Abstract

Compounds of formula (I) have been shown to enhance the release of the neurotransmitter acetylcholine, and thus may be useful in the treatment of diseases of man where subnormal levels of this neurochemical are found, such as in Alzheimer’s disease, and other conditions involving learning and cognition. This invention describes compounds, pharmaceutical compositions and methods of treatment comprising compounds of formula (I).
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Title

NOVEL POLYCYCLIC SYSTEMS, AND DERIVATIVES THEREOF, AS
5 NEUROTRANSMITTER RELEASE ENHANCERS USEFUL IN THE TREATMENT
OF COGNITIVE DISORDERS

FIELD OF INVENTION

10 This invention relates to disubstituted polycyclic
compounds, derivatives thereof, pharmaceutical
compositions, and methods of use in mammals to treat
cognitive disorders and/or neurological dysfunction and/or
mood disturbances such as, but not limited to degenerative
nervous system diseases. Additionally, these compounds can
be used as reagents in studies on the biochemical mechanism
of neurotransmitter based diseases.

BACKGROUND OF THE INVENTION

20 Increasingly there is a need for effective treatments
for nervous system disorders and neurological deficiencies.
Many of these diseases correlate with increasing age, due
mainly to degenerative changes in the nervous systems.

25 Although in early stages of some diseases certain systems
are rather specifically affected (e. g. cholinergic systems
in Alzheimer's Disease and Myasthenia Gravis, the
dopaminergic system in Parkinson's Disease, etc.), multiple
neurotransmitter system deficiencies (acetylcholine,
dopamine, norepinephrine, serotonin) are generally found at
later stages of disease such as senile dementia, multi-
infarct dementia, Huntington's Disease, mental retardation,
etc. This explains the generally observed multiple
symptomatology that includes cognitive, neurological, and
effective/psychotic components (see Gottfries,
Psychopharmacol., (1985) 86: 245). Deficits in the
synthesis and release of acetylcholine in the brain are
generally thought to be related to cognitive impairment
(see Francis, et al., N. Engl. J. Med., (1985) 7: 313) whereas neurological deficits (e. g., Parkinsonian symptoms) and mood/mental changes may be related to impairment of dopaminergic and serotonergic systems, respectively. Other neurological deficits (e. g. Myasthenia Gravis) are related to cholinergic deficiencies in the peripheral nervous system.

Treatment strategies employed previously encompass vasoactive drugs like vincamine and pentoxifylline; metabolic enhancers like ergoloid mesylates, piracetam, and naftidrofuryl; neurotransmitter precursors like L-DOPA, choline, and 5-hydroxytryptamine; transmitter metabolizing enzyme inhibitors such as physostigmine; and neuropeptides like adrenocorticotropic hormone and vasopressin-related peptides. Except for L-DOPA treatment for Parkinson's Disease and cholinesterase inhibitor treatment for Myasthenia Gravis, these treatment strategies have generally failed to enhance the residual function of the affected systems by enhancing the stimulus-induced release of neurotransmitters. Theoretically, such an enhancement would improve the signal-to-noise ratio during chemical transmission of information, thereby reducing deficits in processes related to cognition, neurological function, and mood regulation.


U.S. Patent 5,173,489 issued December 22, 1992 discloses α,α'-disubstituted aromatic or heteroaromatic compounds of the formula:
or a salt thereof:

wherein X and Y are taken together to form a saturated ring or unsaturated carbocyclic or heterocyclic first ring and the shown carbon in said ring is α to at least one additional aromatic ring or heteroaromatic ring fused to the first ring; one of Het\(^1\) or Het\(^2\) is 2, 3, or 4-pyridinyl; or 2,4 or 5-pyrimidinyl, and the other is selected from

(a) 2, 3, or 4-pyridinyl
(b) 2, 4, or 5-pyrimidinyl
(c) 2-pyrazinyl
(d) 3 or 4-pyridazinyl
(e) 3 or 4-pyrazolyl
(f) 2 or 3 tetrahydrofuranyl, and
(g) 3-thienyl

which are useful as cognition enhancers. The above references claim the necessity of two heteroaryl pendant groups for activity.

European Patent Application, WO93/14085, published July 22, 1993 discloses compounds of the formula:

where Q is

which are useful as neurotransmitter release enhancers.

European Patent Application, WO93/14092, published July 22, 1993, discloses compounds of the formula:
where Q is

which are useful as neurotransmitter release enhancers.

None of the above references teach or suggest the compounds of the present invention having fused polycyclic systems of the 6-5-5 variety where A is a six-membered aromatic system; B is a five-membered heterocyclic system and C is a five-membered ring between ring systems A and B. In addition, it has been further demonstrated that certain compounds of the present invention, particularly those bearing a 2-fluoropyridinylmethyl group as a substituent on the polycyclic ring system, have the ability to produce a measurable increase in the level of acetylcholine in the brain. This demonstrated ability to produce increases in acetylcholine levels measurable directly in the brain constitutes a clear and unexpected advantage over compounds previously described in the art.

SUMMARY OF THE INVENTION

It has been found that certain polycyclic compounds enhance the stimulus-induced release of neurotransmitters, specifically acetylcholine, in nervous tissues; thus improving processes involved in learning and memorization of an active avoidance task. Further evidence of this effect is characterized by measurable increases in brain neurotransmitter acetylcholine levels.
Accordingly, there is provided by this invention a class of novel compounds represented by Formula (I) below:

or a pharmaceutically acceptable salt or prodrug thereof wherein:

A is an aromatic or heteroaromatic ring selected from the group consisting of:

and

B is an aromatic or heteroaromatic ring selected from the group consisting of:

SUBSTITUTE SHEET (RULE 26)
and

Z is a bond, \(-\text{C}(=\text{O})-\), \(-\text{O}-\), \(-\text{NP}-\), \(-\text{S}-\), \(-\text{S}(=\text{O})-\) or \(-\text{SO}_2-\);

P is H, phenyl, \(\text{C}_1-\text{C}_4\) alkyl or benzyl

5

\(R^2\) and \(R^3\) are independently H, F, Cl, Br, I, CF\(_3\), OH, R\(^4\), \(-(\text{CH}_2)\_n\text{C}=\text{CR}^5\), \(-\text{OR}^4\), \(\text{NR}^6\text{R}^6\_a\), \(-\text{CO}_2\text{R}^4\), \(-\text{COR}^4\), \(-\text{CONH}_2\), \(-\text{CONHR}^4\), \(-\text{CONR}^4\text{R}^4\_a\), \(-\text{CH}_2\)\(_n\text{NR}^6\text{COR}^4\) or \(-\text{S(O)}\_m\text{R}^4\);

10 \(R^{2a}\) is H, \(\text{C}_1-\text{C}_4\) alkyl or phenyl;

m is 0, 1, or 2;

\(R^4\) and \(R^{4a}\) are independently alkyl of 1 to 4 carbons;

15

Each of Het-1 and Het-2 is independently a heterocycle selected from the group consisting of:

\[\begin{array}{c}
H_2\text{C} \quad \text{X} \\
\text{P} \quad \text{X} \\
\text{X} \\
\end{array}\]

, and

20 Each X is independently H, F, Cl, Br, I, CF\(_3\), OR\(^4\), \(\text{NR}^6\text{R}^6\_a\), NO\(_2\), or CN

R is selected from the group consisting of:

\(\text{H}, \,-\text{CH}_2\text{-Phe-}W, \,-\text{CH}_2\text{-}(\text{Het}-2), \,-(\text{CH}_2)\_n\text{-O-COR}^5, \,-(\text{CH}_2)\_n\text{-CH}=\text{CH-R}^5, \,-(\text{CH}_2)\_n\text{-C}=\text{CR}^5, \,-(\text{CH}_2)\_n\text{-Y};\)

25 W is H, F, Cl, Br, \(-\text{CN}, \text{CO}_2\text{R}^5\), \(\text{R}^4\), \(\text{OR}^4\), \(\text{S(O)}\_m\text{-R}^4\);

Y is \(-\text{OR}^6, \text{NHR}^6, \text{NR}^6\text{R}^6\_a, \text{NHCO}^6, \text{NHCO}_2\text{R}^6, \text{CO}_2\text{R}^6, \text{-CN},\)

30 \text{CONHR}^6, \text{CONR}^6\text{R}^6\_a, \text{-COR}^6, \text{-CH}_2\text{-CH}=\text{CHCO}_2\text{R}^6, \text{-OCOR}^6, \text{or CO}_2\text{Bz}; \text{and}
n is 1 to 5;

R^5, R^6 and R^6a are independently H or alkyl of 1 to 6 carbons.

Provided that when A is a 6-membered aromatic or heteroaromatic ring, Het-1 and Het-2 are not both selected from

\[
\begin{align*}
\text{or} \quad & \quad \text{when } X = \text{H.}
\end{align*}
\]

Preferred compounds of the present invention are compounds of Formula (I) or a pharmaceutically acceptable salt or prodrug form thereof wherein:

A is an aromatic or heteroaromatic ring selected from the group consisting of:

\[
\begin{align*}
\text{Further preferred compounds of this invention are compounds of the Formula (I) or a pharmaceutically acceptable salt or prodrug form thereof wherein:}
\end{align*}
\]

A is an aromatic or heteroaromatic ring selected from the group consisting of:

\[
\begin{align*}
\text{30 B is an aromatic or heteroaromatic ring selected from the group consisting of:}
\end{align*}
\]
Most preferred compounds of the present invention are compounds of Formula (I) or a pharmaceutically acceptable salt or prodrug form thereof wherein:

5

A is a six member aromatic or heteroaromatic ring selected from the group consisting of:

\[ R^3 - \text{phenyl} \quad \text{and} \quad R^3 - \text{pyridinyl} \]

10 B is an aromatic or heteroaromatic ring selected from the group consisting of:

\[ \text{pyridinyl} \quad \text{and} \quad \text{pyrrolyl} \]
R² is H, I, R⁴, -C=CH, -OR⁴, -NR⁶R⁶a, -CO₂R⁴, or
-CH₂)ₙNR⁶COR⁴;

R³ is H;

Het-1 and Het-2 are independently

\[ \text{H}_3\text{C} \quad \text{X} \quad \text{or} \quad \text{X} \quad \text{or} \quad \text{X} \]

10 X is H, F, Cl, Br, or OR⁴;

R is selected from the group consisting of:
- H, 3-cyanobenzyl-,
- CH₂-(Het-2), -(CH₂)₁-CO₂Et,
- (CH₂)₃-CO₂Et, -(CH₂)₄-OCOCH₃, -(CH₂)₄-CO₂H₂, benzyl,
- (CH₂)₄-OH, and -(CH₂)₄-CN;

Specifically preferred compounds of the present invention are selected from:

20 (a) 4-(4-Pyridinylmethyl)-4H-indeno[1,2-B]thiophene;
(b) 4-(4-Pyridinylmethyl)-4H-indeno[1,2-B]thiophene-4-pentanenitrile Hydrobromide Hydrate;
(c) 4-(4-Pyridinylmethyl)-4H-indeno[1,2-B]thiophene-4-acetic acid Ethyl Ester Hydrochloride;
(d) 4-(4-Pyridinylmethyl)-4H-indeno[1,2-B]thiophene-4-butanol Acetate (Ester) Hydrochloride;
(e) 4-(4-Pyridinylmethyl)-4H-indeno[1,2-B]thiophene-4-pentanamide Hydrochloride Hydrate;
(f) 2-Fluoro-4-[4-(4-pyridinylmethyl)-4H-indeno[1,2-B]thiophen-4-ylmethyl]-pyridine;
(g) 4-[4-(Phenyl)-4H-indeno[1,2-B]thiophen-4-ylmethyl]-pyridine;
(h) 4-(4-Pyridinylmethyl)-4H-indeno[1,2-B]thiophene-4-butanol;
(i) 4-(4-Pyridinylmethyl)-4H-thieno[2',3':3,4]cyclopenta[1,2-B]pyridine;
(j) 4-[(2-Fluoro-4-pyridinyl)methyl]-4-(4-pyridinylmethyl)-4H-thieno[3',2':4,5]cyclopenta[1,2-B]pyridine;
(k) 1,4-Dihydro-1-(phenylmethyl)-4,4-bis(4-pyridinylmethyl)-indenol[1,2-C]pyrazole; and
(l) 2,4-Dihydro-2-phenyl-4,4-bis(4-pyridinylmethyl)-pyrazolo[4,3-B]pyrrolizine.
(m) 9,9-Bis[(2-fluoro-4-pyridinyl)methyl]-2-hydroxy-9H-fluorene;
(n) 5-(2-Fluoro-4-pyridinyl)methyl)-5-(4-pyridinylmethyl)-5H-indeno[1,2-b]pyridine;
(o) 5-(2-Fluoro-4-pyridinyl)methyl)-5-(4-pyridinylmethyl)-5H-indeno[2,1-b]pyridine;
(p) 10,10-Bis[(2-fluoro-4-pyridinyl)methyl]-9(10H)-anthraceneone;
(q) 9-[(2-Fluoro-4-pyridinyl)methyl]-9-(4-pyridinylmethyl)-9H-xanthene;
(r) 10-[(2-Fluoro-4-pyridinyl)methyl]-10-(4-pyridinylmethyl)-9(10H)-anthraceneone;
(s) 9,9-Bis[(2-fluoro-4-pyridinyl)methyl]-4-azaxanthene;
(t) 5,5-Bis[(2-fluoro-4-pyridinyl)methyl]-5H-indeno[1,2-b]pyridine;
(u) 4,4-Bis[(2-fluoro-4-pyridinyl)methyl]-4H-thieno[3',2':4,5]cyclopenta[1,2-b]pyridine;
(v) 9-[(2-Fluoro-4-pyridinyl)methyl]-9-(4-pyridinylmethyl)-4-azaxanthene;
(w) 9,9-Bis[(2-fluoro-4-pyridinyl)methyl]-2-methoxyfluorene;
(x) 9,9-Bis[(2-fluoro-4-pyridinyl)methyl]-7-methoxy-4-azaxanthene;
(y) 10,10-Bis[(2-fluoro-4-pyridinyl)methyl]-3-hydroxy-9(10H)-anthraceneone;
(z) 10,10-Bis[(2-fluoro-4-pyridinyl)methyl]-2,6-dimethoxy-9(10H)-anthraceneone;
(aa) 9,9-Bis[(2-fluoro-4-pyridinyl)methyl]-cyclopenta[1,2-b:3,4-b']dipyridine;
(bb) 5,5-Bis((2-fluoro-4-pyridinyl)methyl)-2-phenyl-5H-indeno-[1,2-d]pyrimidine;
(cc) 10,10-Bis((2-fluoro-4-pyridinyl)methyl)-3-methoxy-9(10H)-anthracenone;
(dd) 9,9-Bis((2-fluoro-4-pyridinyl)methyl)-9H-indeno-[2,1-b]pyridine;
(ee) 5,5-Bis((2-fluoro-4-pyridinyl)methyl)-7-(ethynyl)-5H-indeno-[1,2-b]pyridine;
(ff) 9,9-Bis((2-fluoro-4-pyridinyl)methyl)-9H-indeno-[1,2-b]pyrazine;
(gg) 5,5-Bis((2-fluoro-4-pyridinyl)methyl)-5H-indeno-[1,2-d]pyrimidine;
(hh) 5,5-Bis((2-bromo-4-pyridinyl)methyl)-5H-indeno-[1,2-b]pyridine;
(ii) 9,9-Bis((2-fluoro-4-pyridinyl)methyl)-2-((N-methylamino)methyl)fluorene;
(jj) 9,9-Bis((2-fluoro-4-pyridinyl)methyl)-2-((N-methyl-N-methoxycarbonylamino)methyl)fluorene;
(kk) 9,9-Bis((2-fluoro-4-pyridinyl)methyl)-2-((N-methyl-N-acetamino)methyl)fluorene;
(ll) 10,10-Bis((2-bromo-4-pyridinyl)methyl)-9(10H)-anthracenone;
(mn) 5,5-Bis((2-chloro-4-pyridinyl)methyl)-5H-indeno-[1,2-b]pyridine;
(nn) 5,5-Bis((2-fluoro-4-pyridinyl)methyl)-2-methyl-5H-indeno-[1,2-d]pyrimidine;
(oo) 5,5-Bis((2-methoxy-4-pyridinyl)methyl)-5H-indeno-[1,2-b]pyridine;
(pp) 5,5-Bis((2-fluoro-4-pyridinyl)methyl)-7-(ethyl)-5H-indeno-[1,2-b]pyridine;
(qq) 5,5-Bis((2-chloro-6-methyl-4-pyridinyl)methyl)-5H-indeno-[1,2-b]pyridine;
(rr) 5,5-Bis((2-methyl-4-pyridinyl)methyl)-5H-indeno-[1,2-b]pyridine;
(ss) 5,5-Bis((2-fluoro-4-pyridinyl)methyl)-7-(iodo)-5H-indeno-[1,2-b]pyridine;
(tt) 9,9-Bis((2-fluoro-4-pyridinyl)methyl)-9H-fluorene-1-carboxylic acid, methyl ester;
9-((2-Fluoro-4-pyridinyl)methyl)-9-H-fluorene-1-carboxylic acid, methyl ester, racemic;

