried (MgSO₄), filtered, and concentrated. The residue was flash chromatographed on silica gel with 15% ethyl acetate/hexane to provide a white solid 32A (51%, 1.77 g). MS (Cl/NH₃) m/e 365 (M+H)⁺, 382 (M+NH₄)⁺.
5-[(R)-2-amino-1-propyloxy]-2-chloro-3-bromo pyridine p-toluenesulfonic acid 32 was then prepared as follows.

A solution of the product 32A (103 mg, 0.282 mmol) in CH₂Cl₂ (8 mL) was treated with p-toluenesulfonic acid monohydrate (59 mg, 0.310 mmol) and refluxed at 60°C overnight. Then solvent was removed by bubbling nitrogen into the solution. Ethyl ether (30 mL) was added and stirred for 5 minutes. The ether was decanted and the procedure was repeated. The residue was then dried under vacuum to provide 32 as a white solid. mp 159-161°C; MS (Cl/NH₃) m/e 265 (M+H)+, 282 (M+NH₄)+; ¹H NMR (D₂O, 500 MHz) δ: 1.44 (d, J=7 Hz, 3H), 2.40 (s, 3H), 3.85 (m, 1H), 4.14 (dd, J=7, 10 Hz, 1H), 4.32 (dd, J=3, 11 Hz, 1H), 7.36 (d, J=8 Hz, 2H), 7.69 (d, J=8 Hz, 2H), 7.85 (d, J=3 Hz, 1H), 8.09 (d, J=3 Hz, 1H); Analysis calculated for C₈H₁₀N₂BrClO•C₇H₅O₃S•0.4H₂O: C, 41.49; H, 4.26; N, 6.30; Found: C, 40.22; H, 3.90; N, 6.19; [α]D²⁵ = -6.6° (c=2.2, MeOH).

Example 33

5-[(R)-2-dimethylamino-1-propyloxy]-2-chloro-3-bromo pyridine p-toluenesulfonic acid 33 was synthesized according to the following procedure.

First, 5-[(R)-2-dimethylamino-1-propyloxy]-2-chloro-3-bromo pyridine 33A was made as follows.

A solution of the product 32A (218 mg, 0.596 mmol) in a mixture of formaldehyde (37 wt. % in water, 7 mL) and formic acid (4 mL) was stirred at 65°C overnight. The excess reagents were removed under reduced pressure at...
45°C. Aqueous NaOH solution (1N) was added to the residue and extracted
3X with CH₂Cl₂. The combined CH₂Cl₂ extract was washed with brine, dried
(MgSO₄), filtered, and concentrated. The residue was flash chromatographed
on silica gel with 95/5/0.5 CH₂Cl₂/MeOH/NH₄OH to provide 33A as a light
yellow oil (58%, 102 mg). MS (Cl/NH₃) m/e 293 (M+H)⁺.

Then 5-[(R)-2-dimethylamino-1-propyloxy]-2-chloro-3-bromo pyridine
p-toluenesulfonic acid 33 was prepared as follows.

A solution of the product 33A (102 mg, 0.349 mmol) in ethyl acetate (1
mL) at room temperature was treated with p-toluenesulfonic acid monohydrate
(73 mg, 0.384 mmol) and stirred for 5 minutes. Then diethyl ether (30 mL) was
added and stirred for an additional 5 minutes. The ether was decanted and the
procedure was repeated. The residue was then dried under vacuum to provide
33 as a white hygroscopic solid. MS (Cl/NH₃) m/e 293 (M+H)⁺; ¹H NMR
(D₂O, 500 MHz) δ: 1.43 (d, J=7 Hz, 3H), 2.38 (s, 3H), 2.91 (d, J=37 Hz, 6H),
3.90 (m, 1H), 4.26 (dd, J=8, 12 Hz, 1H), 4.38 (dd, J=4, 12 Hz, 1H), 7.34 (d,
J=8 Hz, 2H), 7.67 (d, J=8 Hz, 2H), 7.84 (d, J=3 Hz, 1H), 8.08 (d, J=3 Hz,
1H); Analysis calculated for C₁₀H₁₄N₂BrClO•1.1C₆H₅O₃S•0.2H₂O: C, 43.69; H,
4.81; N, 5.76; Found: C, 43.66; H, 4.62; N, 5.47; [α]²⁰D=−0.87° (c=0.69,
MeOH).

Example 34

5-[(R)-2-methylamino-1-propyloxy]-2-chloro-3-bromo pyridine p-
toluenesulfonic acid 34 was synthesized according to the following procedure.
First, 5-[(R)-2-N-BOC-methylamino-1-propyloxy]-2-chloro-3-bromo pyridine 34A was synthesized as follows.

A solution of the product 32A (225 mg, 0.615 mmol) in THF (10 mL) at room temperature was treated with sodium hydride (60% dispersion in mineral oil, 74 mg, 1.85 mmol) and stirred for 20 minutes. Next, iodomethane (0.31 mL, 4.92 mmol) was added and stirred at room temperature overnight. The reaction was quenched by adding saturated ammonium chloride solution (6 mL). Saturated sodium carbonate (10 mL) was also added. THF and the excess iodomethane were removed under reduced pressure. The water phase was extracted 3X with CH₂Cl₂. The combined CH₂Cl₂ extract was washed with brine, dried (MgSO₄), filtered and concentrated. The residue was flash chromatographed on silica gel with 10% ethyl acetate/hexane to provide a light yellow oil 34A (83%, 195 mg). MS (Cl/CH₃) m/e 379 (M+H)⁺, 396 (M+NH₄)⁺; ¹H NMR (CDCl₃, 300 MHz) δ: 1.25 (d, J=6 Hz, 3H), 1.46 (s, 9H), 2.81 (s, 3H), 3.89-4.06 (m, 2H), 4.50 (bs, 1H), 7.49 (d, J=2 Hz, 1H), 8.03 (d, J=2, 1H).

Then 5-[(R)-2-methylamino-1-propyloxy]-2-chloro-3-bromo pyridine p-toluenesulfonic acid 34 was prepared as follows.

A solution of the product 34A (194 mg, 0.511 mmol) in CH₂Cl₂ (8 mL) was treated with p-toluenesulfonic acid monohydrate (107 mg, 0.563 mmol) and refluxed at 60°C overnight. Then solvent was removed by bubbling nitrogen into the solution. Ethyl ether (30 mL) was added and stirred for 5 minutes. The ether was decanted and the procedure was repeated. The residue
was then dried under vacuum to provide 34 as a hygroscopic white solid. mp 42-44°C; MS (Cl/NH₃) m/e 279 (M+H)+, 296 (M+NH₄)+; ¹H NMR (D₂O, 500 MHz) δ: 1.44 (d, J=7 Hz, 3H), 2.38 (s, 3H), 2.78 (s, 3H), 3.73 (m, 1H), 4.18 (dd, J=6, 10 Hz, 1H), 4.36 (dd, J=3, 10 Hz, 1H), 7.34 (d, J=8 Hz, 2H), 7.67 (d, J=8 Hz, 2H), 7.82 (d, J=3 Hz, 1H), 8.07 (d, J=3 Hz, 1H); Analysis calculated for C₉H₁₂N₂BrClO•C₇H₈O₃S: C, 42.54; H, 4.46; N, 6.20; Found: C, 42.61; H, 4.67; N, 5.98; [α]²⁰D=−5.8° (c=0.65, MeOH).

Example 35

5-[(R)-2-amino-1-propyloxy]-2-chloro-3-methyl pyridine p-toluenesulfonic acid 35 was synthesized according to the following procedure.

First, 5-[(R)-2-N-BOC-amino-1-propyloxy]-2-chloro-3-methyl pyridine 35A was prepared as follows.

A solution of the product 26B (1.32 g, 4.01 mmol) in DMF (20 mL) was treated with potassium hydroxide (561 mg, 10.0 mmol) and 2-chloro-3-methyl-5-hydroxyl pyridine (720 mg, 5.02 mmol), and then stirred at 85°C overnight. DMF was removed under reduced pressure at 60°C. The residue was dissolved in a mixture of H₂O and CH₂Cl₂. The organic layer was washed with water, and brine; then dried (MgSO₄), filtered and concentrated. The residue was flash chromatographed on silica gel with 20% ethyl acetate/hexane to provide a white solid 35A (35%, 424 mg). MS (Cl/NH₃) m/e 301 (M+H)+.
Then 5-[(R)-2-amino-1-propyloxy]-2-chloro-3-methyl pyridine p-toluenesulfonic acid 35 was prepared as follows.

A solution of the product 35A (76 mg, 0.253 mmol) in CH$_2$Cl$_2$ (8 mL) was treated with p-toluenesulfonic acid monohydrate (53 mg, 0.279 mmol) and refluxed at 60°C overnight. Next solvent was removed by bubbling nitrogen into the solution. Ethyl ether (30 mL) was added and stirred for 5 minutes. The ether was decanted and the procedure was repeated. The residue was then dried under vacuum to provide a white solid 35. mp 156-158°C; MS (Cl/NH$_3$) m/e 201 (M+H)$^+$; $^1$H NMR (D$_2$O, 500 MHz) δ: 1.42 (d, J=7 Hz, 3H), 2.33 (s, 3H), 2.38 (s, 3H), 3.82 (m, 1H), 4.09 (dd, J=7, 12 Hz, 1H), 4.28 (dd, J=3, 10 Hz, 1H), 7.37 (d, J=8 Hz, 2H), 7.40 (d, J=2 Hz, 1H), 7.67 (d, J=8 Hz, 2H), 7.92 (d, J=3 Hz, 1H); Analysis calculated for C$_9$H$_{13}$N$_2$ClO·1.2C$_2$H$_5$O$_2$S·0.2H$_2$O: C, 50.86; H, 5.64; N, 6.82; Found: C, 50.68; H, 5.53; N, 6.70; $[\alpha]^{25}$D = -4.4° (c=0.75, MeOH).