9,9'-Bis((2-fluoro-4-pyridinyl)methyl)-9H-fluoren-1-amine;

5,5'-Bis((2-fluoro-4-pyridinyl)methyl)-5H-cyclopenta[2,1-b:3,4-b']dipyridine;

5-((2-Fluoro-4-pyridinyl)methyl)-5-(4-pyridinylmethyl)-5H-cyclopenta[2,1-b:3,4-b']dipyridine-4-carboxylic acid, methyl ester, dihydrochloride salt (racemic);

5-((2-Fluoro-4-pyridinyl)methyl)-5-(4-pyridinylmethyl)-5H-cyclopenta[2,1-b:3,4-b']dipyridine-4-carboxylic acid, methyl ester, hydrochloride salt, (+)-isomer;

5-((2-Fluoro-4-pyridinyl)methyl)-5-(4-pyridinylmethyl)-5H-cyclopenta[2,1-b:3,4-b']dipyridine-4-carboxylic acid, methyl ester, hydrochloride salt, (-)-isomer;

5,5'-Bis((6-fluoro-3-pyridinyl)methyl)-5H-cyclopenta[2,1-b:3,4-b']dipyridine;

5-((6-Fluoro-2-pyridinyl)methyl)-5-(4-pyridinylmethyl)-5H-cyclopenta[2,1-b:3,4-b']dipyridine;

5,5'-Bis((6-fluoro-2-pyridinyl)methyl)-5H-cyclopenta[2,1-b:3,4-b']dipyridine;

5,5'-Bis((3-methyl-4-pyridinyl)methyl)-5H-cyclopenta[2,1-b:3,4-b']dipyridine, trihydrochloride salt;

2-Fluoro-4-((9-(4-pyridinylmethyl)-9H-fluoren-9-yl)methyl)pyridine, hydrochloride salt;

5-((2-Fluoro-4-pyridinyl)methyl)-5-(4-pyridinylmethyl)-5H-cyclopenta[2,1-b:3,4-b']dipyridine;

5,5'-Bis((2-fluoro-4-pyridinyl)methyl)thioxanthene-10,10-dioxide;

5,5'-Bis((2-fluoro-4-pyridinyl)methyl)thioxanthene-10-oxide;
(aj) 2,6-Dimethyl-4-((9-(4-pyridinylmethyl)-9H-fluoren-9-y1)methyl)pyridine, dihydrochloride salt;
(ak) 5-((2,6-Dimethyl-4-pyridinyl)methyl)-5-(4-pyridinylmethyl)-5H-cyclopenta[2,1-b:3,4-b']dipyridine;
(al) 5,5-Bis((2,6-dimethyl-4-pyridinyl)methyl)-5H-cyclopenta[2,1-b:3,4-b']dipyridine, E-2-butendiaote salt.

Also provided are methods for the treatment of cognitive disorders and/or neurological function deficits and/or mood and mental disturbances in patients suffering from nervous system disorders such as Alzheimer's disease, Parkinson's disease, senile-dementia, multi-infarct dementia, Huntington's disease, mental retardation, Myasthenia Gravis, etc., by administering to the host suffering from such disorder a therapeutically effective amount of a compound of Formula (I). The present invention also provides pharmaceutical compositions comprising a therapeutically effective amount of a compound of Formula (I).

The compounds herein described may have asymmetric centers. All chiral, diastereomeric and racemic forms are included in the present invention. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. When any variable (for example, R₁ through R₆, m, n, P, W, Y, A, B, etc.) occurs more than one time in any constituent or in formula (I), or any other formula herein, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein and in the claims, "*" denotes the point of attachment of the A ring and B ring to more clearly specify the regioisomers intended.

As used herein and in the claims, "alkyl" is intended to include both branched and straight-chain saturated...
aliphatic hydrocarbon groups having the specified number of carbon atoms; "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge; "cycloalkyl" is intended to include saturated ring groups, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl; and "bicycloalkyl" is intended to include saturated bicyclic ring groups such as [3.3.0]bicyclooctane, [4.3.0] bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane, and so forth. "Alkenyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl, propenyl and the like; and "alkynyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl, propynyl and the like. "Halo" as used herein and in the claims refers to fluoro, chloro, bromo and iodo; and "counter-ion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, sulfate and the like.

As used herein and in the claims, "aryl" or "aromatic ring" is intended to mean phenyl or naphthyl; "carbocyclic" is intended to mean any stable 5- to 7- membered monocyclic or bicyclic or 7- to 14-membered bicyclic or tricyclic carbon ring, any of which may be saturated, partially unsaturated, or aromatic, for example indanyl, naphthyl, or tetrahydronaphthyl (tetralin).

As used herein and in the claims, the terms "heteroaromatic ring" and "heteroaromatic system" are intended to mean a stable 5- to 6- membered monocyclic or 8- to 10-membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from 1 to 3 heteroatoms selected from the group consisting of N, O and S and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen may optionally be quaternized, and including any bicyclic group in which any of the above-defined
heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. Examples of such heterocycles include, but are not limited to, pyridinyl, pyrimidinyl, furanyl, thietyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, benzothiophenyl, indolyl, indolenyl, quinolinyl, isoquinolinyl or benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolyl, tetrahydrofuranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl or octahydroisoquinolinyl.

The term "substituted", as used herein and in the claims, means that any one or more hydrogen on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound.

By "stable compound" or "stable structure" is meant herein a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

As used herein and in the claims, "pharmaceutically acceptable salts and prodrugs" refer to derivatives of the disclosed compounds that are modified by making acid or base salts, or by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compounds. Examples include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; acetate, formate and benzoate derivatives of alcohols and amines; and the like.

Pharmaceutically acceptable salts of the compounds of the invention can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount
of the appropriate base or acid in water or in an organic
solvent, or in a mixture of the two; generally, nonaqueous
media like ether, ethyl acetate, ethanol, isopropanol, or
acetonitrile are preferred. Lists of suitable salts are
found in Remington's Pharmaceutical Sciences, 17th ed.,
Mack Publishing Company, Easton, PA, (1985), p. 1418, the
disclosure of which is hereby incorporated by reference.

The term "pharmaceutical composition" as used herein
and in the claims refers to a composition comprised of a
compound and a pharmaceutical carrier selected on the basis
of the chosen route of administration and standard
pharmaceutical practice.

The term "therapeutically effective" as used herein
and in the claims refers to that amount of a compound of
formula (I) necessary to enhance the residual function of
the affected systems by enhancing the stimulus-induced
release of neurotransmitters thereby reducing deficits in
processes related to cognition, neurological function, and
mood regulation.

The use of "therapeutically effective amount" herein
and in the claims is intended to mean that amount useful
for the treatment of cognitive disorders and/or
neurological function deficits and/or mood and mental
disturbances in patients suffering from nervous system
disorders such as Alzheimer's disease, Parkinson's disease,
senile-dementia, multi-infarct dementia, Huntington's
disease, mental retardation, Myasthenia Gravis, etc.
Additionally, these compounds can be used as reagents in
studies on the biochemical mechanism of neurotransmitter
based diseases.

Detailed Description of the Invention

The compounds of this invention can be described as
being composed of two parts: the 'core group', that being
the tricyclic ring system formed by A and B and the central
five- and six-membered ring (C); and the 'pendant groups'
that are composed of 'CH₂-Het-1' and 'R'.

The cores can be synthesized by the methods described
below and in the following references which are hereby

Additional "core groups" useful for the synthesis of the compounds present invention can be prepared according to methods described in the literature references below, or by an analogous method to that reported:

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<1>
<2>
<3>
<3>
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<4>
<5>
<6>
<1> Chem Ber 1971, 104, 2975-83;
<2> J Med Chem 1978, 21, 623-8;
<3> Prepared by analogy to <2>, using azaindane none rather than indanone. Other nitrogen positional isomers are also available.
<4> Farmaco, Ed Sci 1985, 40, 979-86;
<5> Farmaco, Ed Sci 1979, 34, 72-80;
<6> Prepared by analogy to <5>, using azaindane none rather than indanone. Other nitrogen positional isomers are also accessible.
<7> Rend Accad Sci Fis Mat, Naples 1983, 50, 353-6;
<8> Tetrahedron 1991, 47, 6851-6886
<9> Prepared by analogy to the above, using azaindane none rather than indanone. Other nitrogen positional isomers are also accessible; see Heterocycles 1991, 22, 41-72.
<11> Prepared by analogy to <10>;
<13> Heterocycles 1988, 27, 2643-50;


Synthesis

Compounds of Formula I wherein R is -CH₂-(Het-2), and Het-1 = Het-2, can be prepared from the appropriate "core group" as illustrated in Scheme I.
Suitable bases for forming the anion include, but are not limited to, sodium or potassium hydroxide, sodamide, lithium diisopropylamide (LDA), sodium hydride, potassium tert-butoxide, sodium alkoxide, potassium alkoxide, potassium hydride, lithium 2, 2, 6, 6-tetramethylpiperidide, butyllithium, sec-butyl lithium, tert-butyl lithium, and lithium- sodium-, or potassium hexamethyldisilazide. The reaction can be conducted in an aprotic solvent, generally in an ether, such as but not limited to, tetrahydrofuran (THF), dioxane, glyme, diglyme, or diethyl ether (Et₂O); or benzene or toluene. Additionally, the reaction can be run in dimethylformamide (DMF) or dimethylacetamide (DMAC). However, if the reactants are soluble in a nonpolar solvent, the reaction can be carried out in a hydrocarbon solvent such as hexanes, heptane, cyclohexane, methylcyclohexane, benzene or toluene. If the reactants are compatible with water, the reactions can be conducted in solvent systems containing water and any of the other above mentioned organic solvents. Depending on the strength of the base, the reactions can be conducted at temperature from -78°C to solvent reflux temperature. Typically, a compound such as (II) is bis-alkylated to give Ia, by reacting (II) under phase transfer conditions (PTC). The active methylene species (II) is suspended in a mixture of 50% sodium hydroxide and toluene containing a catalytic amount of PTC-catalyst such as tetrabutylammonium iodide or bromide, and treating the mixture dropwise with an aqueous solution of,
for example, 4-picolyl chloride hydrochloride (2.2 equivalents) to give Ia.

Alternatively, compounds of Formula I, wherein R is other than \(-\text{CH}_2-(\text{Het}-2)\) or \(\text{Het}-1 \neq \text{Het}-2\), can be synthesized by the sequence shown in Scheme II.

Scheme II.

Methylene compound (II) is subjected to an aldol condensation with a suitably substituted pyridine or pyrimidine carboxaldehyde to give (III), which can be reduced with sodium borohydride, Pd/carbon and formic acid, Pd/carbon and hydrogen or dissolving metal conditions such as zinc in acetic acid to give (IV). Intermediate (IV) is dissolved in dry THF, cooled to 0°C, treated with 1.1 equivalents of sodium or potassium hexamethyldisilazide and a crown ether, stirred for 10 to 60 minutes under an inert gaseous environment, and treated dropwise with a dry THF solution of the alkylating agent \(X-R\), where \(X\) is a leaving group, such as halogen, \(\text{OSO}_2\text{Me}\) or tosyl. The reaction mixture is stirred in the cold for one hour, and at ambient
temperature until no starting material can be detected by chromatographic methods. The reaction mixture is concentrated at reduced pressure, and the residue is partitioned between water and methylene chloride. The organic phase is washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated at reduced pressure. Depending on the purity, the compounds of this invention may be collected as an oil, gum, or amorphous solid; or recrystallized from an appropriate solvent system; or further purified by chromatographic, sublimation, or distillation processes. The compounds may also exist as the 'free base' or as an acid addition salt formed from pharmaceutically acceptable acids. Additionally, compounds of Formula (I) may exist as racemates, diastereomeric mixtures, or their optically pure isomers.

Alternatively, compounds of the present invention wherein X is other than hydrogen can be synthesized and incorporated into the compounds of the present invention using one of the intermediates described below. These compounds, when used in conjunction with methods previously described, along with methods known to one of skill in the art of organic synthesis, would allow for synthesis of compounds of Formula (I).

The substituted pyridine starting materials that are listed below are reported in the literature or are commercially available.

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\text{CH}_3 & \text{H} & \text{H} & \text{CH}_2\text{Cl} & \text{H} & <42> \\
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\end{array}
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<1> J. Med. Chem. 1971 14 557-8
<2> U.S. Patent No. 4,215,123
<3> J. Am. Chem. Soc. 1959 81 704-9
<4> Germa Patent No. DE 2020762
<5> Pol. J. Chem. 1991 65 289-95
<7> Europ. Pat. Application No. 284174
<9> U.S. Patent No. 3,467,659
<10> J. Heterocycl. Chem. 1988 25 81-7
<13> J. Med. Chem. 1971 14 211-4
<16> J. Org. Chem. 1949 14 328
<17> Rocz. Chem. 1970 44 1249-53
The preparation of substituted methylpyridines is outlined in Scheme III.
Scheme III

Reagents:
(a) NaNO₂, HX, CuX₂; (b) H₂, Pd/C or SnCl₂; (c) H₂O₂, H₂SO₄;
(d) HNO₃, H₂SO₄; (e) CF₃I, Cu, HMPT; (f) 1) MCPBA, 2) KCN.

Additionally, where preparation of substituted and unsubsti-
tuted halo-methylene pyridines of the present invention are not described in the literature, conversions from known starting materials and intermediates is outlined in Scheme IV.

Scheme IV

Reagents:
(a) CBr₄, PPh₃; (b) NCS or NBS; (c) NaBH₄, MeOH; (d) 1) SOCl₂, 2) MeOH; (e) PCC; (f) NaBH₄; (g) I₂/DMSO; (h) DIBAL-H.
Compounds of Formula I wherein Het-1 or Het-2 are substituted pyrimidines are prepared from substituted pyrimidine starting materials which are either commercially available or reported in the literature, such as those listed below.

![Image of a pyrimidine structure]

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<td>H</td>
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**SUBSTITUTE SHEET (RULE 26)**
Additional compounds of Formula I can be prepared via functional group conversions of compounds within the scope of this invention using standard methodology known to one
of skill in the art of organic synthesis. Several examples of such conversions are shown in Scheme V.

**Scheme V**

![Scheme Diagram]

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<td>NaOR(^4) or KOR(^4) in R(^4)OH</td>
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<tr>
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<td>$H_2$NR(^6), HN(R(^6))(_2)</td>
</tr>
<tr>
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<td>NH(_2)</td>
<td>$H_2$, Pd/C</td>
</tr>
<tr>
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<td>I</td>
<td>NaNO(_2), HCl, KI</td>
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<tr>
<td>NH(_2)</td>
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<td>NaNO(_2), HBF(_4)</td>
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</table>

Other representative compounds of this invention can be synthesized in an analogous fashion by using methods commonly known to one skilled in the art of organic synthesis, i.e., by converting a $R^2$, $R^3$ or $Y$-group to another functional group. One such example, as in the case of an ester (CO\(_2\)R\(^5\)) being converted to the corresponding acid (CO\(_2\)H); or alcohol (OH) which can be further converted to an ether (OR\(^5\)) or the 'reverse ester' (O-COR\(^5\)). For such a case, the ester can be saponified to give the acid (CO\(_2\)H) which can be reduced to the alcohol. Alternatively, the ester can be directly reduced to the alcohol. An alternative approach to the 'reverse ester' compounds (~-OC(=O)R\(^5\)), can be initiated with the ester, which can be reduced to the alcohol, which can be subsequently acylated.
with an acid halide or anhydride, or by coupling the alcohol to an acid using N,N-dicyclohexyl-carbodiimide, carbonyl diimidazole, or some other coupling agent known to one of skill in the art.

A nitrile can be hydrated to the corresponding amide using the procedure described by Noller, Org. Syn., Coll. Vol. II: p 586. The same amide can be prepared from the corresponding ester by saponification, activation of carboxyl, and reaction with ammonia. By substituting primary or secondary amines for ammonia, other amides of this invention may be prepared. The corresponding amines can be obtained by reduction of the amides.
The compounds of the invention and their synthesis are further illustrated by the following examples and preparations. All temperatures are in degrees Celsius.

**Preparation 1**

A 500 ml three-neck round bottom flask was charged with zinc chloride (75 ml, 1.0M in Et₂O) and cooled to 0°C. A solution of 2-thienyllithium (75 ml, 1.0 M in THF) was added via dropping funnel over a 30 min period. The biphasic solution was stirred for an additional hour, then transferred via cannula to a solution of methyl 2-iodobenzoate (13.1 g, 0.05 mole), tetrakis(triphenylphosphine) palladium (2.9 g, 0.0025 mole) in THF (120 ml). The reaction was allowed to stir at room temperature overnight. Water (500 ml) was added, and the resulting emulsion was filter through Celite. The organic phase was separated, and the aqueous was extracted with EtOAc (1x500 ml, 2x250 ml). The combined EtOAc extract was washed with brine, dried over Na₂SO₄, filtered, then further dried over MgSO₄. Following filtration and concentration, the crude ester was directly saponified with KOH (5.61 g, 0.10 mole), water (16.5 ml) and EtOH (65 ml) at reflux for one hour. The reaction was concentrated at 30°C, diluted with water (200 ml), washed with EtOAc (3x50 ml), Et₂O (1x50 ml) and filtered through Celite. The aqueous was acidified with conc. HCl and extracted with EtOAc (3x100 ml). The organic layer was washed with brine, dried over MgSO₄, filtered, concentrated and azeotroped with benzene. The resulting brown oil was refrigerated overnight to render the acid (10.0g) in quantitative yield.
The impure acid was dissolved in benzene (113 ml) and treated at room temperature with oxalyl chloride (4.7 ml, 0.053 mole) and cat DMF. Following stirring for 1 hour the reaction was evaporated in vacuo. The residue was redissolved in benzene (113 ml) at 40°C and tin (IV) chloride (5.7 ml, 0.053 mole) was added. The reaction was stirred for 15 min (or until complete as judged by TLC), quenched with water and 1N HCl until homogeneous and extracted with Et2O. The Et2O extract was worked up in the usual manner and the crude product was purified on silica gel using 5/1 hexane/ether to give the title compound (5.8g) in 58% yield; mp 99-100°C. Variations of this procedure include the use of 2-thiophene trimethyltin instead of 2-thienyllithium, and the use of thionyl chloride instead of oxalyl chloride to form the acid chloride.

Preparation 2

\[ \text{Structure of the target compound} \]

A solution of starting ketone in Preparation 1 (1.28 g) was allowed to heat in diethylene glycol at 160°C before addition of hydrazine (13.9 ml) and elevation of temperature to 200°C for 40 min. Upon cooling and dilution with water, followed by extractive isolation with Et2O, a brown solid was isolated in quantitative yield; mp 62-64°C.

Preparation of 2-Fluoro-4-chloromethylpyridine

To a 1000 ml Single Neck RBF, equipped with a magnetic stirrer, reflux condenser, heating mantle was added 2-fluoro-4-picoline (13.33 g, 120 mmol) and carbon tetrachloride (-250 ml), N-chlorosuccinimide (23.98 g, 160
mmol, 1.5 eq.) and benzoyl peroxide (1.5 g). The reaction was heated to reflux for 6 hours, additional benzoyl peroxide (1.5g) was added and the heating maintained overnight. Monitor by TLC (1:1 toluene/methylene chloride). [At higher concentrations, more di-chloro product is formed.] The reaction was worked up by cooling to room temperature or below, filtered through Celite, and the precipitate was washed with more CCl₄. The organic solution was washed with sat. sodium thiosulfate (Na₂S₂O₃), saturated sodium bicarbonate, water, and brine. Following drying over magnesium sulfate, the filtrate was evaporated to an oil, determine product ratio by NMR. This material can be used in the next step without further purification. [For the two batches of the above reaction was obtained 32.94 g product mixture, which was 60% desired product, 16 % di-chloro, and 24% SM.]

Example 1

4-(4-Pyridinylmethyl)-4H-indeno[1,2-B]thiophene

A solution of methylene compound from Preparation 2 (1.87 g, 0.011 mole) was reacted with 4-pyridine carboxaldehyde (1.05 ml, 0.011 mole), KOtBu (1.35 g, 0.012 mole) in THF (40 ml) for 5 min. The reaction was quenched with saturated NH₄Cl (100 ml) and extracted with CH₂Cl₂ (3x50 ml). The combined CH₂Cl₂ extract was washed with additional NH₄Cl, dried over MgSO₄. Upon concentration in vacuo, the crude red oil was reacted with zinc (11.0 g) in AcOH (50 ml) at reflux. Normal neutralization and
extractive work up gave the title compound as a solid in 75% yield; mp 91-93°C (hexane/ethyl acetate).

Preparation 3

**General alkylation method**

![Chemical structure](image)

To a solution of Example 1 (1 equiv.) and 18-crown-6 (0.1 equiv.) in THF (50 ml per 2 mmol) was added at 0°C potassium hexamethyldisilazide (1 equiv.), followed by stirring for 45 min. The electrophile (R-Br) [always a bromide] (1 equiv.) in THF (10 ml) was added and the reaction was stirred at room temperature overnight. The reaction was quenched in CHCl₃/satd. NH₄Cl (50 ml each). Following further extraction with CHCl₃, the combined CHCl₃ extract was washed with brine, dried over MgSO₄, filtered and concentrated. The crude residue was purified by column chromatography on silica gel using MeOH/CHCl₃ to give the free base. Characterization was typically done by way of the mineral acid salt (HCl or HBr); however, in some instances, the free base was preferred.
Example 2

\[
\begin{array}{c}
\text{N} \\
\text{CN} \\
\text{HBr H}_2\text{O}
\end{array}
\]

3-(4-Pyridinylmethyl)-4\text{H}-indenol[1,2-B]thiophen-4-ylmethyl-benzonitrile Hydrobromide Hydrate

By using 3-cyanobenzyl bromide in Procedure 3, the title compound (C_{25}H_{18}N_2S HBr H_2O) was obtained in 92% yield; mp 246-251° dec.

Example 3

\[
\begin{array}{c}
\text{N} \\
\text{CN} \\
\text{HBr H}_2\text{O}
\end{array}
\]

4-(4-Pyridinylmethyl)-4\text{H}-indenol[1,2-B]thiophen-4-pentanenitrile Hydrobromide Hydrate

By using 5-bromo valeronitrile in Procedure 3, the title compound (C_{22}H_{20}N_2S HBr H_2O) was obtained in 33% yield; mp 136°C (dec).
Example 4

\[
\begin{array}{c}
\text{CO}_2\text{Et} \\
\text{HCl}
\end{array}
\]

\[
\text{4-}(4\text{-Pyridinylmethyl})\text{-}4\text{H-indeno}[1,2\text{-}b]\text{thiophene-4-acetic acid, Ethyl Ester Hydrochloride}
\]

By using ethyl 2-bromoacetate in Procedure 3, the title compound (C_{21}H_{19}N_{2}OS HCl) was obtained in 75% yield; mp 183-187°C.

Example 5

\[
\begin{array}{c}
\text{OAc} \\
\text{HCl}
\end{array}
\]

\[
\text{4-}(4\text{-Pyridinylmethyl})\text{-}4\text{H-indeno}[1,2\text{-}b]\text{thiophene-4-butanol Acetate (Ester) Hydrochloride}
\]

By using 4-bromobutyl acetate in Procedure 3, the title compound (C_{23}H_{23}NO_{2}S HCl) was obtained in 69% yield; mp 186-190°C.
Example 6

\[
\text{CONH}_2
\]

5

\[
\text{HCl H}_2\text{O}
\]

4-(4-Pyridinylmethyl)-4H-indeno[1,2-B]thiophene-4-pentanamide Hydrochloride Hydrate

Using the method described by Noller, Org. Syn. Coll. Vol. II, p 586, the nitrile in Example 3 was converted to the corresponding amide, \((C_2H_2N_2O_2S HCl H_2O)\) in 65% yield; mp 187-190°C.

Example 7

\[
\begin{align*}
\text{2-Fluoro-4-(4-pyridinylmethyl)-4H-indeno[1,2-B]thiophen-} \\
4\text{-ylmethylpyridine}
\end{align*}
\]

By using 2-fluoro-4-picolyl chloride in Procedure 3, the title compound \((C_{23}H_{17}FN_2S)\) was obtained in 57% yield; mp 117-119°C.
Example 8

\[
\begin{align*}
4'-[4-(\text{Phenyl})-4H\text{-indenol}1,2-B\text{thiophen}-4-y1\text{methyl}]\text{-pyridine}
\end{align*}
\]

By using benzyl bromide in Procedure 3, the title compound (C_{24}H_{19}NS) was obtained in 20% yield; mp 88-92°C.

Example 9

\[
\begin{align*}
4'-[4-(\text{Pyridinylmethyl})-4H\text{-indenol}1,2-B\text{thiophene}-4\text{-butanol}
\end{align*}
\]

By subjecting the product of Example 5 to alkaline hydrolysis, the title compound was isolated as an oil in quantitative yield; C_{21}H_{21}NOS, MW 335.45, mass spec 336 (M+1).

Preparation 4

By a procedure analogous to that described in Preparation 1, and substituting methyl-2-bromo-nicotinate, the title compound can be prepared.
Example 10

\[
\begin{array}{c}
\text{\textbf{4-(4-Pyridinylmethyl)-4H-thieno[2',3':3,4]cyclopenta}} \\
\text{(1,2-B)pyridine}}
\end{array}
\]

By substituting the product from Procedure 4 into Procedures 2 and 3, the title compound (C\textsubscript{16}H\textsubscript{12}N\textsubscript{2}S) was obtained in 45\% yield; mp 178-181°C.

Example 11

\[
\begin{array}{c}
\text{\textbf{4-[(2-Fluoro-4-pyridinyl)methyl]-4-(4-pyridinylmethyl)-4H-}} \\
\text{thieno[3',2':4,5]cyclopenta(1,2-B)pyridine}}
\end{array}
\]

By substituting Example 10 as starting material in Procedure 3 and using 2-fluoro-4-picolyll chloride, the title compound (C\textsubscript{22}H\textsubscript{18}FN\textsubscript{3}S) was obtained in 92\% yield; mp 192-193°C.
Example 12

Using 9H-Pyrrolo[1,2a]indole, which was prepared by the method described by Mazzola, V. J., et al.; J. Org. Chem., (1967) 32: 486, in the procedure described for Example 1, the desired mono-picolyl product could be obtained.