Example 36

5-[(R)-2-dimethylamino-1-propyloxy]-2-chloro-3-methyl pyridine p-toluenesulfonic acid 36 was synthesized according to the following procedure.

First, 5-[(R)-2-dimethylamino-1-propyloxy]-2-chloro-3-methyl pyridine 36A was prepared as follows.

A solution of the product 35A (146 mg, 0.486 mmol) in a mixture of formaldehyde (37 wt. % in water, 7 mL) and formic acid (4 mL) was stirred at 65°C overnight. The excess reagents were removed under reduced pressure at
45°C. Aqueous NaOH solution (1N) was added to the residue and extracted 3X with CH₂Cl₂. The combined CH₂Cl₂ extract was washed with brine, dried (MgSO₄), filtered, and concentrated. The residue was flash chromatographed on silica gel with 95/5/0.5 CH₂Cl₂/MeOH/NH₂OH to provide 36A as a light yellow oil (54%, 60 mg). MS (Cl/NH₃) m/e 229 (M+H)⁺.

Then 5-[(R)-2-dimethylamino-1-propyloxy]-2-chloro-3-methyl pyridine p-toluenesulfonic acid 36 was prepared as follows.

A solution of the product 36A (60 mg, 0.263 mmol) in ethyl acetate (1 mL) at room temperature was treated with p-toluenesulfonic acid monohydrate (55 mg, 0.289 mmol) and stirred for 5 minutes. Next ethyl ether (30 mL) was added and stirred for an additional 5 minutes. The ether was decanted and the procedure was repeated. The residue was then dried under vacuum to provide 36 as a white solid. mp 87-89°C; MS (Cl/ NH₃) m/e 229 (M+H)⁺; ¹H NMR (D₂O, 300 MHz) δ: 1.43 (d, J=7 Hz, 3H), 2.35 (s, 3H), 2.39 (s, 3H), 2.91 (s, 6H), 3.90 (m, 1H), 4.24 (dd, J=8, 12 Hz, 1H), 4.42 (dd, J=3, 11 Hz, 1H), 7.38(d, J=8 Hz, 2H), 7.44 (d, J=3 Hz, 1H), 7.68 (d, J=8 Hz, 2H), 7.93 (d, J=3 Hz, 1H); Analysis calculated for C₁₁H₁₇N₂ClO•1.1C₇H₆O₃S•0.2H₂O: C, 53.26; H, 6.26; N, 6.64; Found: C, 53.17; H, 6.27; N, 6.60; [α]²⁵D=−4.6° (c=0.80, MeOH).

Example 37

5-[(R)-2-methylamino-1-propyloxy]-2-chloro-3-methyl pyridine p-toluenesulfonic acid 37 was synthesized according to the following procedure.
First, 5-[(R)-2-N-BOC-methylamino-1-propyloxy]-2-chloro-3-methyl pyridine 37A was prepared as follows.

A solution of the product 35A (183 mg, 0.608 mmol) in THF (8 mL) at room temperature was treated with sodium hydride (60% dispersion in mineral oil, 73 mg, 1.83 mmol) and stirred for 20 minutes. Next, iodomethane (0.31 mL, 4.87 mmol) was added and stirred at room temperature overnight. The reaction was quenched by adding saturated ammonium chloride solution (6 mL). Saturated sodium carbonate (10 mL) was also added. THF and the excess iodomethane were removed under reduced pressure. The water phase was extracted 3X with CH₂Cl₂. The combined CH₂Cl₂ extract was washed with brine, dried (MgSO₄), filtered and concentrated. The residue was flash chromatographed on silica gel with 15% ethyl acetate/hexane to provide a clear oil 37A (79%, 152 mg). MS (Cl/ NH₃) m/e 315 (M+H)⁺, 332 (M+NH₄)⁺; ¹H NMR (CDCl₃, 300 MHz) δ: 1.25 (d, J=7 Hz, 3H), 1.46 (s, 9H), 2.35 (s, 3H), 2.80 (s, 3H), 3.89-4.03 (m, 2H), 4.51 (bs, 1H), 7.10 (bs, 1H), 7.89 (bs, 1H).

Then 5-[(R)-2-methylamino-1-propyloxy]-2-chloro-3-methyl pyridine p-toluenesulfonic acid 37 was prepared as follows.

A solution of the product 37A (152 mg, 0.483 mmol) in CH₂Cl₂ (10 mL) was treated with p-toluenesulfonic acid monohydrate (101 mg, 0.532 mmol) and refluxed at 60°C overnight. Then solvent was removed by bubbling nitrogen into the solution. Ethyl ether (30 mL) was added and stirred for 5 minutes. The ether was decanted and the procedure was repeated. The residue was then dried under vacuum to provide 37 as a hygroscopic white solid. MS
(Cl/NH₃) m/e 215 (M+H)⁺; ¹H NMR (D₂O, 500 MHz) δ: 1.44 (d, J=7 Hz, 3H), 2.37 (s, 3H), 2.41 (s, 3H), 2.77 (s, 3H), 3.72 (m, 1H), 4.19 (dd, J=7, 11 Hz, 1H), 4.37 (dd, J=3, 10 Hz, 1H), 7.33 (d, J=8 Hz, 2H), 7.45 (d, J=3 Hz, 1H), 7.67 (d, J=8 Hz, 2H), 7.94 (d, J=3 Hz, 1H); Analysis calculated for C₁₀H₁₅N₂ClO•1.6C₆H₅O₃S•0.8H₂O: C, 50.46; H, 5.87; N, 5.55; Found: C, 50.74; H, 6.08; N, 5.28; [α]²⁵D=-4.9° (c=3.9, MeOH).

Example 38

5-[(R)-2-amino-1-propyloxy]-2-chloro-3-(4-vinylpyridinyl) pyridine

p-toluensulfonic acid 38 was synthesized according to the following procedure. First, 5-[(R)-2-N-BOC-amino-1-propyloxy]-2-chloro-3-(4-vinylpyridinyl) pyridine 38A was prepared as follows.

A solution of the product 32A (1.19 g, 3.25 mmol), 4-vinyl pyridine (0.44 mL, 4.07 mmol), palladium (II) acetate (29 mg, 0.130 mmol), tri-o-tolylphospine (79 mg, 0.260 mmol), and triethylamine (1.62 mL, 11.7 mmol) in acetonitrile (10 mL) was refluxed at 100°C for 2 days. Then the reaction mixture was diluted with ethyl acetate, washed with saturated sodium carbonate, brine, dried (MgSO₄), filtered and concentrated. The residue was flash chromatographed with 30% ethyl acetate/hexane to provide 38A as a white solid (48%, 610 mg); MS (Cl/NH₃) m/e 390 (M+H)⁺.

Next, 5-[(R)-2-amino-1-propyloxy]-2-chloro-3-(4-vinylpyridinyl) pyridine 38B was prepared as follows.
A solution of the product 38A (128 mg, 0.329 mmol) in CH₂Cl₂ (4 mL) was treated with trifluoroacetic acid (2 mL) and stirred at room temperature overnight. Then solvent and the excess reagent were removed under reduced pressure. The residue was dissolved in saturated sodium carbonate solution and extracted 3X with CH₂Cl₂. The combined CH₂Cl₂ extract was dried (MgSO₄), filtered and concentrated. The residue was flash chromatographed on silica gel with 95/5/0.5 CH₂Cl₂/CH₃OH/NH₄OH to provide a light yellow solid 38B (61%, 58 mg). MS (Cl/ NH₃) m/e 290 (M+H)⁺.

Then 5-[(R)-2-amino-1-propyloxy]-2-chloro-3-(4-vinylpyridinyl) pyridine p-toluenesulfonic acid 38 was prepared as follows.

A solution of the product 38B (58 mg, 0.201 mmol) in ethyl acetate (1 mL) was treated with p-toluenesulfonic acid monohydrate (42 mg, 0.221 mmol) and stirred for 5 minutes. Next ethyl ether (30 mL) was added and stirred for an additional 5 minutes. The ether was decanted and the procedure was repeated. The residue was then dried under vacuum to provide 38 as a light yellow solid. mp 47-49°C; MS (Cl/ NH₃) m/e 290 (M+H)⁺; ¹H NMR (D₂O, 500 MHz) δ: 1.48 (d, J=7 Hz, 3H), 2.35 (s, 3H), 3.87 (m, 1H), 4.14 (m, 1H), 4.31 (dd, J=4, 10 Hz, 1H), 7.10 (d, J=6 Hz, 2H), 7.29 (d, J=8 Hz, 2H), 7.45 (d, J=16 Hz, 2H), 7.64 (d, J=8 Hz, 2H), 7.68 (d, J=3 Hz, 1H), 7.93 (d, J=3 Hz, 1H), 8.45 (d, J=6 Hz, 2H); Analysis calculated for C₁₉H₁₆N₅ClO•1.19C₂H₅O₂S•0.95H₂O: C, 54.75; H, 5.40; N, 8.21; Found: C, 54.43; H, 5.36; N, 8.61; [α]D²⁵=−1.6° (c=0.55, MeOH).
Example 39

5-{[(R)-2-N-dimethylamino-1-propyloxy]-2-chloro-3-(4-vinylpyridinyl) pyridine p-toluenesulfonic acid 39} was synthesized according to the following procedure.