Example 13

9-((4-pyridinyl)methyl)9-((2-fluoro-4-pyridinyl)methyl)-9H-pyrrolo[1,2-a]indole

By substituting Example 12 as starting material for the preparation of Example 11, the title compound could be obtained.
Example 14

1,4-Dihydro-1-(phenylmethyl)-4,4-bis(4-pyridinylmethyl)-indenol1,2-Cpyrazole

A solution of N-benzyl pyrazoindene (6.1 mmol) in 10 ml DMSO was added dropwise to a mixture of KOt-Bu (1.44 g, 12.8 mmol) in 20 ml DMSO/Et2O (1:1) at 10°C while stirring under dry nitrogen. The mixture was treated dropwise over 30 min with a solution of 4-picoly Chloride (free base) (14.6 mmol) in 30 ml Et2O. The mixture was stirred at room temperature for 16 hr and poured into 100 ml water. The mixture was extracted with 100 ml Et2O. The extract was washed with water and brine, dried over MgSO4, filtered, and concentrated in vacuo to a foam (1.8 g). The foam was column chromatographed on silica gel using CH2Cl2 as mobile phase. Appropriate fractions were combined and concentrated in vacuo. The residue was recrystallized from EtOAc/hexanes to give the title compound in 74% yield; mp 154-155°C; Anal calcd for C29H24N4: C, 81.28; H, 5.65; N, 13.08. Found: C, 80.73; H, 5.77; N, 12.82. Mass spec m/e 429 (M+1).
Example 15

2,4-Dihydro-2-phenyl-4,4-bis(4-pyridinylmethyl)-pyrazolo[4,3-B]pyrrolizine

To a solution of 2,4-dihydro-2-phenylpyrazolo[4,3-B]pyrrolizine (6.1 mmol) and 18-Crown-6 (6.1 mmol) in tetrahydrofuran at 0°C was added potassium hexamethyldisilazide, followed by 4-picoly1 chloride (14.6 mmol, free-based in toluene) and the reaction allowed to warm to room temperature overnight. Following normal extractive workup and purification, the title compound was isolated as a solid in 4% yield; mp 169-170°C; Anal calc'd. for C_{26}H_{31}N_{5}: C, 77.40; H, 5.25; N, 17.36. Found: C, 77.01; H, 5.12; N, 17.18. Mass spec m/e 404 (M+1).

By using the methods illustrated in the above examples, the compounds in Table I were prepared.

Table I

(R^2 = R^3 = H)
<table>
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<tr>
<th>Ex</th>
<th>A</th>
<th>B</th>
<th>R</th>
<th>m.p. °C</th>
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<tr>
<td>1</td>
<td>(Phe)</td>
<td>(2,3-Thi)</td>
<td>H</td>
<td>91-93</td>
</tr>
<tr>
<td>2</td>
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<td>2,3-Thi</td>
<td>-CH₂-3-CN-C₆H₅</td>
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<td>2,3-Thi</td>
<td>-(CH₂)₄CN</td>
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<td>4</td>
<td>Phe</td>
<td>2,3-Thi</td>
<td>-CH₂-CO₂Et</td>
<td>183-187</td>
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<tr>
<td>5</td>
<td>Phe</td>
<td>2,3-Thi</td>
<td>-(CH₂)₄-OAc</td>
<td>186-190</td>
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<tr>
<td>6</td>
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<td>2,3-Thi</td>
<td>-(CH₂)₄-CΟΝΗ₂</td>
<td>187-190</td>
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<tr>
<td>7</td>
<td>Phe</td>
<td>2,3-Thi</td>
<td>-CH₂-2-F-(4-Pyr)</td>
<td>117-119</td>
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<tr>
<td>8</td>
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<td>2,3-Thi</td>
<td>-CH₂-C₆H₅</td>
<td>88-92</td>
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<tr>
<td>9</td>
<td>Phe</td>
<td>2,3-Thi</td>
<td>-(CH₂)₄-OH</td>
<td>oil</td>
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<tr>
<td>10</td>
<td>(2,3-Pyr)</td>
<td>2,3-Thi</td>
<td>H</td>
<td>178-181</td>
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<tr>
<td>11</td>
<td>(2,3-Pyr)</td>
<td>2,3-Thi</td>
<td>-CH₂-2-F-4-Pyr</td>
<td>192-193</td>
</tr>
<tr>
<td>12</td>
<td>Phe</td>
<td>N</td>
<td>H</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Phe</td>
<td>N</td>
<td>-CH₂-2-F-4-Pyr</td>
<td></td>
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<tr>
<td>14</td>
<td>Phe</td>
<td>N</td>
<td>-CH₄-4-Pyr</td>
<td>154-155</td>
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</table>

(N-Bn-4,5-Pyz)
15 $\text{Ph} - N - N^* - N^* - \text{-CH}_2\text{-4-Pyr} - 169-170$

(1,2-Prr)

16 Phe N-Ph- -CH$_2$-4-Pyr

4,5-Pyz

17 Phe N-Ph- -CH$_2$-2-F-4-Pyr

4,5-Pyz

18 Phe 2,3-Thi -(CH$_2$)$_2$-CO$_2$Et

19 Phe 2,3-Thi -(CH$_2$)$_3$-CO$_2$Et

20 Phe 2,3-Thi -(CH$_2$)$_4$-CO$_2$Et

21 Phe 2,3-Thi -(CH$_2$)$_5$-CO$_2$Et

22 Phe 2,3-Thi -(CH$_2$)$_2$-CN

23 Phe 2,3-Thi -(CH$_2$)$_3$-CN

24 Phe 2,3-Thi -(CH$_2$)$_5$-CN

25 Phe 2,3-Thi -(CH$_2$)$_2$-OCOC$_2$H$_3$

26 Phe 2,3-Thi -(CH$_2$)$_3$-OCOC$_2$H$_3$

27 Phe 2,3-Thi -(CH$_2$)$_4$-OCOC$_2$H$_3$

28 Phe 2,3-Thi -(CH$_2$)$_5$-OCOC$_2$H$_3$

29 Phe $\cdot$ H

(2,3-Fur)

30 Phe 2,3-Fur -CH$_2$-3-CN-C$_6$H$_5$

31 Phe 2,3-Fur -(CH$_2$)$_4$CN

32 Phe 2,3-Fur -CH$_2$-CO$_2$Et

33 Phe 2,3-Fur -(CH$_2$)$_4$-OAc

34 Phe 2,3-Fur -(CH$_2$)$_4$-CONH$_2$

35 Phe 2,3-Fur -CH$_2$-2-F-(4-Pyr)

36 Phe 2,3-Fur -CH$_2$C$_6$H$_5$

37 Phe 2,3-Fur -(CH$_2$)$_4$-OH

SUBSTITUTE SHEET (RULE 26)
38 Phe  2,3-Fur  -CH₂CH=CH-CO₂Et
39 Phe  2,3-Fur  2-F-(4-Pyr)-CH₂
40 Phe  2,3-Fur  -CH₂CH=CH-CO₂Et
41 Phe  2,3-Fur  -CH₂-2-F-4-Pyr
42 Phe  N\[N\]  H
(1,5-Imi)
43 Phe  1,5-Imi  -CH₂-3-CN-C₆H₅
44 Phe  1,5-Imi  -(CH₂)₄CN
45 Phe  1,5-Imi  -CH₂-CO₂Et
46 Phe  1,5-Imi  -(CH₂)₄-OAc
47 Phe  N\[N\]  -(CH₂)₄-CO-NH₂
(4,5-Imi)
48 Phe  4,5-Imi  -CH₂-2-F-(4-Pyr)
49 Phe  4,5-Imi  -CH₂-C₆H₅
50 Phe  4,5-Imi  -(CH₂)₄-OH
51 Phe  4,5-Imi  -CH₂CH=CH-CO₂Et
57 1,2-Pyr  4,5-Imi  -CH₂-2-F-4-Pyr
58 1,2-Pyr  N-Bn-  -CH₂-2-F-4-Pyr
4,5-Pyz
59 5,6-Pyr  N-Bn-  -CH₂-2-F-4-Pyr
4,5-Pyz
60 1,2-Pyr  1-Bn-  -CH₂-2-F-4-Pyr
2,3-Pyr

By using the methods illustrated in the above examples, the following compounds were also prepared.

SUBSTITUTE SHEET (RULE 26)
Example 61

9,9-Bis((2-fluoro-4-pyridinyl)methyl)-2-hydroxy-9H-fluorene
m.p. 200-201 °C. MS (NH₃/Cl) m/e 401 (M+H); Analysis
calc'd for C₂₅H₁₈F₂N₂O • 0.25H₂O:  C, 74.15; H, 4.61; N, 6.92; F, 9.38; found: C, 73.91; H, 5.10; N, 6.39; F, 8.94.
49% yield.

Example 62

5-(2-Fluoro-4-pyridinyl)methyl)-5-(4-pyridinylmethyl)-5H-
indeno[1,2-b]pyridine

m.p 164-5 °C. MS (NH₃/Cl) m/e 368 (M+H). Analysis calc'd
for C₂₄H₁₈FN₃·0.25 H₂O:  C, 77.50; H, 5.01; N, 11.30.
Found: C, 77.63; H, 4.85; N, 11.20. 22% yield.
Example 63

5-(2-Fluoro-4-pyridinyl)methyl-5-(4-pyridinylmethyl)-5H-indeno[2,1-b]pyridine

mp 163-4 °C. MS (NH₃/CI) m/e 368 (M+H). Analysis calc'd for C₂₄H₁₈F₁₈N₃: C, 78.44; H, 4.94; N, 11.11. Found: C, 78.10; H, 4.78; N, 11.36. 22% yield.

Example 64

10,10-Bis(2-fluoro-4-pyridinyl)methyl)-9(10H)-anthracenone

m.p. 156-157 °C. MS (NH₃/CI) m/e 413 (M+H). Analysis calc'd for C₂₆H₁₈F₂N₂O • 0.25 H₂O: C, 75.72; H, 4.40; N, 6.70; F, 9.21; found: C, 75.54; H, 4.38; N, 6.76; F, 9.27. 44% yield.

Example 65

SUBSTITUTE SHEET (RULE 26)
9-((2-Fluoro-4-pyridinyl)methyl)-9-(4-pyridinylmethyl)-9H-xanthene

5 m.p. 180-1 ºC. MS (NH3-CI) m/e 363 (M+H). Analysis calc'd for C25H19FN2O • 0.25H2O: C, 77.60; H, 5.08; N, 7.24; found: C, 77.94; H, 4.97; N, 7.25. 3% yield.

Example 66

Example 67

9-((2-Fluoro-4-pyridinyl)methyl)-9-(4-pyridinylmethyl)-9H-xanthene

15 m.p. 199-201 ºC. MS (NH3-CI) m/e 395 (M+H). Analysis calc'd for C26H19FN2O: C, 79.17; H, 4.86; N, 7.10; found: C, 78.84; H, 4.80; N, 7.13. 12% yield.

Example 67

9,9-Bis((2-fluoro-4-pyridinyl)methyl)-4-azaxanthene

m.p. 185-189 ºC. MS (NH3-CI) m/e 402 (M+H). Analysis calc'd for C24H17N3F2O: C, 71.81; H, 4.27; N, 10.47; found: C, 71.50; H, 4.25; N, 10.28. 10% yield.
Example 68

5.5-Bis((2-fluoro-4-pyridinyl)methyl)-5H-indeno[1,2-b]pyridine

m.p. 137-40 °C. MS (Cl/NH₃) m/e 386 (M+H). Analysis calc’d for C₂₄H₁₇N₃F₂:  C, 74.79; H, 4.45; N, 10.90; F, 9.86; found: C, 74.39; H, 4.51; N, 10.91; F, 9.91. 46% yield.

Example 69

4,4-Bis((2-fluoro-4-pyridinyl)methyl)-4H-thieno[3',2':4,5]cyclopenta[1,2-b]pyridine

m.p. 157-9 °C. MS (Cl/NH₃) m/e 392 (M+H). Analysis calc’d for C₂₂H₁₅F₂N₃S:  C, 67.50; H, 3.86; N, 10.73; S, 8.19; found: C, 67.11; H, 3.88; N, 10.69; S, 8.34. 55% yield.

Example 70

SUBSTITUTE SHEET (RULE 26)
9-((2-Fluoro-4-pyridinyl)methyl)-9-(4-pyridinylmethyl)-4-azaxanthene

m.p. 206-208 °C. MS (NH₃-CI) m/e 384 (M+H). Analysis calc'd for C₂₄H₁₈FN₃O · 0.25H₂O: C, 74.31; H, 4.81; N, 10.83; found: C, 74.17; H, 4.69; N, 10.67. 12% yield.

Example 71

9,9-Bis((2-fluoro-4-pyridinyl)methyl)-2-methoxyfluorene

m.p. 143-146 °C. MS (NH₃-CI) m/e 415 (M+H). Analysis calc'd for C₂₆H₂₀F₂N₂O: C, 75.35; H, 4.86; N, 6.76; found: C, 75.33; H, 4.78; N, 6.67. 54% yield.

Example 72

9,9-Bis((2-fluoro-4-pyridinyl)methyl)-7-methoxy-4-azaxanthene

m.p. 196-197 °C. MS (NH₃-CI) m/e 432 (M+H). Analysis calc'd for C₂₅H₁₉F₂N₃O₂: C, 69.60; H, 4.44; N, 9.74; found: C, 69.55; H, 4.37; N, 9.74. 8% yield.
Example 73

\[
\begin{align*}
10,10-\text{Bis((2-fluoro-4-pyridinyl)methyl)-3-hydroxy-9(10H)-} & \\
\text{anthracenone} & \\
\text{m.p. 219-221 °C. MS (NH}_3\text{-Cl}) m/e 429 (M+H); Analysis} & \\
\text{calc'd for C}_{26}\text{H}_{18}\text{F}_{2}\text{N}_{2}\text{O}_{2}: C, 72.89; H, 4.23; N, 6.54;} & \\
\text{found: C, 72.97; H, 4.19; N, 6.48. 26% yield.} & 
\end{align*}
\]

Example 74

\[
\begin{align*}
10,10-\text{Bis((2-fluoro-4-pyridinyl)methyl)-2,6-dimethoxy-} & \\
\text{9(10H)-anthracenone} & \\
\text{m.p. 151-2 °C. MS (Cl/NH}_3\text{-H}) m/e 473 (M+H). Analysis calc'd} & \\
\text{for C}_{28}\text{H}_{22}\text{F}_{2}\text{N}_{2}\text{O}_{4}: C, 71.17; H, 4.69; N, 5.93; F, 8.04;} & \\
\text{found: C, 70.76; H, 4.86; N, 5.90; F, 7.91. 12% yield.} & 
\end{align*}
\]
Example 75

9,9-Bis((2-fluoro-4-pyridinyl)methyl)-cyclopenta[1,2-b:3,4-b']dipyridine

m.p. 134-5 °C. MS (Cl/NH₃) m/e 387 (M+H). Analysis calc'd for C₂₃H₁₆F₂N₄: C, 71.49; H, 4.17; N, 14.50; F, 9.83; found: C, 71.08; H, 4.00; N, 14.29; F, 9.96. 27% yield.

Example 76

5,5-Bis((2-fluoro-4-pyridinyl)methyl)-2-phenyl-5H-indeno[1,2-d]pyrimidine

m.p. 213-5 °C. MS (Cl/NH₃) m/e 463 (M+H). Analysis calc'd for C₂₉H₂₀F₂N₄: C, 75.31; H, 4.36; N, 12.11; F, 8.22; found: C, 74.98; H, 4.31; N, 12.01; F, 8.36. 30% yield.
Example 77

10,10-Bis((2-fluoro-4-pyridinyl)methyl)-3-methoxy-9(10H)-anthracenone

m.p. 155-7 °C. MS (CI/NH3) m/e 443 (M+H). Analysis calc'd for C27H20F2N2O2: C, 73.29; H, 4.56; N, 6.33; F, 8.59; found: C, 72.90; H, 4.54; N, 6.24; F, 8.55. 27% yield.

Example 78

9,9-Bis((2-fluoro-4-pyridinyl)methyl)-9H-indeno[12,1-b]pyridine

m.p. 128-30 °C. MS (CI/NH3) m/e 386 (M+H). Analysis calc'd for C24H17F2N3: C, 74.79; H, 4.45; N, 10.90; F, 9.86; found: C, 74.50; H, 4.24; N, 10.75; F, 9.87. 35% yield.
Example 79

5.5-Bis{(2-fluoro-4-pyridinyl)methyl}-7-(ethynyl)-5H-indeno-[1,2-b]pyridine

m.p. 139-40 °C. MS (CI/NH₃) m/e 410 (M+H). Analysis calc'd for C₂₆H₁₇F₂N₃: C, 76.27; H, 4.19; N, 10.26; F, 9.28; found: C, 75.95; H, 4.14; N, 10.09; F, 9.18. 43% yield.

Example 80

9,9-Bis{(2-fluoro-4-pyridinyl)methyl}-9H-indeno-[1,2-b]pyrazine

m.p. 119-20 °C. MS (CI/NH₃) m/e 387 (M+H); Analysis calc'd for C₂₃H₁₆F₂N₂: C, 71.49; H, 4.17; N, 14.50; F, 9.83; found: C, 71.28; H, 4.12; N, 14.47; F, 9.73. 68% yield.

Example 81

SUBSTITUTE SHEET (RULE 26)
5,5-Bis((2-fluoro-4-pyridinyl)methyl)-5H-indeno[1,2-d]pyrimidine

m.p. 171-4 °C. MS (Cl/\text{NH}_3) \text{ m/e 387 (M+H)}. Analysis calc'd for \text{C}_{23}\text{H}_{16}\text{F}_2\text{N}_4: C, 71.49; H, 4.17; N, 14.50; F, 9.83; found: C, 71.30; H, 4.09; N, 14.40; F, 9.96. 64\% yield.

Example 82

5,5-Bis((2-bromo-4-pyridinyl)methyl)-5\text{H}-indenol[1,2-d]pyridine

m.p. 190 °C. MS (Cl/\text{NH}_3) \text{ m/e 508 (M+H)}. Analysis calc'd for \text{C}_{24}\text{H}_{17}\text{Br}_2\text{N}_3: C, 56.83; H, 3.38; N, 8.28; Br, 31.51; found: C, 57.20; H, 3.43; N, 8.20; Br, 31.12. 63\% yield.

Example 83

9,9-Bis((2-fluoro-4-pyridinyl)methyl)-2-((\text{N-methylamino})methyl)fluorene

SUBSTITUTE SHEET (RULE 26)
m.p. 130-4 °C. MS (CI/NH₃) m/e 428 (M+H). 92% yield.

Example 84

9,9-Bis((2-fluoro-4-pyridinyl)methyl)-2-((N-methyl-N-methoxycarbonylamino)methyl)fluorene

oil. MS (CI/NH₃) m/e 486 (M+H). Analysis calc'd for C₂₉H₂₅F₂N₃O₂ • 0.5 H₂O: C, 70.43; H, 5.30; N, 8.50; found: C, 70.65; H, 5.08; N, 8.53. 85% yield.

Example 85

9,9-Bis((2-fluoro-4-pyridinyl)methyl)-2-((N-methyl-N-acetylamino)methyl)fluorene

m.p. 136-7 °C. MS (CI/NH₃) m/e 470 (M+H); Analysis calc'd for C₂₉H₂₅F₂N₃O • 0.25H₂O: C, 73.48; H, 5.42; N, 8.86; found: C, 73.30; H, 5.34; N, 8.67. 79% yield.
Example 86

10,10-Bis((2-bromo-4-pyridinyl)methyl)-9(10H)-anthracenone
m.p. 182-3 °C. MS (Cl/ NH₃) m/e 535 (M+H). Analysis calc'd for C₂₆H₁₈Br₂N₂O: C, 58.45; H, 3.40; N, 5.24; Br, 29.91; found: C, 58.69; H, 3.26; N, 5.22; Br, 29.68. 54% yield.

Example 87

5,5-Bis((2-chloro-4-pyridinyl)methyl)-5H-indeno[1,2-b]pyridine
m.p. 188-90 °C. MS (Cl/ NH₃) m/e 418 (M+H). Analysis calc'd for C₂₄H₁₇Cl₂N₃: C, 68.91; H, 4.10; N, 10.04; Cl, 16.95; found: C, 68.70; H, 3.99; N, 9.95; Cl, 16.76. 46% yield.

Example 88
5,5-Bis((2-fluoro-4-pyridinyl)methyl)-2-methyl-5H-indeno-11.2-dipyrimidine

m.p. 114-5 °C. MS (CI/NH₃) m/e 401 (M+H). Analysis calc'd for C₂₄H₁₈F₂N₄: C, 71.99; H, 4.53; N, 13.99; F, 9.49; found: C, 71.88; H, 4.52; N, 13; F, 9.87. 31% yield.

Example 89

5,5-Bis((2-methoxy-4-pyridinyl)methyl)-5H-indeno-11.2-dipyridine

m.p. 138-40 °C. MS (CI/NH₃) m/e 410 (M+H). Analysis calc'd for C₂₆H₂₃N₃O₂: C, 76.26; H, 5.66; N, 10.26; found: C, 75.64; H, 5.54; N, 10.14. 50% yield.

Example 90

5,5-Bis((2-fluoro-4-pyridinyl)methyl)-7-(ethyl)-5H-indeno-11.2-dipyridine

Oil. MS (CI/NH₃) m/e 414 (M+H). Analysis calc'd for C₂₆H₂₁F₂N₃: C, 75.53; H, 5.12; N, 10.16; found: C, 75; H, 5.36; N, 9.95. 90% yield.
Example 91

5.5-Bis((2-chloro-6-methyl-4-pyridinyl)methyl)-5H-indeno-1,2-bipyridine

m.p. 159-60 °C. MS (Cl/NH3) m/e 446 (M+H). Analysis calc'd for C_{26}H_{21}Cl_{2}N_{3}: C, 69.96; 4.74, 4.68; N, 9.41; Cl, 15.88; found: C, 70.00; 4.74, ; N, 9.31; Cl, 15.82. 14% yield.

Example 92

5.5-Bis((2-methyl-4-pyridinyl)methyl)-5H-indeno-1,2-bipyridine

m.p. 177-9 °C. MS (Cl/NH3) m/e 378 (M+H); Analysis calc'd for C_{26}H_{23}N_{3}: C, 82.73; H, 6.14; N, 11.13; found: C, 82.54; H, 6.12; N, 11.10. 90% yield.
Example 93

5.5-Bis((2-fluoro-4-pyridinyl)methyl)-7-(iodo)-5H-indeno[1,2-b]pyridine

m.p. 158-61 °C. MS (Cl/NH₃) m/e 512 (M+H); Analysis calc'd for C₂₄H₁₆F₂IN₃: C, 56.38; H, 3.15; F, 7.43; N, 8.22;
found: C, 56.83; H, 3.17; F, 7.58; N, 8.17. 25% yield.

Example 94

9.9-Bis((2-fluoro-4-pyridinyl)methyl)-9H-fluorene-1-carboxylic acid methyl ester

m.p. 126-127°C. MS (NH₃/Cl) m/e 443 (M+H); Analysis calc'd for C₂₇H₂₀F₂N₂O₂: C, 73.29; H, 4.56; N, 6.33; F, 8.59;
found: C, 72.99; H, 4.56; N, 6.24; F, 8.59. 49% yield.
Example 95

\[
9-((2\text{-Fluoro}-4\text{-pyridinyl})\text{methyl})-9-(4\text{-pyridinylmethyl})-9H\text{-}
\quad \text{fluorene-1-carboxylic acid, methyl ester, racemic}
\]

mp 144-6°C. MS (NH\textsubscript{3}/CI) m/e 425 (M + H). Analysis calc’d for C\textsubscript{27}H\textsubscript{21}FN\textsubscript{2}O\textsubscript{2} • 0.25 H\textsubscript{2}O: C, 75.60; H, 5.05; N, 6.53; F, 4.43. Found: C, 75.69; H, 4.85; N, 6.42; F, 4.26. 55% yield.

Example 96

\[
9,9\text{-Bis((2\text{-fluoro}-4\text{-pyridinyl)methyl})-9H\text{-fluoren-1-amine}
\]

mp 182-4°C. MS (NH\textsubscript{3}/CI) m/e 400 (M+H). Analysis calc’d for C\textsubscript{25}H\textsubscript{19}F\textsubscript{2}N\textsubscript{3} • 0.25 H\textsubscript{2}O: C, 74.34; H, 4.87; N, 10.40; F, 9.41. Found: C, 74.43; H, 4.68; N, 10.37; F, 9.39. 25% yield.
Example 97

5,5-Bis[(2-fluoro-4-pyridinyl)methyl]-5H-cyclopenta[2,1-b:3,4-b']dipyridine
m.p. 239-241°C. MS (NH₃/CI) m/e 387 (M+H). Analysis calc'd for C₂₃H₁₆F₂N₄ • 0.25 H₂O: C, 70.67; H, 4.25; N, 14.33; F, 9.72; found: C, 70.95; H, 4.05; N, 14.24; F, 9.37. 44% yield.

Example 98

5-((2-Fluoro-4-pyridinyl)methyl)-5-((4-pyridinylmethyl)-5H-cyclopenta[2,1-b:3,4-b']dipyridine-4-carboxylic acid methyl ester, dihydrochloride salt (racemic)
m.p. 181-9°C. MS (NH₃/CI) m/e 427 (M+H). Analysis calc'd for C₂₅H₁₉FN₄O₂ • 2HCl • H₂O: C, 58.04; H, 4.48; N, 10.83; Cl, 13.70; found: C, 58.45; H, 4.30; N, 10.76; Cl, 13.73. 79% yield.

SUBSTITUTE SHEET (RULE 26)
Example 99

\[
\begin{align*}
\text{(-) isomer} \\
5-\left(2\text{-Fluoro-4-pyridinylmethyl}\right) - 5\text{-\left(4-pyridinylmethyl\right)} - 5H- \\
cyclopenta\{2,1-b;3,4-b'\}dipyridine-4-carboxylic acid. \\
methyl ester, hydrochloride salt. (\text{-})-isomer \\
m.p.-hygroscopic. \ \ [\alpha]_D^{25} = -14.95^\circ \ (c=0.6, \text{CHCl}_3). \ MS \ (\text{NH}_3- \\
\text{CI}) \ m/e 427 \ (M+H). \ Analysis \ calc'd \ for \ C_{25}H_{19}F_{11}N_{4}O_{2}\cdot\text{HCl}\cdot0.5 \\
\text{H}_2\text{O}: \ C, \ 63.63; \ H, \ 4.49; \ N, \ 11.87; \ Cl, \ 7.51; \ found: \ C, \ 63.47; \ H, \ 4.06; \ N, \ 11.73; \ Cl, \ 7.26. \ 73\% \ yield.
\end{align*}
\]

Example 100

\[
\begin{align*}
\text{(+) isomer} \\
5-\left(2\text{-Fluoro-4-pyridinylmethyl}\right) - 5\text{-\left(4-pyridinylmethyl\right)} - 5H- \\
cyclopenta\{2,1-b;3,4-b'\}dipyridine-4-carboxylic acid. \\
methyl ester, hydrochloride salt. (\text{+})-isomer \\
m.p.-hygroscopic. \ \ [\alpha]_D^{25} = +14.29^\circ \ (c=0.6, \text{CHCl}_3). \ MS \\
(\text{NH}_3-\text{Cl}) \ m/e 427 \ (M+H). \ Analysis \ calc'd \ for \\
C_{25}H_{19}F_{11}N_{4}O_{2}\cdot\text{HCl}\cdot0.5 \ \text{H}_2\text{O}: \ C, \ 63.63; \ H, \ 4.49; \ N, \ 11.87; \ Cl, \\
7.51; \ found: \ C, \ 63.60; \ H, \ 4.03; \ N, \ 11.80; \ Cl, \ 7.01. \ 90\% \ yield.
\end{align*}
\]
Example 101

\[
5-(((2\text{-fluoro-4-\text{pyridinyl}})\text{methyl})\text{-}5-\text{-(4-\text{pyridinyl}}\text{methyl})\text{-}5\text{H-}
cyclopenta[2.1-b;3.4-b']dipyridine-4-\text{carboxylic acid, methyl ester, hydrochloride salt, (+)-isomer}
\]

m.p. 237-238°C. MS (NH₃-CI) m/e 387 (M+H). Analysis calc'd for C₂₃H₁₆N₄F₂·0.25 H₂O: C, 70.67; H, 4.25; N, 14.33; F, 9.72; found: C, 70.81; H, 4.40; N, 14.26; F, 9.70. 88% yield.

Example 102

\[
5-(((6\text{-fluoro-2-\text{pyridinyl}})\text{methyl})\text{-}5-\text{-(4-\text{pyridinyl}}\text{methyl})\text{-}5\text{H-}
cyclopenta[2.1-b;3.4-b']dipyridine
\]

m.p. 180-182°C. MS (NH₃-CI) m/e 369 (M+H). Analysis calc'd for C₂₃H₁₇N₄F·0.25 H₂O: C, 74.08; H, 4.73; N, 15.02; F, 5.09; found: C, 73.94; H, 4.53; N, 14.93; F, 4.84. 81% yield.