First 5-{[(R)-2-N-dimethylamino-1-propyloxy]-2-chloro-3-(4-vinylpyridinyl) pyridine 39A} was prepared as follows.

A solution of the product 38A (300 mg, 0.771 mmol) in a mixture of formaldehyde (37 wt. % in water, 7 mL) and formic acid (4 mL) was stirred at 65°C overnight. The excess reagents were removed under reduced pressure at 45°C. Aqueous NaOH solution (1N) was then added to the residue and extracted 3X with CH₂Cl₂. The combined CH₂Cl₂ extract was washed with brine, dried (MgSO₄), filtered, and concentrated. The residue was flash chromatographed on silica gel with 95/5/0.5 CH₂Cl₂/MeOH/NH₄OH to provide 39A as a yellow oil (58%, 143 mg). MS (Cl/NH₄) m/e 318 (M+H)⁺.

Then 5-{[(R)-2-N-dimethylamino-1-propyloxy]-2-chloro-3-(4-vinylpyridinyl) pyridine p-toluenesulfonic acid 39} was prepared as follows.

A solution of the product 39A (140 mg, 0.442 mmol) in ethyl acetate (1 mL) at room temperature was treated with p-toluenesulfonic acid monohydrate (88 mg, 0.462 mmol) and stirred for 5 minutes. Ethyl ether (30 mL) was added and stirred for an additional 5 minutes. The ether was decanted and the procedure was repeated. It was then dried under vacuum to provide 39 as a light yellow solid. mp 81-83°C; MS (Cl/NH₄) m/e 318 (M+H)⁺; ¹H NMR (D₂O, 500 MHz) δ: 1.47 (d, J=7 Hz, 3H), 2.31 (s, 3H), 2.95 (s, 6H), 3.89 (m,
1H), 4.22 (dd, J=8, 11 Hz, 1H), 4.33 (dd, J=3, 11 Hz, 1H), 6.98 (d, J=16 Hz, 1H), 7.24 (d, J=8 Hz, 2H), 7.27 (s, 1H), 7.42 (d, J=5 Hz, 2H), 7.56 (s, 1H), 7.63 (d, J=8 Hz, 2H), 7.87 (d, J=1 Hz, 1H), 8.34 (d, J=5 Hz, 1H); Analysis calculated for C_{17}H_{20}N_{3}ClO•1.45C_{7}H_{4}O_{3}S•0.45H_{2}O: C, 56.65; H, 5.69; N, 7.30; Found: C, 56.36; H, 5.83; N, 7.50; [α]^{25}D=−2.80° (c=1.2, MeOH).

Example 40

5-[(R)-2-methylamino-1-propyloxy]-2-chloro-3-(4-vinylpyridinyl) pyridine p-toluenesulfonic acid 40 was synthesized according to the following procedure.

First, 5-[(R)-2-N-BOC-methylamino-1-propyloxy]-2-chloro-3-bromo pyridine 40A was prepared as follows.

A solution of the product 34A (440 mg, 1.20 mmol) in THF (15 mL) at room temperature was treated with sodium hydride (60% dispersion in mineral oil, 144 mg, 3.61 mmol) and stirred for 20 minutes. Then iodomethane (0.60 mL, 9.60 mmol) was added and stirred at room temperature overnight. The reaction was quenched by adding saturated ammonium chloride solution (6 mL). Saturated sodium carbonate (10 mL) was also added. THF and the excess iodomethane were removed under reduced pressure. The water phase was extracted 3X with CH_{2}Cl_{2}. The combined CH_{2}Cl_{2} extract was washed with brine, dried (MgSO_{4}), filtered and concentrated. The residue was flash chromatographed on silica gel with 10% ethyl acetate/hexane to provide a light
yellow oil 40A (72%, 330 mg). MS (CI/NH₃) m/e 455 (M+H)⁺, 472 (M+NH₄)⁺.

Then 5-[(R)-2-N-BOC-methylamino-1-propyloxy]-2-chloro-3-(4-vinylpyridinyl) pyridine 40B was made as follows.

A solution of the product 40A (230 mg, 0.606 mmol), 4-vinyl pyridine (0.082 mL, 0.757 mmol), palladium (II) acetate (10 mg, 0.045 mmol), tri-o-tolylphosphine (42 mg, 0.138 mmol), and triethylamine (0.30 mL, 2.18 mmol) in acetonitrile (10 mL) was refluxed at 100°C for 2 days. The reaction mixture was diluted with ethyl acetate, washed with saturated sodium carbonate, brine, dried (MgSO₄), filtered and concentrated. The residue was flash chromatographed with 30% ethyl acetate/hexane to provide 40B (34%, 84 mg); MS (CI/NH₃) m/e 404 (M+H)⁺.

Then 5-[(R)-2-methylamino-1-propyloxy]-2-chloro-3-(4-vinylpyridinyl) pyridine di-p-toluenesulfonic acid 40 was made as follows.

A solution of the product 40B (71 mg, 0.176 mmol) in ethyl acetate (1 mL) was treated with p-toluenesulfonic acid monohydrate (70 mg, 0.368 mmol) and stirred for 5 minutes. Then ethyl ether (30 mL) was added and stirred for an additional 5 minutes. The ether was decanted and the procedure was repeated. The residue was then dried under vacuum to provide 40 as a light yellow solid. mp 66-68°C; MS (Cl/NH₃) m/e 304 (M+H)⁺; ¹H NMR (D₂O, 400 MHz) δ: 1.49 (d, J=7 Hz, 3H), 2.33 (s, 6H), 2.82 (s, 3H), 3.77 (m, 1H), 4.24 (dd, J=6, 11 Hz, 1H), 4.41 (dd, J=3, 11 Hz, 1H), 7.26 (d, J=7 Hz, 4H), 7.61 (d, J=8 Hz, 4H), 7.68 (s, 1H), 7.73 (d, J=3 Hz, 2H), 7.99 (d, J=7 Hz, 2H), 8.04 (d, J=2 Hz, 1H), 8.60 (d, J=8 Hz, 2H); Analysis calculated for
C_{16}H_{18}N_{2}ClO\cdot 2.1C_{7}H_{6}O_{3}S\cdot 1.4H_{2}O: C, 53.39; H, 5.49; N, 6.08; Found: C, 53.38; H, 5.48; N, 6.01; [\alpha]^{25D}_{D}=-4.5^\circ (c=1.1, MeOH).

Example 41

5-[(R)-2-ethylamino-1-propyloxy]-2-chloro pyridine p-toluenesulfonic acid 41 was synthesized according to the following procedure.

First, 5-[(R)-2-N-BOC-ethylamino-1-propyloxy]-2-chloro pyridine 41A was made as follows.

A solution of the product 26C (298 mg, 1.04 mmol) in THF (20 mL) at room temperature was treated with sodium hydride (60% dispersion in mineral oil, 125 mg, 3.12 mmol) and stirred for 20 minutes. Iodoethane (0.67 mL, 8.32 mmol) was added and the solution was then stirred at room temperature overnight. The reaction was quenched by adding saturated ammonium chloride solution (6 mL). Saturated sodium carbonate (10 mL) was also added. THF and the excess iodoethane were removed under reduced pressure. The water phase was extracted 3X with CH_{2}Cl_{2}. The combined CH_{2}Cl_{2} extract was washed with brine, dried (MgSO_{4}), filtered and concentrated. The residue was flash chromatographed on silica gel with 10% ethyl acetate/hexane to provide a clear oil 41A (54%, 178 mg). MS (Cl/\text{NH}_{3}) m/e 315 (M+H)^{+}; 332 (M+2\text{NH}_{3})^{+};

^{1}H NMR (CDCl_{3}, 300 MHz) \delta: 1.12 (t, J=7 Hz, 3H), 1.31 (d, J=7 Hz, 3H), 1.46 (s, 9H), 3.22 (bs, 2H), 3.95 (m, 1H), 4.09 (m, 1H), 4.30 (bs, 1H), 7.18-7.26 (m, 2H), 8.04 (d, J=3 Hz, 1H).
Then 5-[(R)-2-ethylamino-1-propyloxy]-2-chloro pyridine p-toluenesulfonic acid 41 was made as follows.

A solution of the product 41A (177 mg, 0.563 mmol) in CH₂Cl₂ (8 mL) was treated with p-toluenesulfonic acid monohydrate (118 mg, 0.621 mmol) and refluxed at 60°C overnight. Solvent was removed by bubbling nitrogen into the solution. Ethyl ether (30 mL) was added and stirred for 5 minutes. The ether was decanted and the procedure was repeated. It was then dried under vacuum to provide 41 as a white hygroscopic solid. MS (ESI⁺) m/z 215 (M+H)⁺; ¹H NMR (D₂O, 400 MHz) δ: 1.33 (t, J=7 Hz, 3H), 1.45 (d, J=7 Hz, 3H), 2.36 (s, 3H), 3.18 (m, 2H), 3.75 (m, 1H), 4.16 (dd, J=7, 11 Hz, 1H), 4.32 (dd, J=3, 11 Hz, 1H), 7.32 (d, J=8 Hz, 2H), 7.39 (d, J=9 Hz, 1H), 7.45 (dd, J=3, 9 Hz, 1H), 7.66 (d, J=8, 2H), 8.03 (d, J=3 Hz, 1H); Analysis calculated for C₁₀H₁₅N₂ClO₂•1.2C₇H₈O₃S•0.3H₂O: C, 51.79; H, 5.95; N, 6.56; Found: C, 51.86; H, 6.18; N, 6.53; [α]²⁵D=−5.6° (c=1.5, MeOH).

Example 42

5-[(R)-2-(1-propyl)amino-1-propyloxy]-2-chloro pyridine p-toluenesulfonic acid 42 was prepared according to the following procedure.

First, 5-[(R)-2-N-BOC-(1-propylamino-1-propyloxy]-2-chloro pyridine 42A was made as follows.

A solution of the product 26C (290 mg, 1.01 mmol) in THF (20 mL) at room temperature was treated with sodium hydride (60% dispersion in mineral oil, 122 mg, 3.04 mmol) and stirred for 20 minutes. 1-iodopropane (0.78 mL,
8.09 mmol) was added and stirred at room temperature overnight. The reaction was quenched by adding saturated ammonium chloride solution (6 mL). Saturated sodium carbonate (10 mL) was also added. THF and the excess reagent were removed under reduced pressure. The water phase was extracted 3X with CH₂Cl₂. The combined CH₂Cl₂ extract was washed with brine, dried (MgSO₄), filtered and concentrated. The residue was flash chromatographed on silica gel with 15% ethyl acetate/hexane to provide a clear oil 42A (39%, 130 mg). MS (Cl/ND₃) m/e 329 (M+H)+.

Then 5-[(R)-2-(1-propyl)amino-1-propyloxy]-2-chloro pyridine p-toluenesulfonic acid 42 was made as follows. A solution of the product 42A (127 mg, 0.387 mmol) in CH₂Cl₂ (10 mL) was treated with p-toluenesulfonic acid monohydrate (89 mg, 0.468 mmol) and refluxed at 60°C overnight. Solvent was removed by bubbling nitrogen into the solution. Next, ethyl ether (30 mL) was added and stirred for 5 minutes. The ether was decanted and the procedure was repeated. It was then dried under vacuum to provide 42 as a white hygroscopic solid. MS (ESI+) m/e 229 (M+H)+; ¹H NMR (D₂O, 400 MHz) δ: 0.95-1.00 (m, 3H), 1.45 (d, J=7 Hz, 3H), 1.67-1.77 (m, 2H), 2.37 (s, 3H), 3.02-3.12 (m, 2H), 3.76 (m, 1H), 4.17 (dd, J=6, 11 Hz, 1H), 4.34 (dd, J=3, 11 Hz, 1H), 7.33 (d, J=8 Hz, 2H), 7.44-7.48 (m, 2H), 7.67 (d, J=9 Hz, 2H), 8.06 (m, 1H); Analysis calculated for C₁₁H₁₇N₂ClO•1.25C₇H₈O₃S•0.4H₂O: C, 52.58; H, 6.21; N, 6.21; Found: C, 52.63; H, 6.30; N, 6.03; [α]²⁵D=+3.1° (c=0.16, MeOH).
Example 43

5-(3-Amino-1-butyloxy)-2-fluoro pyridine p-toluenesulfonic acid 43 was synthesized according to the following procedure.

3-(N-(BOC)amino)butyric acid 43A was made as follows. A solution of 3-aminobutyric acid (2.0 g, 19.4 mmol) in CH₂Cl₂ (40 mL) at room temperature was treated with triethylamine (13.4 mL, 97 mmol) and di-tert-butyl dicarbonate (4.44 g, 20.4 mmol), stirred overnight. THF (40 mL) was introduced and refluxed for 2 hours. The reaction mixture was then evaporated to provide the crude product 43A (110%, 4.35 g). MS (Cl/NH₃) m/e 204 (M+H)⁺.

Next, 3-(N-BOC)-butanol 43B was made as follows.

A solution of the product from 43A (4.30 g, 21.0 mmol) in anhydrous THF (15 mL) at 0°C was treated with borane (1M solution in THF, 32 mL) over a period of 45 minutes. The ice bath was then removed and the reaction mixture was stirred at room temperature for 3 hours. Saturated NaHCO₃ solution was added slowly to quench the reaction. The resultant solution was then stirred overnight. Solvent was removed under reduced pressure. The remaining water phase was extracted 4X with ethyl ether. The combined ether extract was washed with brine, dried (MgSO₄), filtered, and concentrated. The residue was flash chromatographed on silica gel with 95/5 CH₂Cl₂/CH₃OH to provide a yellow oil 43B (25%, 980 mg). MS (Cl/NH₃) m/e 190 (M+H)⁺, 207 (M+NH₄)⁺; ¹H NMR (CDCl₃, 300 MHz) δ: 1.19 (d, J=6 Hz, 3H), 1.45 (s, 9H), 1.74-1.87 (m, 2H), 3.34 (bs, 1H), 3.62 (bs, 1H), 3.90 (bs, 1H), 4.41 (bs, 1H).
3-((N-(BOC)amino)butyl 4-methylbenzene sulfonate 43C was next made as follows.

A solution of the product 43B (970 mg, 5.13 mmol) in THF (10 mL) at room temperature was treated with sodium anhydride (246 mg, 6.16 mmol) and p-toluenesulfonyl chloride (1.08 g, 5.65 mmol), stirred overnight. The reaction mixture was diluted with CH₂Cl₂ to 50 mL, washed with water, 5% NaHCO₃, and brine. It was then dried (MgSO₄), filtered and concentrated. The residue was flash chromatographed on silica gel with 20% ethyl acetate/hexane to provide a white solid 43C (65%, 1.14 g). MS (Cl/NH₃) m/e 344 (M+NH₃)⁺;

¹H NMR (CDCl₃, 300 MHz) δ: 1.12 (d, J=7 Hz, 3H), 1.41 (s, 9H), 1.75-1.86 (m, 2H), 2.45 (s, 3H), 3.68 (m, 1H), 4.08 (t, J=7 Hz, 2H), 4.32 (bs, 1H), 7.35 (d, J=8 Hz, 2H), 7.80 (d, J=10 Hz, 2H).

5-((3-((N-(BOC)amino)-1-butyloxy)-2-fluoro pyridine 43D was then made as follows.

A solution of the product 43C (990 mg, 2.89 mmol) in DMF (20 mL) was treated with potassium hydroxide (405 mg, 7.23 mmol) and 2-fluoro-5-hydroxyl pyridine (359 mg, 3.17 mmol), and then stirred at 85°C overnight. DMF was removed under reduced pressure at 60°C. The residue was dissolved in a mixture of H₂O and CH₂Cl₂. The organic layer was washed with water, and brine. It was then dried (MgSO₄), filtered and concentrated. The residue was flash chromatographed on silica gel with 20% ethyl acetate/hexane to provide a light yellow solid 43D (34%, 280 mg). MS (Cl/NH₃) m/e 285 (M+H)⁺, 302 (M+NH₃)⁺; ¹H NMR (CDCl₃, 300 MHz) δ: 1.22 (d, J=7 Hz, 3H), 98
1.42 (s, 9H), 1.86-2.00 (m, 2H), 3.91 (m, 1H), 4.02-4.09 (m, 2H), 4.57 (bs, 1H), 6.85 (dd, J=3, 9 Hz, 1H), 7.32 (m, 1H), 7.82 (dd, J=2, 3 Hz, 1H).

Then 5-(3-N-BOC-amino-1-butyloxy]-2-fluoro pyridine 43E was made as follows.

A solution of the product from Example 43D (270 mg, 0.951 mmol) in CH₂Cl₂ (5 mL) was treated with trifluoroacetic acid (2 mL) and stirred at room temperature overnight. Solvent and excess reagent were removed under reduced pressure. The residue was dissolved in saturated sodium carbonate solution and extracted 3X with CH₂Cl₂. The combined CH₂Cl₂ extract was dried (MgSO₄), filtered and concentrated to provide a light yellow oil 43E (58%, 102mg). MS (Cl/ NH₃) m/e 185 (M+H)⁺.

Then 5-(3-amino-1-butyloxy)-2-fluoro pyridine p-toluenesulfonic acid 43 was made as follows.

A solution of the product 43E (34 mg, 0.185 mmol) in ethyl acetate (1 mL) was treated with p-toluenesulfonic acid monohydrate (37 mg, 0.195 mmol) and stirred for 5 minutes. Next ethyl ether (30 ml) was added and stirred for an additional 5 minutes. The ether was decanted and the procedure was repeated. The residue was then dried under vacuum to provide 43 as a white solid. mp 142-144°C; MS (Cl/ NH₃) m/e 185 (M+H)⁺; ¹H NMR (D₂O, 300 MHz) δ: 1.39 (d, J=7 Hz, 3H), 2.08-2.25 (m, 2H), 2.41 (s, 3H), 3.68 (dd, J=7, 13 Hz, 1H), 4.20-4.30 (m, 2H), 4.14 (dd, J=4, 11 Hz, 1H), 7.08 (dd, J=3, 9 Hz, 1H), 7.38 (d, J=8 Hz, 2H), 7.61 (m, 1H), 7.70 (d, J=8 Hz, 2H), 7.87 (dd, J=1,
3 Hz, 1H). Analysis calculated for C₈H₁₃N₂F₀•C₇H₅O₃S: C, 53.92; H, 5.94; N, 7.86; Found: C, 53.81; H, 5.89; N, 7.72.