Example 103

SUBSTITUTE SHEET (RULE 26)
5.5-Bis((6-fluoro-2-pyridinyl)methyl)-5H-cyclopenta[2,1-b:3,4-b']dipyridine

m.p. 221-225°C. MS (NH₃-Cl) m/e 387 (M+H). Analysis calc'd for C_{23}H_{16}N₄F₂·0.33 H₂O: C, 70.40; H, 4.28; N, 14.28; F, 9.68; found: C, 70.71; H, 4.04; N, 14.30; F, 9.53. 81% yield.

Example 104

5.5-Bis((3-methyl-4-pyridinyl)methyl)-5H-cyclopenta[2,1-b:3,4-b']dipyridine, trihydrochloride salt

m.p. 301°C (dec). MS (NH₃-Cl) m/e 379 (M+H). Analysis calc'd for C_{25}H_{22}N₄·3 HCl·2 H₂O: C, 57.32; H, 5.58; N, 10.69; Cl, 20.30; found: C, 57.68; H, 5.41; N, 9.96; Cl, 20.76. 71% yield.

Example 105

2-Fluoro-4-((9-((4-pyridinyl)methyl)-9H-fluoren-9-yl)methyl)pyridine, hydrochloride salt
m.p. >220°C. MS (CI/NH₃) m/z 386 (M+H). Analysis calc'd for C₂₅H₂₁N₂F·1.2 HCl·0.5 H₂O: C, 71.63; H, 5.10; N, 6.68; F, 4.53; Cl, 10.15; found: C, 71.40; H, 4.86; N, 6.54; F, 4.14; Cl, 10.55. 13% yield.

Example 106

5-((2-Fluoro-4-pyridinyl)methyl)-5-(4-pyridinylmethyl)-5H-cyclopenta[2,1-b:3,4-b'd]dipyridine

m.p. 228-230°C. MS (CI/NH₃) m/z 369 (M+H). Analysis calc'd for C₂₃H₁₇FN₄·0.25 H₂O: C, 74.08; H, 4.73; N, 15.02; found: C, 74.25; H, 4.53; N, 15.11. 69% yield.

Example 107

5,5-Bis-(2-fluoropyridin-4-ylmethyl)thioxanthene-10,10-dioxe

A mixture of thioxanthene-10,10-dioxe (1.00 g, 4.3 mmol), 4-chloromethyl-2-fluoropyridine (1.45 g, 9.6 mmol), benzyltriethylammonium chloride (90 mg, 0.4 mmol), and a 50% NaOH solution (2.5 mL) in toluene (60 mL) was stirred at 50-60°C (internal temperature) for 18 h. After being cooled to ambient temperature, the reaction mixture was poured onto water (100 mL) and extracted three times with ethyl acetate. The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo.
Column chromatography (ether:hexanes::1:1) afforded the title product (0.68 g, Rf 0.2): mp >200°C; NMR (300 MHz, CDCl₃): δ 8.3 (d, 2H, J = 7), 7.9 (d, 2H, J = 7), 7.6 (t, 2H, J = 7), 7.45 (t, 2H, J = 7), 7.25 (d, 2H, J = 7) 6.45-6.35 (m, 2H), 6.2 (s, 2H), 3.8 (s, 4H); CI-HRMS: calcd for C₂₅H₁₈F₂N₂O₂S: 449.1135 (M + H); found: 449.1150.

Example 108

5,5-Bis-(2-fluoropyridin-4-ylmethyl)thioxanthene-10-oxide

A mixture of thioxanthene-10-oxide (1.00 g, 4.7 mmol), 4-chloromethyl-2-fluoropyridine (1.73 g, 10.3 mmol), benzyltriethyl ammonium chloride (90 mg, 0.4 mmol), and a 50% NaOH solution (2.5 mL) in toluene (60 mL) was stirred at 50-60°C (internal temperature) for 18 h. After being cooled to ambient temperature, the reaction mixture was poured onto water (100 mL) and extracted three times with ethyl acetate. The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. Column chromatography (ether:hexanes 1:1), followed by preparative TLC, afforded the title product (contaminated with 5,5-bis-(2-fluoropyridin-4-ylmethyl)-thioxanthene-10,10-dioxide) (0.12 g, Rf 0.1): mp >200°C; NMR (300 MHz, CDCl₃): δ

8.3 (d, 1H, J = 7), 8.2 (d, 2H, J = 7), 7.9 (d, 1H, J = 7), 7.85 (d, 2H, J = 7), 7.6 (t, 2H, J = 7), 7.5 (t, 1H, J = 7), 7.45 (t, 1H, J = 7), 7.35 (t, 2H, J = 7), 7.25 (d, 1H, J = 7), 7.15 (d, 2H, J = 7), 6.45-6.35 (m, 2H), 6.2 (s, 2H), 3.9 (s, 2H), 3.8 (s, 2H), 3.15 (s, 2H); CI-MS: 433 (M + H).
Example 109

\[
\text{2.6-Dimethyl-4-} \left( \text{9-} \left( \text{4-pyridinylmethyl} \right) \text{-9H-fluoren-9-yl} \right) \text{methyl} \text{pyridine, dihydrochloride salt}
\]

m.p. 180°C. MS (Cl/NH₃) m/e 372 (M+H for free base). \(^1\)H NMR (300 MHz, CDCl₃) δ: 8.05 (d, 2H), 7.45 (d, 2H), 7.38 (d, 2H), 7.30 (m, 4H), 6.45 (d, 2H), 6.20 (s, 2H), 3.40 (s, 2H), 3.25 (s, 2H), 2.20 (s, 6H). 91% yield (for free base).

Example 110

\[
\text{5-} \left( \text{2.6-Dimethyl-4-pyridinylmethyl} \right) \text{-5-} \left( \text{4-pyridinylmethyl} \right) \text{-5H-cyclopenta[2.1-b;3.4-b']dipyridine}
\]

m.p. >240°C. MS (Cl/NH₃) m/e 378 (M+H). Analysis calc'd for C₂₅H₂₂N₄•0.25 H₂O: C, 78.40; H, 5.92; N, 14.63; found: C, 78.05; H, 5.58; N, 14.32. 73% yield.

Example 111

\[
\text{5.5-Bis(2.6-dimethyl-4-pyridinylmethyl)-5H-cyclopenta[2.1-b;3.4-b']dipyridine, F-2-butendiazoate salt}
\]
m.p. 98-101°C (dec.). MS (NH₃·Cl) m/e 407 (M+H). Analysis calc'd for C₂₇H₂₆N₄·C₄H₄O₄·1.2 H₂O: C, 67.74; H, 6.05; N, 10.19; found: C, 67.64; H, 6.48; N, 8.71. 50% yield.

Example 112

![Chemical Structure]

5.5-Bis((2-fluoro-4-pyridinyl)methyl)-5H-

indenolo[1,2-c]pyridazine

m.p. 219-20 °C. (dec.). MS (Cl/NH₃) m/e 367 (M+H), 278 (M+H-C₆H₄NF), 169 (M+H-2(C₆H₄NF)); Analysis calc'd for C₂₃H₁₆F₂N₄: C, 71.49; H, 4.17; F, 9.83; N, 14.50; found: C, 71.21; H, 4.13; F, 9.80; N, 14.45. 22% yield.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations. Various equivalents, changes and modifications may be made by one skilled in the art without departing from the spirit and scope of this invention, and it is understood that such equivalent embodiments are part of this invention.

The compounds of Formula (I) possess neurotransmitter release activity and are effective in diminishing memory disruption caused. As such, the compounds of this invention have utility in the treatment of cognitive disorders and/or neurological function deficits and/or mood and mental disturbances in patients suffering from nervous system disorders such as Alzheimer's disease, Parkinson's disease, senile dementia, multi-infarct dementia, Huntington's disease, mental retardation, Myasthenia Gravis, etc.
The neurotransmitter release activities of the compounds of this invention were determined using standard biochemical assay procedures for example, the neurotransmitter release assay as described below. The ability of compounds of present invention to be effective in diminishing memory disruption is demonstrated in standard behavioral assay procedures for example the rat passive avoidance (PA) hypoxia induced amnesia model as described below.

**Neurotransmitter release assay.**


Male Wistar rats (Charles River) weighing 175-200 grams were used. Rats were decapitated and brains were dissected immediately. Slices (0.3 mm thick) from the parietal cortex were prepared (approximately 100 mg wet weight) and were incubated in 10 ml KrebsRinger medium (KR) containing NaCl (116 mM), KCl (3 mM), CaCl₂ (1.3 mM), MgCl₂ (1.2 mM), KH₂PO₄ (1.2 mM), Na₂SO₄ (1.2 mM), NaHCO₃ (25.0 mM), and glucose (11.0 mM), to which was added 10 uCi ³H-choline (specific activity approximately 35 Ci/mM; NEN) and 10 mM unlabeled choline to give a final concentration of one micromole. The brain preparations were incubated for 30 min. at 37° C under a steady flow of 95% O₂/5% CO₂. Under these conditions, part of the radioactive choline taken up by the preparation was converted into radioactive acetylcholine (ACh) by the cholinergic nerve endings stored in synaptic vesicles, and released upon depolarization by high potassium ion (K+) containing media.

After labelling of the ACh stores, the slices were washed three times with non-radioactive KR medium and transferred to a superfusion apparatus to measure the drug effects on ACh release. The superfusion apparatus c
consisted of 10 thermostated glass columns of 5 mm diameter that were provided with GF/F glass fiber filters to support the slices (approximately 10 mg tissue/column). Superfusion was carried out in KR-medium (0.3 ml/min.) containing 10 mM hemicholine-3 (HC-3). The HC-3 prevents the reuptake of choline formed during the superfusion from phospholipids and released ACh, which would be converted into unlabeled ACh and released in preference to the preformed labeled ACh. The medium was delivered by a 25-channel peristaltic pump (Ismatec by Brinkman) and warmed to 37°C in a thermostated stainless steel coil before entering the superfusion column. Each column was provided with a 4-way slider valve (Beckmann instruments) which allowed rapid change of low to high K+/KR-medium, and with two 10-channel 3-way valves that were used to change from drug-free to drug-containing low and high K+/KR-medium. After 15 min. of washout of non-specifically bound radioactivity, collection of 4 min. fractions was initiated. After three 4 min. collections, the original medium was changed to a KR-medium in which the KCl concentration had been increased to 25 mM (high K+ medium) (S1). Depolarization-induced stimulation of release by high K+/KR-medium lasted for 4 min. Drug-free low and high K+/KR-media were then substituted by drug- and vehicle-containing low- and high- K+/KR-medium, and superfusion was continued for three 4 min. collections with low K+/KR-medium, one 4 min. collection with high K+/KR-medium (S2), and two 4 min. collections with low K+/KR-medium.

Drug was added to the media by 100-fold dilutions of appropriate concentrations of the drug (in 0.9% saline) with either low- or high-K+/KR-medium. For comparative purposes, linopirdine was also run.

All superfusion fractions were collected in liquid scintillation counting vials. After superfusion, the slices were removed from the superfusion columns and extracted with 1.0 ml of 0.1 N HCl. Liquiscint (NEN) counting fluid (12 ml) was added to superfusion fractions.
and extracts, and the samples were counted in a Packard
Tricarb Liquid Scintillation Counter. No corrections were
made for quenching.

The ratio of S2/S1 (as compared to controls where no
drug was present during S2) was a measure of the ability of
the drug to enhance or depress stimulus-induced
acetylcholine release.

Representative compounds of this invention were tested
in the neurotransmitter release assay and found to be
effective in causing drug-induced release of
neurotransmitters. The results, expressed as % increase of
drug-induced Ach release, are shown in Table II below.

Rat Passive Avoidance (PA) Hypoxia Induced Amnesia:

Unfasted male CD rats, weighing between 165-210 grams,
were trained in a PA apparatus using the following
procedure: rats were placed in the clear side of the two
compartment chamber and allowed 90 seconds to enter the
dark compartment. Ten seconds after entering the dark
chamber, a 3 second footshock (1.0 mA) was applied to the
grid floor followed by an additional 10 second delay, and
another 3 second footshock was applied. Retentions were
tested 4 hours later. The rats were allowed 300 seconds
to enter the dark compartment; time was taken. Memory
disruption was induced by exposing the rats to a gas
mixture containing 6.5% oxygen supplemented with nitrogen
for 30 minutes before passive avoidance training. Doses
of the test compound were administered (0.1 ml/100 g, SC.)
relative to time of PA training.

Representative compounds of this invention were tested
in the rat passive avoidance (PA) hypoxia induced amnesia
model and found to be effective in diminishing the memory
disruption caused by hypoxia (significantly different from
vehicle, using a Mann-Whitney U Test). The results,
median retention latencies, are shown in Table II and
Table III below.
Microdialysis procedure

Male Wistar Rats are anaesthetized and guide cannulas stereotaxically implanted into the brain at the level of the dorsal hippocampus. Following a minimum recovery period of 72 h, dialysis probes (0.5 mm diameter, 4.0 mm long, from BAS) are inserted into the hippocampus through the guide cannulas. The probes are perfused at a rate of 2 μl/min with artificial cerebrospinal fluid containing 100 μM physostigmine sulfate (a cholinesterase inhibitor).

Rats are allowed to acclimate for 2 hours prior to sample collection. Dialysate samples are collected every 20 min (40 μl) and immediately injected onto a high performance liquid chromatograph equipped for electrochemical detection (HPLC-EC) of acetylcholine (ACh). Following collection of 3 baseline samples, drugs or vehicle control are administered in .01 ml/g body weight and dialysate samples are collected for an additional 3 h. The ACh peak heights of the 3 samples prior to drug administration are averaged together to determine baseline ACh levels. ACh peak heights post drug administration are measured and used to determine percent change over baseline ACh levels. At the end of experiments, probe placement is verified histologically.

HPLC-EC ACh Assay

ACh is separated by reverse phase chromatography (Hamilton PRP-1 column 150 x 4.5 mm) and converted to acetate, betaine and hydrogen peroxide on an immobilized enzyme reactor column (BAS). Hydrogen peroxide is then detected electrochemically. Mobile phase for the chromatography consists of 0.2 M Na₂HPO₄, 0.1 mM EDTA, 0.5 mM TMA.Cl, with pH adjusted to 8.0 with phosphoric acid and 50 ml Kathon CG (ESA) added to each liter of mobile phase to retard bacterial growth.
Results.