Example 44

5-(3-Amino-1-butyloxy)-2-chloropyridine p-toluenesulfonate 44 was synthesized according to the following procedure.

First, 5-(3-N-(BOC)-1-butyloxy)-2-chloropyridine 44A was synthesized as follows. A solution of the product 43C (320 mg, 0.93 mmol) in DMF (3 mL) was treated with potassium hydroxide (92 mg, 1.83 mmol) and 2-chloro-5-hydroxyl pyridine (130 mg, 1.03 mmol), and then stirred at 60°C for 48 hours. DMF was removed under reduced pressure at 60°C. The residue was dissolved in a mixture of H₂O and CH₂Cl₂. The organic layer was washed with water, and brine; then dried (MgSO₄), filtered and concentrated. The residue was flash chromatographed on silica gel with 50% ethyl acetate/hexane to provide a light yellow solid 44A (43%, 120 mg). MS (Cl/NH₃) m/e 301 (M+H)⁺, 303 (M+NH₄)⁺; ¹H NMR (CDCl₃, 300 MHz) δ: 1.22 (d, J=7 Hz, 3H), 1.42 (s, 9H), 1.86-2.02 (m, 2H), 3.92 (m, 1H), 4.02-4.12 (m, 2H), 4.45 (bs, 1H), 7.19 (d, J=5.6 Hz, 1H), 7.22 (d, J=3 Hz, 1H), 8.04 (d, J= 3 Hz, 1H).

5-(Amino-1-butyloxy)-2-fluoro pyridine p-toluenesulfonic acid 44 was prepared next as follows.

A solution of the product 44A (69 mg, 0.26 mmol) in CH₂Cl₂ (2 mL) was treated with p-toluenesulfonic acid (31mg, 0.28 mmol) and stirred at reflux for 4 hours. Next, solvent was removed under reduced pressure. Ethyl ether
(30 ml) was added and stirred for an additional 5 minutes. The ether was
decanted and the procedure was repeated. The residue was then dried under
vacuum to provide 44 as a white solid. mp 190-191°C; MS (Cl/ NH₃) m/e 201
(M+H)⁺; 218 (M+NH₄)⁺. ¹H NMR (D₂O, 300 MHz) δ: 1.38 (d, J=7 Hz, 3H),
2.05-2.25 (m, 2H), 2.40 (s, 3H), 3.68 (dd, J=7, 13 Hz, 1H), 4.22-4.32 (m, 2H),
7.37 (d, J=8.5 Hz, 2H), 7.4-7.6 (m, 2H), 7.69 (d, J=8 Hz, 2H), 8.06 (d, J=3 Hz,
1H). Analysis calculated for C₉H₁₄N₂ClO·1.1 C₇H₆O₃S: C, 51.42; H, 5.81; N,
7.11; Found: C, 51.06; H, 5.81; N, 7.11.

Example 45

5-(3-Dimethylamino-1-butyloxy]-2-chloro pyridine p-toluenesulfonic
acid 45 was synthesized according to the following procedure.

First, 5-(3-dimethylamino-1-butyloxy]-2-chloro pyridine 45A was made
as follows.

A solution of the product 44A (120 mg, 0.44 mmol) in formic acid (2.5
mL) was treated with 37% formalin solution (5 mL) and the resultant mixture
was heated at 60 °C for 5 hours. Solvent and excess reagent were removed
under reduced pressure. The residue was dissolved in saturated sodium
carbonate solution and extracted 3X with CH₂Cl₂. The combined CH₂Cl₂ extract
was dried (MgSO₄), filtered and concentrated to provide a light yellow oil 45A
(58%, 102 mg). MS (Cl/ NH₃) m/e 229 (M+H)⁺, m/e 231 (M+NH₄)⁺; ¹H NMR
(CDCℓ₃, 300 MHz) δ: 1.05 (d, J=6 Hz, 3H), 1.45-1.85 (m, 4H), 2.03 (m, 1H),
2.29 (s, 6H), 4.00-4.15 (m, 2H), 7.17-7.24 (m, 2H), 8.05 (d, J=1 Hz, 1H).
Next, 5-(3-dimethylamino-1-butoxy)-2-chloro pyridine p-toluenesulfonic acid 45 was made as follows.

A solution of the product 45A (67 mg, 0.29 mmol) in ethyl acetate (1 mL) was treated with p-toluenesulfonic acid monohydrate (32 mg, 0.30 mmol) and stirred for 5 minutes. Next, ethyl ether (30 ml) was added and stirred for an additional 5 minutes. The ether was decanted and the procedure was repeated. The residue was then dried under vacuum to provide 45 as a white solid. mp 100-102°C; MS (Cl/ NH₃) m/e 229(M+H)⁺. ¹H NMR (D₂O, 300 MHz) δ: 1.39 (d, J=7 Hz, 3H), 2.08 (m, 1H), 2.34 (m, 1H), 2.41 (s, 3H), 2.8 (s, 6H), 3.70 (m, 1H), 4.15-4.32 (m, 2H), 7.38 (d, J=8 Hz, 2H), 7.42-7.51 (m, 2H), 7.69 (d, J=8 Hz, 2H), 8.06 (d, J=3 Hz, 1H). Analysis calculated for C₁₁H₁₇N₂ClO•1C₂H₄O₃S: C, 53.93; H, 6.24; N, 6.99; Found: C, 53.67; H, 6.24; N, 7.02.

**Example 46**

5-(3-Dimethylamino-1-butoxy)-2-chloro-3-bromopyridine p-toluenesulfonic acid 46 was synthesized according to the following procedure.

First, 5-(3-N-BOC-amino-1-butoxy)-2-chloro-3-bromo pyridine 46A was made as follows. A solution of the product 43C (1.0 g, 2.9 mmol) in THF (4 mL) was treated with potassium hydroxide (290 mg, 5.8 mmol) and 2-chloro-3-bromo-5-hydroxyl pyridine (667 mg, 3.19 mmol), stirred at 70°C for 16 hours. THF was removed under reduced pressure at 25°C. The residue was dissolved in a mixture of H₂O and CH₂Cl₂. The organic layer was washed with water, and brine; then dried (MgSO₄), filtered and concentrated. The residue
was flash chromatographed on silica gel with 33 % ethyl acetate/hexane to provide a light yellow solid 46A (37 %, 412 mg). MS (Cl/\textsubscript{NH}_3) m/e 381 (M+H)+, 398 (M+\textsubscript{NH}_4)+; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz) δ: 1.22 (d, J=7 Hz, 3H), 1.42 (s, 9H), 1.86-2.02 (m, 2H), 3.92 (m, 1H), 4.02-4.12 (m, 2H), 4.45 (bs, 1H), 7.22 (d, J=2 Hz, 1H), 8.03 (s, 1H).

Then 5-(dimethylamino-1-butyloxy]-2-chloro-3-bromo pyridine p-toluenesulfonic acid 46B was made as follows.

A solution of the product from Example 46A (84 mg, 0.22 mmol) in formic acid (2.5 mL) was treated with 37% formalin solution (5 mL) and the resultant mixture was heated at 60 °C for 5 hours. Solvent and excess reagent were removed under reduced pressure. The residue was dissolved in saturated sodium carbonate solution and extracted 3X with CH\textsubscript{2}Cl\textsubscript{2}. The combined CH\textsubscript{2}Cl\textsubscript{2} extract was dried (MgSO\textsubscript{4}), filtered and concentrated to provide a light yellow oil as the title compound. The residue was then purified on the column. Elution with ethyl acetate/methanol/ammonium hydroxide (10:1:0.1) gave the desired product 46B.(62%, 42mg). MS (Cl/\textsubscript{NH}_3) m/e 309 (M+H)+, m/e 311 (M+\textsubscript{NH}_4)+; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz) δ: 1.03 (d, J=6 Hz, 3H), 1.75 (m, 1H), 2.03 (m, 1H), 2.85 (bs, 1H), 2.28 (s, 6H), 4.00-4.16 (m, 2H), 7.53 (d, J=3 Hz, 1H), 8.04 (d, J= 3 Hz, 1H).

5-(3-Dimethylamino-1-butyloxy]-2-chloro-3-bromopyridine p-toluenesulfonic acid 46 was then prepared as follows.

A solution of the product from Example 46B (42 mg, 0.14 mmol) in ethyl acetate (1 mL) was treated with p-toluenesulfonic acid monohydrate (26
mg, 0.15 mmol) and stirred for 5 minutes. Next, ethyl ether (30 ml) was added and stirred for an additional 5 minutes. The ether was decanted and the procedure was repeated. The residue was then dried under vacuum to provide 46 as a white solid. mp 95-97 °C; MS (Cl/ NH₃) m/e 307 (M+H)⁺. ¹H NMR (D₂O, 300 MHz) δ: 1.39 (d, J=7 Hz, 3H), 2.08 (m, 1H), 2.34 (m, 1H), 2.41 (s, 3H), 2.87 (s, 3H), 3.70 (m, 1H), 4.15-4.32 (m, 2H), 7.37 (d, J=8 Hz, 2H), 7.69 (d, J=8 Hz, 2H), 7.84 (d, J=3 Hz, 1H), 8.07 (d, J=3 Hz, 1H). Analysis calculated for C₁₃H₁₆N₂B₃ClO• C₇H₈O₃S: C, 45.02; H, 5.00; N, 5.84; Found: C, 44.88; H, 5.15; N, 5.61.

Example 47

5-(3-Amino-1-butyloxy)-2-chloro-3-bromo-pyridine p-toluenesulfonic acid 47 was synthesized according to the following procedure.

First, a solution of the product 46A (90 mg, 0.24 mmol) in CH₂Cl₂ (2 mL) was treated with trifluoroacetic acid (2 mL) and stirred at room temperature overnight. Solvent and excess reagent were removed under reduced pressure. The residue was dissolved in saturated sodium carbonate solution and extracted 3X with CH₂Cl₂. The combined CH₂Cl₂ extract was dried (MgSO₄), filtered and concentrated to provide a light yellow oil 5-(3-amino-1-butyloxy)-2-chloro-3-bromopyridine 47A. The residue was then purified on the column. Elution with ethyl acetate/methanol/ammonium hydroxide (10:1:0.1) gave the desired product (58%, 39 mg). MS (Cl/ NH₃) m/e 279 (M+H)⁺; ¹H
NMR (CDCl₃, 300 MHz) δ: 1.19 (d, J=6 Hz, 3H), 1.60-2.00 (m, 3H), 3.20 (m, 1H), 4.05-4.20 (m, 2H), 7.53 (d, J=3 Hz, 1H), 8.04 (d, J= 3 Hz, 1H).

Next, 5-(3-amino-1-butyloxy)-2-chloro-3-bromo-pyridine p-toluenesulfonic acid 47 was made as follows.

A solution of the product 47A (39 mg, 0.185 mmol) in ethyl acetate (1 mL) was treated with p-toluenesulfonic acid monohydrate (37 mg, 0.14 mmol) and stirred for 5 minutes. Ethyl ether (30 ml) was added and stirred for an additional 5 minutes. The ether was decanted and the procedure was repeated. The residue was then dried under vacuum to provide 47 as a white solid. mp 140-142 °C; MS (CI/ NH₃) m/e 279 (M+H)⁺; 311 (M+NH₄)⁺ ¹H NMR (D₂O, 300 MHz) δ: 1.38 (d, J=7 Hz, 3H), 2.08-2.25 (m, 2H), 2.41 (s, 3H), 3.65 (dd, J=7, 13 Hz, 1H), 4.20-4.32 (m, 2H), 7.38 (d, J=8 Hz, 2H), 7.69 (d, J=8 Hz, 2H), 7.87 (d, J=3 Hz, 1H), 8.09 (d, J=0 Hz, 1H). Analysis calculated for C₉H₁₂N₂BrClO • C₇H₈O₃S: C, 42.50; H, 4.43; N, 6.20; Found: C, 42.58; H, 4.60; N, 5.94.

Example 48

5-(3-dimethylamino-1-butyloxy]-2-chloro-methylpyridine p-toluenesulfonic acid 48 was synthesized according to the following procedure.

First, 5-(3-(N-(BOC) amino-1-butyloxy)-2-chloro-3-methylpyridine 48A was synthesized as follows. A solution of the product 43C (0.85 g, 2.48 mmol) in THF (6 mL) was treated with potassium hydroxide (373 mg, 7.4 mmol) and 2-chloro-3-methyl-5-hydroxyl pyridine (395 mg, 2.73 mmol), and then stirred at
80°C for 16 hours. THF was removed under reduced pressure at 25°C. The residue was dissolved in a mixture of H₂O and CH₂Cl₂. The organic layer was washed with water, and brine; then dried (MgSO₄), filtered and concentrated. The residue was flash chromatographed on silica gel with 33% ethyl acetate/hexane to provide a light yellow solid 48A (39%, 270 mg). MS (Cl/NH₃) m/e 315 (M+H)⁺, 317 (M+NH₄)⁺; ¹H NMR (CDCl₃, 300 MHz) δ:
1.21 (d, J=7 Hz, 3H), 1.42 (s, 9H), 1.86-2.02 (m, 2H), 2.34 (s, 3H), 3.92 (m, 1H), 4.02-4.12 (m, 2H), 4.45 (bs, 1H), 7.12 (bs, 1H), 7.89 (s, 1H).

Next, 5-(3-dimethylamino-1-butoxy)-2-chloro-3-methyl pyridine 48B was made as follows.

A solution of the product 48A (57 mg, 0.18 mmol) in formic acid (1 mL) was treated with 37% formalin solution (2.5 mL) and the resultant mixture was heated at 70°C for 5 hours. Solvent and excess reagent were removed under reduced pressure. The residue was dissolved in saturated sodium carbonate solution and extracted 3X with CH₂Cl₂. The combined CH₂Cl₂ extract was dried (MgSO₄), filtered and concentrated to provide a light yellow oil as the title compound. The residue was then purified on the column. Elution with ethyl acetate/methanol/ammonium hydroxide (10:1:0.1) gave 48B (100%, 63 mg). MS (Cl/NH₃) m/e 243 (M+H)⁺; ¹H NMR (CDCl₃, 300 MHz) δ: 1.09 (d, J=6 Hz, 3H), 1.78 (m, 1H), 2.03 (m, 1H), 2.35 (s, 6H), 2.93 (bs, 1H), 4.00-4.15 (m, 2H), 7.12 (d, J=3 Hz, 1H), 7.90 (d, J=3 Hz, 1H).

Then, 5-(3-dimethylamino-1-butoxy)-2-chloro-methylpyridine p-toluenesulfonic acid 48 was made as follows.
A solution of the product 45A (63 mg, 0.26 mmol) in ethyl acetate (1 mL) was treated with p-toluenesulfonic acid monohydrate (49 mg, 0.27 mmol) and stirred for 5 minutes. Then ethyl ether (30 ml) was added and stirred for an additional 5 minutes. The ether was decanted and the procedure was repeated. The residue was then dried under vacuum to provide 48 as a white solid. MS (Cl/ NH₃) m/e 243(M+H)⁺. ¹H NMR (D₂O, 300 MHz) δ: 1.39 (d, J=7 Hz, 3H), 2.09 (m, 1H), 2.33 (m, 1H), 2.37 (s, 3H), 2.38 (s, 3H), 2.87 (s, 6H), 3.70 (m, 1H), 4.15–4.27 (m, 2H), 7.35 (d, J=8 Hz, 2H), 7.37 (d, J=4 Hz, 1H) 7.68 (d, J=8 Hz, 2H), 7.87 (d, J=3 Hz, 1H). Analysis calculated for C₁₂H₁₉N₂ClO•1.3
C₇H₆O₃S·H₂O: C, 52.30; H, 6.53; N, 5.78; Found: C, 52.00; H, 6.33; N, 6.10

Example 49

5-(3-Amino-1-butyloxy)-2-chloro-3-methyl-pyridine p-toluenesulfonic acid 49 was synthesized according to the following procedure.

A solution of the product 48A (99 mg, 0.36 mmol) in methylene chloride (5 mL) was treated with p-toluenesulfonic acid monohydrate (74 mg, 0.39 mmol) and stirred at reflux for 5 hours. After ethanol was reduced to a smaller volume, ethyl ether (30 ml) was added and stirred for an additional 5 minutes. The ether was decanted and the procedure was repeated. The residue was then dried under vacuum to provide 49 as a white solid. mp 163-165 °C; MS (Cl/ NH₃) m/e 215(M+H)⁺, 232(M+NH₄)⁺ ¹H NMR (D₂O, 300 MHz) δ: 1.37 (d, J=7 Hz, 3H), 2.02–2.22 (m, 2H), 2.33 (s, 3H), 2.38 (s, 3H), 3.64 (m, 1H), 4.15–4.30 (m, 2H), 7.35 (d, J=8 Hz, 2H), 7.40 (d, J=3Hz, 1H), 7.68(d, J=8
Hz, 1H), 7.87 (d, J=3 Hz, 1H). Analysis calculated for C₁₀H₁₄N₂ClO•1.3
C₂H₂O₂S•0.5 H₂O: C, 51.26; H, 5.95; N, 6.26; Found: C, 51.35; H, 5.85; N,
6.28.

Example 50

_in vitro_

Compounds of the invention were subjected to _in vitro_ assays against
the nicotinic acetylcholine receptor as described below and were found to be
effective binders to the receptor. The _in vitro_ protocols for determination of
nicotinic acetylcholine channel receptor binding potencies of ligands was
determined as follows.

Binding of [³H]-cytisine ([³H]-CYT) to neuronal nicotinic acetylcholine
receptors was accomplished using crude synaptic membrane preparations from
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 MgCl₂, 2 mM CaCl₂ 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.

The test compounds were dissolved in water to make 10 mM stock
solutions. Each solution was then diluted (1:100) with buffer (as above) and
further taken through seven serial log dilutions to produce test solutions from 10^{-5} to 10^{-11} M.

Homogenate (containing 125-150 μg protein) was added to triplicate tubes containing the range of concentrations of test compound described above and [³H]-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. IC₅₀ values were determined with a four-parameter non-linear regression and IC₅₀ values were converted to Kᵢ values using the Cheng and Prusoff correction (Kᵢ=IC₅₀/(1+[^{1}][ligand])/Kᵢ of ligand).