Figures A and B show the effects of fluorine substitution to the pendant groups of the anthrone and azafluorene core series on the ability of compounds to increase the level of ACh in the rat hippocampus in vivo. All compounds were tested at 5 mg/kg except Ex. No 64 which was administered at 1 mg/kg. The compounds were dosed orally except in the case of Ex. No 611 of U.S. Patent 5,137,489 which was given i.p. Ex. No. 611 of U.S. Patent 5,137,489 had no effect on ACh levels over what was observed after vehicle administration (Fig A). This was observed even though the compound was administered by a route (i.p.) which should lead to greater bioavailability than the oral route. Example 68 of the present invention, the bis-fluorinated analogue of Example 611 or U.S. Patent 5,137,489, on the other hand, led to a 2-fold increase in ACh levels which was maintained for over 1 hour (Fig A). The anthrone compound Ex. No. 440 of U.S. Patent 5,137,489, at 5 mg/kg, led to a peak ACh level of 72 % over baseline (Fig B). Ex. No. 64 of the present invention, which is the bis-fluoro analogue of Ex. No. 440 of U.S. Patent 5,137,489, at 1 mg/kg, led to a delayed increase in ACh levels reaching a peak of over 100% above baseline (Fig B). In contrast to the observed effects of Example 440 of U.S. Patent 5,137,489, the increase in ACh level after administration of Example 64 of the present invention was maintained for the entire duration of testing (3 hours). Tabular data from all microdialysis test is shown in Table IV.
Figure 1. Comparison of the effects of *Example 611 of U.S. Patent 5,137,489 to Example 88 of the present invention on ACh levels in the rat hippocampus in vivo. Assays were performed as described in Methods. Data are the results from at least 4 animals in each treatment category.
Figure 2. Comparison of the effects of *Example 440 of U.S. Patent 5,137,489 to Example 64 of the present invention on ACh levels in the rat hippocampus in vivo. Assays were performed as described in Methods. Data are the results from at least 4 animals in each treatment category.
### Table II

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<th>Example</th>
<th>Ach Release</th>
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(ExNo 4 of US Patent No.

### Table III

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% ACh (cor) - calculated from the raw data using the following formula (% ACh test - 100%) / (pos. control - 100%) x 100%

EC₅₀ - calculated slope of the dose-response curve of at least three data points (concentrations 0.3 µM to 10µM).

Table IV

<table>
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<tr>
<th>Ex No.</th>
<th>Dose mg/kg (no. tests)</th>
<th>Vehicle</th>
<th>AUC</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>(7)</td>
<td>water</td>
<td>36 ± 25</td>
<td>24 ± 9 @ 40</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>(14)</td>
<td>methocel 16 ± 71</td>
<td></td>
<td>23 ± 10 @ 60</td>
<td>NSP</td>
<td></td>
</tr>
<tr>
<td>Ex 4</td>
<td>US4,760,083</td>
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<td></td>
<td></td>
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<tr>
<td>5 (5)</td>
<td>water</td>
<td>83 ± 73</td>
<td>50 ± 16 @ 40</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>10 (9)</td>
<td>water</td>
<td>191 ± 68</td>
<td>56 ± 7 @ 40</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>20 (6)</td>
<td>water</td>
<td>315 ± 108</td>
<td>68 ± 26 @ 100</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>10 (10)</td>
<td>methocel 212 ± 61</td>
<td></td>
<td>62 ± 15 @ 40</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>20 (3)</td>
<td>methocel 600 ± 71</td>
<td></td>
<td>117 ± 36 @ 40</td>
<td>140</td>
<td></td>
</tr>
<tr>
<td>Ex 440</td>
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<tr>
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<tr>
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<td>water</td>
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<tr>
<td>1 (4)</td>
<td>methocel 711 ± 158</td>
<td></td>
<td>115 ± 27 @ 180</td>
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<tr>
<td>73</td>
<td>5 (3) methocel</td>
<td>170 ± 126</td>
<td>36 ± 12 @ 20</td>
<td>NSP</td>
<td></td>
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<tr>
<td>Ex 456</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>5 (4)</td>
<td>water</td>
<td>79 ± 45</td>
<td>36 ± 15 @ 20</td>
<td>NSP</td>
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</tr>
<tr>
<td>10 (4)</td>
<td>water</td>
<td>157 ± 108</td>
<td>72 ± 30 @ 40</td>
<td>40</td>
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</tr>
<tr>
<td>10 (4)</td>
<td>methocel 126 ± 74</td>
<td></td>
<td>34 ± 16 @ 60</td>
<td>NSP</td>
<td></td>
</tr>
<tr>
<td>71</td>
<td>5 (3) methocel</td>
<td>95 ± 61</td>
<td>48 ± 22 @ 20</td>
<td>40</td>
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<tr>
<td>61</td>
<td>5 (3) methocel</td>
<td>160 ± 187</td>
<td>47 ± 32 @ 40</td>
<td>NSP</td>
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<tr>
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<td>221 ± 85</td>
<td>52 ± 10 @ 20</td>
<td>&gt;40</td>
<td></td>
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<tr>
<td>68</td>
<td>2 (5) water</td>
<td>240 ± 82</td>
<td>47 ± 12 @ 40</td>
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<tr>
<td>Ex No.</td>
<td>Dose mg/kg (no. tests)</td>
<td>Vehicle</td>
<td>AUC</td>
<td>Peak</td>
<td>Duration</td>
</tr>
<tr>
<td>--------</td>
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<td>---------</td>
<td>------</td>
<td>-------</td>
<td>----------</td>
</tr>
<tr>
<td>5 (5)</td>
<td>water</td>
<td>871 ± 272</td>
<td>121 ± 25 @ 100</td>
<td>120</td>
<td></td>
</tr>
<tr>
<td>1 (7)</td>
<td>methocel</td>
<td>304 ± 88</td>
<td>74 ± 29 @ 100</td>
<td>120</td>
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<tr>
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<td>methocel</td>
<td>942 ± 324</td>
<td>201 ± 68 @ 80</td>
<td>&gt;80</td>
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<td>432 ± 106</td>
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<tr>
<td>67</td>
<td>1 (4) methocel</td>
<td>666 ± 212</td>
<td>123 ± 62 @ 200</td>
<td>&gt;</td>
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<tr>
<td>5 (3)</td>
<td>methocel</td>
<td>1423 ± 595</td>
<td>199 ± 80 @ 160</td>
<td>&gt;</td>
<td></td>
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<tr>
<td>107</td>
<td>5 (5) methocel</td>
<td>281 ± 226</td>
<td>41 ± 10 @ 20</td>
<td>NSP</td>
<td></td>
</tr>
<tr>
<td>108</td>
<td>1 (5) methocel</td>
<td>184 ± 124</td>
<td>34 ± 19 @ 100</td>
<td>NSP</td>
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</tr>
<tr>
<td>5 (5)</td>
<td>methocel</td>
<td>799 ± 202</td>
<td>108 ± 80 @ 80</td>
<td>&gt;</td>
<td></td>
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<tr>
<td>76</td>
<td>5 (3) methocel</td>
<td>96 ± 67</td>
<td>39 ± 25 @ 20</td>
<td>NSP</td>
<td></td>
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<tr>
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<td>302 ± 35</td>
<td>67 ± 12 @ 20</td>
<td>60</td>
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<tr>
<td>65</td>
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<td>147 ± 69</td>
<td>40 ± 11 @ 20</td>
<td>60</td>
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<tr>
<td>7</td>
<td>5 (3) water</td>
<td>235 ± 87</td>
<td>53 ± 19 @ 180</td>
<td>NSP</td>
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</tr>
<tr>
<td>69</td>
<td>5 (5) water</td>
<td>285 ± 40</td>
<td>44 ± 14 @ 20</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>72</td>
<td>5 (3) methocel</td>
<td>138 ± 109</td>
<td>34 ± 22 @ 60</td>
<td>NSP</td>
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</tr>
<tr>
<td>532</td>
<td>10 (5) methocel</td>
<td>76 ± 88</td>
<td>58 ± 22 @ 40</td>
<td>40</td>
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<tr>
<td>D55.137.489</td>
<td>10 (5) methocel</td>
<td>76 ± 88</td>
<td>58 ± 22 @ 40</td>
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<tr>
<td>97</td>
<td>10 (6) methocel</td>
<td>649 ± 188</td>
<td>102 ± 29 @ 100</td>
<td>120</td>
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<td>81</td>
<td>5 (6) methocel</td>
<td>250 ± 68</td>
<td>53 ± 17 @ 60</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

AUC - Area % under the curve (from graphical figure).
Peak - maximal % increase of ACh release over baseline @ minutes after administration.
Duration - minutes of release above statistical significance.
NSP - no significant points.
The compounds of this invention may also be used as reagents or standards in the biochemical study of neurological function, dysfunction, and disease.

**Dosage and Formulation**

Compounds of this invention can be administered to treat cognitive disorders and/or neurological function deficits and/or mood and mental disturbances by any means that produces contact of the active agent with the agent's site of action in the body of a mammal or patient. The compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals either as individual therapeutic agent or in combination of therapeutic agents. They can be administered alone, but are generally administered as a pharmaceutical composition comprised of a compound and a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage administered will vary depending on the use and known factors such as the pharmacodynamic character of the particular agent, and its mode and route of administration; the recipient's age, weight, and health; nature and extent of symptoms; kind of concurrent treatment; frequency of treatment; and the desired effect. For use in the treatment of said diseases or conditions, the compounds of this invention can be orally administered daily at a dosage of the active ingredient of 0.001 to 100 mg/kg of body weight. Ordinarily, a dose of 0.01 to 10 mg/kg/day in divided doses one to four times a day, or in sustained release formulation was effective in obtaining the desired pharmacological effect.

Dosage forms (pharmaceutical compositions) suitable for administration contain from about 1 mg to about 100 mg of active ingredient per unit. In these pharmaceutical compositions, the active ingredient will ordinarily be
present in an amount of about 0.5 to 95% by weight based on the total weight of the composition.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders; or in liquid forms such as elixirs, syrups, and/or suspensions. The compounds of this invention can also be administered parenterally in sterile liquid dose formulations.

Gelatin capsules can be used to contain the active ingredient and a suitable carrier such as but not limited to lactose, starch, magnesium stearate, steric acid, or cellulose derivatives. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of time. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste, or used to protect the active ingredients from the atmosphere, or to allow selective disintegration of the tablet in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring agents to increase patient acceptance.

In general, water, pharmaceutically acceptable oils, saline, aqueous dextrose (glucose), and related sugar solutions and glycols, such as propylene glycol or polyethylene glycol, are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, butter substances. Anti-oxidizing agents, such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or in combination, are suitable stabilizing agents. Also used are citric acid and its salts, and EDTA. In addition, parenteral solutions can contain preservatives such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.
Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences". A. Osol, a standard reference in this field.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

**Capsules**

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 mg of powdered active ingredient, 150 mg lactose, 50 mg cellulose, and 6 mg magnesium stearate.

**Soft Gelatin Capsules**

A mixture of active ingredient in a digestible oil such as soybean, cottonseed oil, or olive oil was prepared and injected by means of a positive displacement was pumped into gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules are washed and dried.

**Tablets**

A large number of tablets are prepared by conventional procedures so that the dosage unit was 100 mg of active ingredient, 0.2 mg of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg of starch, and 98.8 mg lactose. Appropriate coatings may be applied to increase palatability or delayed absorption.

**Injectable**

A parenteral composition suitable for administration by injection is prepared by dissolving 1.5% by weight of active ingredient in a solution containing 10% by volume of propylene glycol in water. The solution is sterilized by commonly used techniques.
Suspension

An aqueous suspension is prepared for oral administration so that each 5 milliliters contains 25 milligrams of finely divided active ingredients, 200 milligrams of sodium carboxymethyl cellulose, 5 milligrams of sodium benzoate, 1.0 gram of sorbitol solution, U.S.P., and 0.025 milliliter of vanillin.

Nasal Spray

An aqueous solution is prepared such that each 1 milliliter contains 10 milligrams of active ingredient, 1.8 milligrams methylparaben, 0.2 milligram propylparaben and 10 milligrams methylcellulose. The solution is dispensed into 1 milliliter vials.

Lung Inhaler

A homogeneous mixture of the active ingredient in polysorbate 80 is prepared such that the final concentration of the active ingredient will be 10 milligrams per container and the final concentration of polysorbate 80 in the container will be 1% by weight. The mixture is dispensed into each can, the valves are crimped onto the can and the required amount of dichlorotetrafluoroethane is added under pressure.

The foregoing disclosure includes all the information deemed essential to enable those of skill in the art to practice the claimed invention. Because the cited applications may provide further useful information these cited materials are hereby incorporated by reference.
What is claimed is:

1. A compound of the formula (I):

![Chemical Structure](image)

or a pharmaceutically acceptable salt or prodrug thereof wherein:

A is an aromatic or heteroaromatic ring selected from the group consisting of:

![Ring Structures](image)

B is an aromatic or heteroaromatic ring selected from the group consisting of:

![Ring Structures](image)
Z is a bond, -C(=O)-, -O-, -NP-, -S-, -S(=O)- or -SO₂-;

P is H, phenyl, C₁-C₄ alkyl or benzyl

R² and R³ are independently H, F, Cl, Br, I, CF₃, OH, R⁴, 
-(CH₂)ₙC≡CR⁵, -OR⁴, N⁶R⁶a, -CO₂R⁴, -COR⁴, -CONH₂, 
-CONHR⁴, -CONR⁴R⁴a, -CH₂)nN⁶COR⁴ or -S(O)mR⁴;

R²a is H, C₁-C₄ alkyl or phenyl;

m is 0, 1, or 2;

R⁴ and R⁴a are independently alkyl of 1 to 4 carbons;

Each of Het-1 and Het-2 is independently a heterocycle
selected from the group consisting of:

H₃C

, and

Each X is independently H, F, Cl, Br, I, CF₃, OR⁴, 
N⁶R⁶a, NO₂, or CN

R is selected from the group consisting of:

H, -CH₂-Phe-W, -CH₂-(Het-2), -(CH₂)ₙ-O-COR⁵,
-(CH₂)ₙ-CH=CH-R⁵, -(CH₂)ₙ-C≡C-R⁵, -(CH₂)ₙ-Y;
W is H, F, Cl, Br, -CN, CO₂R⁵, R⁴, OR⁴, S(O)ₘ₋R⁴;  

Y is -OR⁶, NHR⁶, NR₆R⁶ᵃ, NHCO₂R⁶, NHCO₂R⁶, -CN,  
CONHR⁶, CONR₆R⁶ᵃ, -COR⁶, -CH₂=CH=CHCO₂R⁶, -OCOR⁶, or  
CO₂Bz; and 

n is 1 to 5;  

R⁵, R⁶ and R₆ᵃ are independently H or alkyl of 1 to 6  
carbons. 