The results are detailed in Tables 1 and 2. Each Example number corresponds to the synthetic Examples described above. Examples 1-49 in these tables are the compounds of the present invention. The lower the Kᵢ value, the more affinity for neuronal nicotinic acetylcholine receptors.

**in vivo**

An in vivo protocol was utilized to determine the effectiveness of nicotinic acetylcholine receptor ligands as analgesic agents in the mouse hot plate paradigm.

Separate groups of mice, (n=8/group) were utilized for each dose group. All drugs were administered by the intraperitoneal route of administration. Test
drugs were dissolved in water to make a 6.2 mM stock solution. Animals were
dosed with this solution (10 mL/kg body weight) for a 62 micromol/kg dose.
Lower doses were administered similarly, following serial dilution of the stock
solution in half-log increments. Animals were dosed 30 minutes prior to testing
in the hot plate. The hot-plate utilized was an automated analgesia monitor
(Model #AHP16AN, Omnitech Electronics, Inc. of Columbus, Ohio). The
temperature of the hot plate was maintained at 55°C and a cut-off time of 180
seconds was utilized. A control was run against each compound tested.
Latency until the tenth jump was recorded as the dependent measure. An
increase in the tenth jump latency relative to the control was considered a
significant effect.

Tables 1 and 2 below illustrates the results obtained by following the
above procedures.

Table 1 also shows the minimally effective dose (MED), among the
doses tested, at which a significant effect, as defined above, was observed for
the present compounds in the column labelled dosage. The lower the dosage at
which the significant effect is observed, the more effective the compound. The
data shows that selected compounds of the invention show a significant
antinociceptive effect at doses ranging from 6.2 to 62 µmol/kg.
Table 1

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<td>Analgesia MED (μmol/kg)</td>
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* no effect at 62; ** no effect at 6.2

N/T = not tested

Table 2

All references cited are hereby incorporated by reference.

The present invention is illustrated by way of the foregoing description and examples. The foregoing description is intended as a non-limiting illustration, since many variations will become apparent to those skilled in the
art in view thereof. It is intended that all such variations within the scope and spirit of the appended claims be embraced thereby.

Changes can be made in the composition, operation and arrangement of the method of the present invention described herein without departing from the concept and scope of the invention as defined in the following claims:
Claims

We claim:

1. A compound of the structure

wherein n is an integer of 1 to 4;

R¹ and R³ are independently selected from the group consisting of
hydrogen, lower alkyl, alkenyl, alkynyl, aralkyl and cyanomethyl;

R³, at each occurrence, is selected from the group consisting of
hydrogen, haloalkyl and lower alkyl;

R⁴, at each occurrence, is independently selected from the
group consisting of hydrogen, hydroxyl, lower alkyl, lower
alkenyl, lower alkynyl, lower alkoxy, alkenoxy, alkynoxy,
thioalkoxy, aliphatic acyl, -CF₃, nitro, cyano, -N(C₁-C₃
alkyl)-C(O)(C₁-C₃ alkyl), -C₁-C₃ alkylamino, alkenylamino,
alkynylamino, di(C₁-C₃ alkyl)amino, amino, halogen,
-C(O)O-(C₁-C₃ alkyl), -C(O)NH-(C₁-C₃ alkyl),
-C(O)N(C_1-C_3 alkyl)$_2$, haloalkyl, alkoxy carbonyl, alkoxyalkoxy, carboxaldehyde, carboxamide, cycloalkyl, cycloalkenyl, aliphatic acyl, -CH=NOH, -PO$_2$H$_2$, -OPO$_2$H$_2$, heterocyclylalkyl, cycloalkynyl, aryl, aroyl, aryloxy, arylamino, biaryl, thioaryl, heterocyclyl, heterocyclyl, alkylaryl, aralkyl, aralkenyl, alkylheterocyclyl, sulfonyl, sulfonamido, carbamate, aryloxyalkyl, carboxyl and -C(O)NH(phenyl);

$R^5$ is selected from the group consisting of hydrogen, halogen, lower alkyl, nitro, lower alkylamino and lower alkoxy;

$R^6$ is selected from the group consisting of hydrogen, halogen, hydroxyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, alkenoxy, alkynoxy, thioalkoxy, aliphatic acyl, -CF$_3$, nitro, amino, cyano, -N(C$_1$-C$_3$ alkyl)-C(O)(C$_1$-C$_3$ alkyl), -C$_1$-C$_3$

alkylamino, alkenylamino, alkynylamino, di(C$_1$-C$_3$ alkyl)amino, -C(O)O-(C$_1$-C$_3$ alkyl), -C(O)NH-(C$_1$-C$_3$ alkyl), -CH=NOH, -C(O)N(C$_1$-C$_3$ alkyl)$_2$, haloalkyl, alkoxy carbonyl, alkoxyalkoxy, carboxaldehyde, carboxamide, cycloalkyl, cycloalkenyl, aliphatic acyl, -CH=NOH, -PO$_2$H$_2$, -OPO$_2$H$_2$, heterocyclylalkyl, cycloalkynyl, aryl, aroyl, aryloxy, arylamino, biaryl, thioaryl, heterocyclyl, heterocyclyl, alkylaryl, aralkenyl, aralkyl, alkylheterocyclyl, sulfonyl, sulfonamido, carbamate, aryloxyalkyl, carboxyl and -C(O)NH(phenyl); and
A is selected from the group consisting of -O-, -S-, -N(R\(^1\))-, -SO\(_2\)N(R\(^1\))- and -NR\(^1\)SO\(_2\)-; wherein R\(^1\), R\(^2\), R\(^3\), R\(^4\), R\(^5\) and R\(^6\) are unsubstituted or substituted with at least one electron donating or electron withdrawing group; and pharmaceutically acceptable salts thereof;

with the proviso that when A = O at least one of R\(^5\) or R\(^6\) is halogen;

and with the further proviso that when R\(^3\) and R\(^4\) are attached to a carbon which is alpha to a heteroatom, R\(^4\) is not halogen,

2. A compound of claim 1 further comprising derivatives of said compound selected from the group consisting of esters, carbamates, aminals, amides and pro-drugs thereof.

3. A compound of claim 1 of the structure
wherein n is an integer of 1 to 4;

R^1 and R^2 are independently selected from the group consisting of

hydrogen, lower alkyl, alkenyl, alkynyl, aralkyl and cyanomethyl;

R^3, at each occurrence, is selected from the group consisting of

hydrogen, haloalkyl and lower alkyl;

R^4, at each occurrence, is independently selected from the

group consisting of hydrogen, hydroxyl, lower alkyl, lower

alkenyl, lower alkynyl, lower alkoxy, alkenoxy, alkynoxy,

thioalkoxy, aliphatic acyl, -CF_3, nitro, cyano, -N(C_1-C_3

alkyl)-C(O)(C_1-C_3 alkyl), -C_1-C_3 alkylamino, alkenylamino,

alkynylamino, di(C_1-C_3 alkyl)amino, amino, halogen,

-C(OO)-(C_1-C_3 alkyl), -C(O)NH-(C_1-C_3 alkyl), aliphatic acyl,

-CH=NOH, -PO_2H_2, -OPO_3H_2, heterocyclalkyl,

-C(O)N(C_1-C_3 alkyl), haloalkyl, alkoxy carbonyl, alkoxyalkoxy,

carboxaldehyde, carboxamide, cycloalkyl, cycloalkenyl,

cycloalkynyl, aryl, aroyl, arylxy, arylamino, biaryl, thioaryl,

heterocyclyl, heterocycloyl, alkylaryl, aralkyl, aralkenyl,

alkylheterocyclyl, sulfonyl, sulfonamido, carbamate, arlyoxyalkyl,

carboxyl and -C(O)NH(benzyl);

R^2 is selected from the group consisting of hydrogen, halogen, lower

alkyl, nitro, lower alkylamino and lower alkoxy; and

R^5 is selected from the group consisting of hydrogen, halogen, hydroxyl,

lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy,
alken ox y, alkyn ox y, thioalk ox y, aliphatic acyl, -CF₃, nitro,
amino, cyano, -N(C₁₋C₃ alkyl)-C(O)(C₁₋C₃ alkyl), -C₁₋C₃
alkylamino, alkenylamino, alkynylamino, di(C₁₋C₃ alkyl)amino,
-C(O)O-(C₁₋C₃ alkyl), -C(O)NH-(C₁₋C₃ alkyl), -CH=NOH,
-C(O)N(C₁₋C₃ alkyl)₂, haloalkyl, alkoxy carbonyl, alkoxyalkoxy,
carboxaldehyde, carboxamide, cycloalkyl, cycloalkenyl,
aliphatic acyl, -CH=NOH, -PO₂H₂, -OPO₂H₂, heterocyclylalkyl,
cycloalkynyl, aryl, aroyl, aryloxy, arylamino, biaryl, thioaryl,
heterocyclyl, heterocycloyl, alkylaryl, aralkyl, aralkenyl,
alkylheterocyclyl, sulfonyl, sulfonamido, carbamate, aryloxyalkyl,
carboxyl and -C(O)NH(benzyl);

wherein R¹, R², R³, R⁴, R⁵ and R⁶ are unsubstituted or substituted with
at least one electron donating or electron withdrawing group;
and pharmaceutically acceptable salts thereof;

with the proviso that when R³ and R⁴ are attached to a carbon
which is alpha to a heteroatom, R⁴ is not halogen,
hydroxy or amino,
and with further proviso that at least one of R⁵ or R⁶ is halogen.

A compound of claim 3 further comprising derivatives of said
compound selected from the group consisting of esters, carbamates, aminals,
amides and pro-drugs thereof
5. A compound of claim 3 wherein \( n = 2 \), \( R^5 \) is halogen and \( R^6 \) is selected from the group consisting of hydrogen, lower alkyl and halogen.

6. A compound of claim 1 of the structure

\[
\begin{align*}
\text{\( R^1 \)} & \quad \text{\( R^3 \)} \\
\text{\( R^2 \)} & \quad \text{\( \text{O} \)} \\
\text{\( \text{N} \)} & \quad \text{\( \text{O} \)} \\
\text{\( \text{N} \)} & \quad \text{\( R^5 \)} \\
\text{\( \text{R}^{\text{6}} \)} & \quad \text{\( \text{N} \)} \\
\end{align*}
\]

wherein \( n \) is an integer of 1 to 4;
\( R^1 \) and \( R^2 \) are independently selected from the group consisting of hydrogen and lower alkyl;
\( R^3 \) is selected from the group consisting of hydrogen, haloalkyl and lower alkyl;
\( R^5 \) is selected from the group consisting of hydrogen, halogen, lower alkyl, nitro, lower alkylamino and lower alkoxy; and
\( R^6 \) is selected from the group consisting of hydrogen, halogen, hydroxyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, alkenoxy, alkynoxy, thioalkoxy, aliphatic acyl, \(-\text{CF}_3\), nitro, amino, cyano, \(-\text{N}(\text{C}_1-\text{C}_3 \text{ alkyl})\)-\( \text{CO}(\text{C}_1-\text{C}_3 \text{ alkyl}) \), \(-\text{C}_1-\text{C}_3\) alkylamino, alkenylamino, alkynylamino, di(\text{C}_1-\text{C}_3 \text{ alkyl})amino, \(-\text{C(O)O}(\text{C}_1-\text{C}_3 \text{ alkyl})\), \(-\text{CH}=\text{NOH}\), \(-\text{C(O)NH}(\text{C}_1-\text{C}_3 \text{ alkyl})\),
-C(O)N(C\textsubscript{1}-C\textsubscript{3} alkyl)\textsubscript{2}, haloalkyl, alkoxy carbonyl, alkoxyalkoxy, carboxaldehyde, carboxamide, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, aroyl, aryl oxo, arylamino, biaryl, thioaryl, heterocyclyl, heterocyclyl alkyl, aralkyl, aralkenyl, alkylheterocyclyl, sulfonyl, sulfonamido, carbamate, aliphatic acyl, -CH=NOH, -PO\textsubscript{2}H\textsubscript{2}, -OPO\textsubscript{2}H\textsubscript{2}, heterocyclic alkyl, aryloxyalkyl, carboxyl and -C(O)NH(benzyl);

wherein R\textsubscript{1}, R\textsubscript{2}, R\textsubscript{3}, R\textsubscript{5} and R\textsubscript{6} are unsubstituted or substituted with at least one electron donating or electron withdrawing group;

and pharmaceutically acceptable salts thereof;

with the proviso that at least one of R\textsubscript{5} or R\textsubscript{6} is halogen.

7. A compound of claim 6 further comprising derivatives of said compound selected from the group consisting of esters, carbamates, aminals, amides and pro-drugs thereof.

8. The compound of claim 6 wherein R\textsubscript{5} and R\textsubscript{6} are each independently selected from the group consisting of lower alkyl, -F, -Cl and -Br; n is 1 and R\textsubscript{3} is selected from the group consisting of haloalkyl and lower alkyl.

9. The compound of claim 6 wherein R\textsubscript{5} and R\textsubscript{6} are each independently selected from the group consisting of lower alkyl, -F, -Cl and
-Br; n is 2 and R¹ is selected from the group consisting of haloalkyl and lower alkyl.

10. The compound according to claim 3 selected from the group consisting of 5-[(S)-2-amino-1-propyloxy]-2-chloro pyridine, 5-[(S)-2-methylamino-1-propyloxy]-2-chloro pyridine, 5-[(S)-2-amino-1-propyloxy]-2-fluoro pyridine, 5-[(S)-2-methylamino-1-propyloxy]-2-fluoro pyridine, 5-[(S)-2-methylamino-1-propyloxy]-2-chloro-3-bromo pyridine, 5-[(S)-2-methylamino-1-propyloxy]-2-chloro-3-methyl pyridine and pharmaceutically acceptable salts thereof.

11. A compound of claim 10 further comprising derivatives of said compound selected from the group consisting of esters, carbamates, aminals, amides and pro-drugs thereof.

12. A method for controlling neurotransmitter release in a mammal comprising administering to said mammal a therapeutically effective amount of a compound of claim 1.

13. A pharmaceutical composition comprising:

a compound of claim 1 and pharmaceutically acceptable salts thereof;

in a pharmaceutically acceptable carrier.
### INTERNATIONAL SEARCH REPORT

**A. CLASSIFICATION OF SUBJECT MATTER**

| IPC | C07D213/65 | A61P25/00 | A61K31/44 |

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

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

| IPC | C07D |

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

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

- EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BEILSTEIN Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
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<td>P,X</td>
<td>WO 00 71520 A (CONSLIVIO MICHAEL B ; DULL GARY MAURICE (US); WAGNER JARED MILLER ( ) 30 November 2000 (2000-11-30) examples 5,6</td>
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<td>US 5 616 707 A (CROOKS PETER A ET AL) 1 April 1997 (1997-04-01) claim 1</td>
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**X** Further documents are listed in the continuation of box C.

**X** Patent family members are listed in annex.

* Special categories of cited documents:

- **A** document defining the general state of the art which is not considered to be of particular relevance
- **E** earlier document published on or after the international filing date
- **L** document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- **O** document referring to an oral disclosure, use, exhibition or other means
- **P** document published prior to the international filing date but later than the priority date claimed

- **T** document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- **X** document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- **Y** document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- **R** document member of the same patent family

**Date of the actual completion of the international search**

17 May 2001

**Name and mailing address of the ISA**

European Patent Office, P.B. 5816 Pestelaan 2 NL-2280 HV Rijswijk
Tel. (+31-70) 940-2040, Tx. 31 651 eipo nl
Fax: (+31-70) 340-3016

**Authorized officer**

Gettins, M

Form PCT/ISA/210 (second sheet) (July 1990)
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<td>US 5 852 041 A (VERNIER JEAN-MICHEL ET AL) 22 December 1998 (1998-12-22) cited in the application column 2 - column 7</td>
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</table>
### Box I  Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

1. **X** Claims Nos.: 
   because they relate to subject matter not required to be searched by this Authority, namely:
   
   Although claim 12 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. **X** Claims Nos.: 1,2,4,7,11 
   because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
   
   see FURTHER INFORMATION sheet PCT/ISA/210

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

### Box II  Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

1. **☐** As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

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

3. **☐** As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. **☐** No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- **☐** The additional search fees were accompanied by the applicant's protest.
- **☐** No protest accompanied the payment of additional search fees.
Continuation of Box 1.2

Claims Nos.: 1,2,4,7,11

Present claim 1 relates to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds (II) of claim 3. Claim 1 has not been searched.

It is noted that the application (e.g. claims 2, 7 and 11) refers to prodrugs. "Prodrugs" is a functional definition which attempts to define a chemical compound in terms of a result to be achieved. This is not allowable. The said term has not been searched. "Prodrugs" is a functional definition without a specific technical guidance for the selection of the suitable derivatives in the description and without proven general knowledge to show which derivatives are suitable prodrugs. the term could be seen as a mere invitation to the skilled person to perform a research program in order to find the suitable variants. In such a situation, when the invention cannot be carried out over the whole claimed area without imposing an undue burden, the disclosure may be considered insufficient, even when simple in vivo or in vitro tests are available to determine whether or not a particular compound is covered by the claims. The same applies to the term "electron donating or electron withdrawing group". this has been understood to be as defined on pages 16-17. From page 16, line 11 it is apparent that the Applicant intends that, contrary to standard nomenclature practice. The terms in claims 2, 4, 7 and 11 "esters, carbamates, aminals, amides" provides no indication as to the specific substitution nor as to the position which is substituted. ("aminal is described on page 16, but the reference to "any other suitable substituent" cannot be described as a well defined limitation). In the absence of any further specification in the description the scope of these definitions is fully unclear.

Prodrug and the other terms in claims 2, 4, 7 and 11 are taken to mean any compound which is a derivative of the compounds of claims 1, 3 and 6 which have the same qualitative activity as the compounds of claims 1, 3 and 6. The claims cover all prodrugs having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed.
namely those parts relating to the compounds of claim 3 interpreted in
the light of pages 16–17 and taking note of the fact that contrary to all
standard rules of nomenclature the description (pages 15–16) indicates
that groups can be substituted even when this is not specifically
mentioned in the claims. Claims 2, 4, 7 and 11 have not been searched.

It should be noted that all of the examples fall within the scope of the
searched matter.

The applicant's attention is drawn to the fact that claims, or parts of
claims, relating to inventions in respect of which no international
search report has been established need not be the subject of an
international preliminary examination (Rule 66.1(e) PCT). The applicant
is advised that the EPO policy when acting as an International
Preliminary Examining Authority is normally not to carry out a
preliminary examination on matter which has not been searched. This is
the case irrespective of whether or not the claims are amended following
receipt of the search report or during any Chapter II procedure.
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