With the proviso that when A is a 6-membered aromatic or  
heteroaromatic ring, Het-1 and Het-2 are not both  
selected from  

\[
\begin{align*}
\text{or} \\
\text{when } X \text{ is } H.
\end{align*}
\]

2. A compound of claim 1 wherein:  

A is an aromatic or heteroaromatic ring selected from  
the group consisting of:  

\[
\begin{align*}
\text{or} \\
\text{when } X \text{ is } H.
\end{align*}
\]

3. A compound of claim 1 wherein:  

B is an aromatic or heteroaromatic ring selected from  
the group consisting of:
4. A compound of claim 1 wherein:

R is selected from the group consisting of:

5. A compound of claim 2 wherein:

B is an aromatic or heteroaromatic ring selected from the group consisting of:

6. A compound of claim 5 wherein:
\[ R^2 \text{ is } H, \text{ I, } R^4, \text{ -C=CH, } \text{ -OR}^4, \text{ -NR}^6\text{R}^6\text{a, -CO}_2\text{R}^4, \text{ or -CH}_2\text{)}\text{nNR}^6\text{COR}^4; \]

\[ R^3 \text{ is } H; \]

\[ P \text{ is } H, \text{ phenyl or benzyl; and} \]

\[ R \text{ is selected from the group consisting of:} \]

\[ \text{H, 3-cyanobenzyl-, -CH}_2\text-} (\text{Het-2), -(CH}_2\text{)}\text{1-CO}_2\text{Et,} \]
\[ -(CH}_2\text{)}\text{3-CO}_2\text{Et, -(CH}_2\text{)}\text{4-OCOCH}_3, -(CH}_2\text{)}\text{4-CONH}_2, \]
\[ \text{benzyl, -(CH}_2\text{)}\text{4-OH, and -(CH}_2\text{)}\text{4-CN;} \]

7. A compound of claim 1 wherein:

15

\[ A \text{ is a six member aromatic or heteroaromatic ring} \]
\[ \text{selected from the group consisting of:} \]

\[ R^3 \]

and

\[ R^2 \]

20

\[ B \text{ is an aromatic or heteroaromatic ring selected from the group consisting of:} \]

\[ \text{and} \]

\[ R^2 \text{ is } H, \text{ I, } R^4, \text{ -C=CH, } \text{ -OR}^4, \text{ -NR}^6\text{R}^6\text{a, -CO}_2\text{R}^4, \text{ or -CH}_2\text{)}\text{nNR}^6\text{COR}^4; \]
R³ is H;

Het-1 and Het-2 are independently

\( \text{H}_3\text{C} \)

or

\( \text{X} \)

5

X is H, F, Cl, Br, or OR⁴;

R is selected from the group consisting of:

- H, 3-cyanobenzyl-, -(CH₂)₂-(Het-2), -(CH₂)₁-CO₂Et,
- -(CH₂)₃-CO₂Et, -(CH₂)⁴-OCOCH₃, -(CH₂)⁴-CNH₂,
- benzyl, -(CH₂)⁴-OH, and -(CH₂)⁴-CN;

8. A compound of claim 1 selected from the group consisting of:

(a) 4-[(4-Pyridinylmethyl)-4H-indeno[1,2-B]thiophene;
(b) 4-[(4-Pyridinylmethyl)-4H-indeno[1,2-B]thiophene-4-pentanenitrile Hydrobromide Hydrate;
(c) 4-[(4-Pyridinylmethyl)-4H-indeno[1,2-B]thiophene-4-acetic acid Ethyl Ester Hydrochloride;
(d) 4-[(4-Pyridinylmethyl)-4H-indeno[1,2-B]thiophene-4-butanol Acetate (Ester) Hydrochloride;
(e) 4-[(4-Pyridinylmethyl)-4H-indeno[1,2-B]thiophene-4-pentanamide Hydrochloride Hydrate;
(f) 2-Fluoro-4-[(4-pyridinylmethyl)-4H-indeno[1,2-B]thiophen-4-ylmethyl]-pyridine;
(g) 4-[(4-(Phenyl)-4H-indeno[1,2-B]thiophen-4-ylmethyl]-pyridine;
(h) 4-[(4-Pyridinylmethyl)-4H-indeno[1,2-B]thiophene-4-butanol;

(i) 4-[(4-Pyridinylmethyl)-4H-thieno[2',3':3,4]cyclopenta[1,2-B]pyridine;
(j) 4-[(2-Fluoro-4-pyridinyl)methyl]-4-[(4-pyridinylmethyl)-4H-thieno[3',2':4,5]cyclopenta[1,2-B]pyridine;
(k) 1,4-Dihydro-1-(phenylmethyl)-4,4-bis(4-pyridinylmethyl)-indenol[1,2-C]pyrazole; and
(l) 2,4-Dihydro-2-phenyl-4,4-bis(4-pyridinylmethyl)-pyrazolo[4,3-B]pyrrolizine.

(m) 9,9-Bis((2-fluoro-4-pyridinyl)methyl)-2-hydroxy-9H-fluorene;
(n) 5-(2-Fluoro-4-pyridinyl)methyl)-5-(4-pyridinylmethyl)-5H-indeno[1,2-b]pyridine;
(o) 5-(2-Fluoro-4-pyridinyl)methyl)-5-(4-pyridinylmethyl)-5H-indeno[2,1-b]pyridine;
(p) 10,10-Bis((2-fluoro-4-pyridinyl)methyl)-9(10H)-anthracene;
(q) 9-((2-Fluoro-4-pyridinyl)methyl)-9-(4-pyridinylmethyl)-9H-xanthene;
(r) 10-((2-Fluoro-4-pyridinyl)methyl)-10-(4-pyridinylmethyl)-9(10H)-anthracene;
(s) 9,9-Bis((2-fluoro-4-pyridinyl)methyl)-4-azaxanthene;
(t) 5,5-Bis((2-fluoro-4-pyridinyl)methyl)-5H-indeno[1,2-b]pyridine;
(u) 4,4-Bis((2-fluoro-4-pyridinyl)methyl)-4H-thieno[3',2':4,5]cyclopenta[1,2-b]pyridine;
(v) 9-((2-Fluoro-4-pyridinyl)methyl)-9-(4-pyridinylmethyl)-4-azaxanthene;
(w) 9,9-Bis((2-fluoro-4-pyridinyl)methyl)-2-methoxyfluorene;
(x) 9,9-Bis((2-fluoro-4-pyridinyl)methyl)-7-methoxy-4-azaxanthene;
(y) 10,10-Bis((2-fluoro-4-pyridinyl)methyl)-3-hydroxy-9(10H)-anthracenone;
(z) 10,10-Bis((2-fluoro-4-pyridinyl)methyl)-2,6-dimethoxy-9(10H)-anthracenone;
(aa) 9,9-Bis((2-fluoro-4-pyridinyl)methyl)-cyclopenta[1,2-b:3,4-b']dipyridine;
(bb) 5,5-Bis((2-fluoro-4-pyridinyl)methyl)-2-phenyl-5H-indeno[1,2-d]pyrimidine;
(cc) 10,10-Bis((2-fluoro-4-pyridinyl)methyl)-3-methoxy-9(10H)-anthracenone;
(dd) 9,9-Bis((2-fluoro-4-pyridinyl)methyl)-9H-indeno-[2,1-b]pyridine;
(ee) 5,5-Bis((2-fluoro-4-pyridinyl)methyl)-7-(ethyl)-5H-indeno-[1,2-b]pyridine;
(ff) 9,9-Bis((2-fluoro-4-pyridinyl)methyl)-9H-indeno-[1,2-b]pyrazine;
10  (gg) 5,5-Bis((2-fluoro-4-pyridinyl)methyl)-5H-indeno-[1,2-d]pyrimidine;
(hh) 5,5-Bis((2-bromo-4-pyridinyl)methyl)-5H-indeno-[1,2-b]pyridine;
(ii) 9,9-Bis((2-fluoro-4-pyridinyl)methyl)-2-((N-methylamino)methyl)fluorene;
(jj) 9,9-Bis((2-fluoro-4-pyridinyl)methyl)-2-((N-methyl-N-methoxycarbonylamino)methyl)fluorene;
(kk) 9,9-Bis((2-fluoro-4-pyridinyl)methyl)-2-((N-methyl-N-acetylamino)methyl)fluorene;
20  (ll) 10,10-Bis((2-bromo-4-pyridinyl)methyl)-9(10H)-anthracenone;
(mm) 5,5-Bis((2-chloro-4-pyridinyl)methyl)-5H-indeno-[1,2-b]pyridine;
(nn) 5,5-Bis((2-fluoro-4-pyridinyl)methyl)-2-methyl-5H-indeno-[1,2-d]pyrimidine;
25  (oo) 5,5-Bis((2-methoxy-4-pyridinyl)methyl)-5H-indeno-[1,2-b]pyridine;
(pp) 5,5-Bis((2-fluoro-4-pyridinyl)methyl)-7-(ethyl)-5H-indeno-[1,2-b]pyridine;
30  (qq) 5,5-Bis((2-chloro-6-methyl-4-pyridinyl)methyl)-5H-indeno-[1,2-b]pyridine;
(rr) 5,5-Bis((2-methyl-4-pyridinyl)methyl)-5H-indeno-[1,2-b]pyridine;
(ss) 5,5-Bis((2-fluoro-4-pyridinyl)methyl)-7-(iodo)-5H-indeno-[1,2-b]pyridine;
(tt) 9,9-Bis((2-fluoro-4-pyridinyl)methyl)-9H-fluorene-1-carboxylic acid, methyl ester;
(uu) 9-((2-Fluoro-4-pyridinyl)methyl)-9-(4-pyridinylmethyl)-9H-fluorene-1-carboxylic acid, methyl ester, racemic;
(vv) 9,9-Bis((2-fluoro-4-pyridinyl)methyl)-9H-fluoren-1-amine;
(ww) 5,5-Bis((2-fluoro-4-pyridinyl)methyl)-5H-cyclopenta[2,1-b:3,4-b']dipyr dine;
(xx) 5-((2-Fluoro-4-pyridinyl)methyl)-5-(4-pyridinylmethyl)-5H-cyclopenta[2,1-b:3,4-b']dipyridine-4-carboxylic acid, methyl ester, dihydrochloride salt (racemic);
(yy) 5-((2-Fluoro-4-pyridinyl)methyl)-5-(4-pyridinylmethyl)-5H-cyclopenta[2,1-b:3,4-b']dipyr dine-4-carboxylic acid, methyl ester, hydrochloride salt, (-)-isomer;
(zz) 5-((2-Fluoro-4-pyridinyl)methyl)-5-(4-pyridinylmethyl)-5H-cyclopenta[2,1-b:3,4-b']dipyr dine-4-carboxylic acid, methyl ester, hydrochloride salt, (+)-isomer;
(ab) 5,5-Bis((6-fluoro-3-pyridinyl)methyl)-5H-cyclopenta[2,1-b:3,4-b']dipyr dine;
(ac) 5-((6-Fluoro-2-pyridinyl)methyl)-5-(4-pyridinylmethyl)-5H-cyclopenta[2,1-b:3,4-b']dipyr dine;
(ad) 5,5-Bis((6-fluoro-2-pyridinyl)methyl)-5H-cyclopenta[2,1-b:3,4-b']dipyr dine;
(ae) 5,5-Bis((3-methyl-4-pyridinyl)methyl)-5H-cyclopenta[2,1-b:3,4-b']dipyr dine, trihydrochloride salt;
(af) 2-Fluoro-4-((9-(4-pyridinylmethyl)-9H-fluoren-9-yl)methyl)pyridine, hydrochloride salt;
(ag) 5-((2-Fluoro-4-pyridinyl)methyl)-5-(4-pyridinylmethyl)-5H-cyclopenta[2,1-b:3,4-b']dipyr dine;
(ah) 5,5-Bis((2-fluoro-4-pyridinyl)methyl)thioxanthene-10,10-dioxide;
(ai) 5,5-Bis((2-fluoro-4-pyridinyl)methyl)thioxanthene-10-oxide;
(aj) 2,6-Dimethyl-4-((9-(4-pyridinylmethyl)-9H-fluoren-9-yl)methyl)pyridine, dihydrochloride salt;
(ak) 5-((2,6-Dimethyl-4-pyridinyl)methyl)-5-(4-pyridinylmethyl)-5H-cyclopenta[2,1-b:3,4-b']dipyridine;
(al) 5,5-Bis((2,6-dimethyl-4-pyridinyl)methyl)-5H-cyclopenta[2,1-b:3,4-b']dipyridine, E-2-butendiaote salt.

9. A pharmaceutical composition comprising a suitable pharmaceutical carrier and a therapeutically effective amount of a compound of claim 1.

10. A pharmaceutical composition comprising a suitable pharmaceutical carrier and a therapeutically effective amount of a compound of claim 2.

11. A pharmaceutical composition comprising a suitable pharmaceutical carrier and a therapeutically effective amount of a compound of claim 3.


13. A pharmaceutical composition comprising a suitable pharmaceutical carrier and a therapeutically effective amount of a compound of claim 5.

15. A pharmaceutical composition comprising a suitable pharmaceutical carrier and a therapeutically effective amount of a compound of claim 7.

16. A pharmaceutical composition comprising a suitable pharmaceutical carrier and a therapeutically effective amount of a compound of claim 8.

17. A method for the treatment of cognitive or neurological dysfunction comprising administering to a host in need of such treatment a therapeutically effective amount of a compound of claims 1-8.
### A. CLASSIFICATION OF SUBJECT MATTER

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### B. FIELDS SEARCHED

#### Minimum documentation searched (classification system followed by classification symbols)

- IPC 5 C07D A61K

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

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

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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### Date of the actual completion of the international search

25 July 1994

### Date of mailing of the international search report

28.07.94

### Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer
Voyiazoglou, D
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 5 (C07D487/04, 209:00, 209:00), (C07D487/14, 231:00, 209:00, 209:00),
(C07D491/04, 311:00, 221:00)

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)

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

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

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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NL - 2280 HV Rijswijk
Tel: (+31-70) 340-2040, Tx: 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer: Voyazoglu, D
## INTERNATIONAL SEARCH REPORT

### 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. □ Claims Nos.:  
   because they relate to subject matter not required to be searched by this Authority, namely:  
   Although claim 17 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. □ Claims Nos.:  
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

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.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)
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