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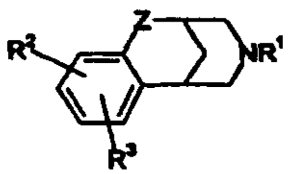
(54) Title: ARYL FUSED AZAPOLYCYCLIC COMPOUNDS



(I)

(57) Abstract

Compounds of formula (I) and their pharmaceutically acceptable salts, wherein R^1, R^2, R^3 and Z are defined as in the specification, intermediates in the synthesis of such compounds, pharmaceutical compositions containing such compounds and methods of using such compounds in the treatment of neurological and psychological disorders are claimed.

ARYL FUSED AZAPOLYCYCLIC COMPOUNDS

Background of the Invention

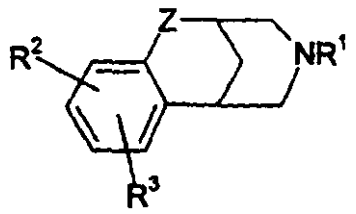
This invention relates to aryl fused azapolycyclic compounds, as defined more specifically by formula I below. Compounds of formula I bind to neuronal nicotinic acetylcholine specific receptor sites and are useful in modulating cholinergic function. Such compounds are useful in the treatment of inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyiotropic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supramuscular palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbituates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder, psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome.

The compounds of this invention may also be used in combination with an antidepressant such as, for example, a tricyclic antidepressant or a serotonin reuptake inhibiting antidepressant (SRI), in order to treat both the cognitive decline and depression associated with AD, PD, stroke, Huntington's Chorea or traumatic brain injury (TBI); in combination with muscarinic agonists in order to stimulate both central muscarinic and nicotinic receptors for the treatment, for example, of ALS, cognitive dysfunction, age related cognitive decline, AD, PD, stroke, Huntington's Chorea and TBI; in combination with neurotrophic factors such as NGF in order to maximize cholinergic enhancement for the treatment, for example, of ALS, cognitive dysfunction, age related cognitive decline, AD, PD stroke, Huntington's Chorea and TBI; or in combination with agents that slow or arrest AD such as cognition enhancers, amyloid aggregation inhibitors, secretase inhibitors, tau kinase inhibitors, neuronal antiinflammatory agents and estrogen-like therapy.

Other compounds that bind to neuronal nicotinic receptor sites are referred to in United States Patent Application 08/963,852, which was filed on November 4, 1997, and in United States Provisional Patent Application 60/070,245, which was filed on December 31, 1997. Both of the foregoing applications are owned in common with the present application, and both are incorporated herein by reference in their entireties.

Summary of the Invention

This invention relates to aryl fused azapolycyclic compounds of the formula



(I)

wherein Z is CH_2, C(=O) or CF_2;

R^1 is hydrogen, $(C_1$-$C_6)$alkyl, unconjugated $(C_3$-$C_6)$alkenyl, benzyl, $XC(=O)R^{13}$ or $-CH_2CH_2$-O-$(C_1$-$C_4)$alkyl;

R^2 and R^3 are selected independently, from hydrogen, $(C_2$-$C_6)$ alkenyl, $(C_2$-$C_6)$ alkynyl, hydroxy, nitro, amino, halo, cyano, $-SO_q(C_1$-$C_6)$alkyl wherein q is zero, one or two, $(C_1$-$C_6)$alkylamino, $[(C_1$-$C_6)$alkyl$]_2$amino, CO_2R^4, $CONR^5R^6$, $SO_2NR^7R^8$, $C(=O)R^{13}$, $XC(=O)R^{13}$, aryl-$(C_0$-$C_3)$ alkyl or aryl-$(C_0$-$C_3)$alkyl-O- wherein said aryl is selected from phenyl and naphthyl, heteroaryl-$(C_0$-$C_3)$alkyl or heteroaryl-$(C_0$-$C_3)$alkyl-O-, wherein said heteroaryl is selected from five to seven membered aromatic rings containing from one to four heteroatoms selected from oxygen, nitrogen and sulfur, and $X^2(C_0$-$C_6)$alkoxy-$(C_0$-$C_6)$alkyl, wherein X^2 is absent or X^2 is $(C_1$-$C_6)$alkylamino or $[(C_1$-$C_6)$alkyl$]_2$amino, and wherein the $(C_0$-$C_6)$alkoxy-$(C_0$-$C_6)$alkyl moiety of said $X^2(C_0$-$C_6)$alkoxy-$(C_0$-$C_6)$alkyl contains at least one carbon atom, and wherein from one to three of the carbon atoms of said $(C_0$-$C_6)$alkoxy-$(C_0$-$C_6)$alkyl moiety may optionally be replaced by an oxygen, nitrogen or sulfur atom, with the proviso that any two such heteroatoms must be separated by at least two carbon atoms, and wherein any of the alkyl moieties of said $(C_0$-$C_6)$alkoxy-$(C_0$-$C_6)$alkyl may be optionally substituted with from two to seven fluorine atoms, and wherein one of the carbon atoms of each of the alkyl moieties of said aryl-$(C_0$-$C_3)$alkyl and said heteroaryl-$(C_0$-$C_3)$alkyl may optionally be replaced by an oxygen, nitrogen or sulfur atom, and wherein each of the foregoing aryl and heteroaryl groups may optionally be substituted with one or more substituents, preferably from zero to two substituents, independently selected from $(C_1$-$C_6)$ alkyl optionally substituted with from one to seven fluorine atoms, $(C_1$-$C_6)$ alkoxy optionally substituted with from two to seven fluorine atoms, halo (e.g., chloro, fluoro, bromo or iodo), hydroxy, nitro, cyano, amino, $(C_1$-$C_6)$ alkylamino and $[(C_1$-$C_6)$ alkyl$]_2$ amino;

or R^2 and R^3, together with the carbons to which they are attached, form a four to seven membered monocyclic, or a ten to fourteen membered bicyclic, carbocyclic ring that can be saturated or unsaturated, wherein from one to three of the nonfused carbon atoms of said monocyclic rings, and from one to five of the carbon atoms of said bicyclic rings that are not part of the benzo ring shown in formula I, may optionally and independently be replaced by a nitrogen, oxygen or sulfur, and wherein said monocyclic and bicyclic rings may optionally be substituted with one or more substituents, preferably from zero to two substituents for the monocyclic rings and from zero to three substituents for the bicyclic rings, that are selected, independently, from $(C_0$-$C_6)$

alkoxy-(C_0-C_6)alkyl-, wherein the total number of carbon atoms does not exceed six and wherein any of the alkyl moieties may optionally be substituted with from one to seven fluorine atoms; nitro, oxo, cyano, halo, hydroxy, amino, (C_1 -C_6)alkylamino, [(C_1 -C_6) alkyl]$_2$amino, phenyl and monocyclic heteroaryl wherein said heteroaryl is defined as in the definition of R^2 and R^3 above;

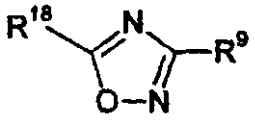
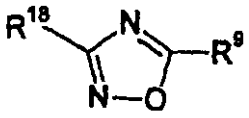
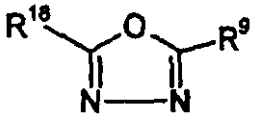
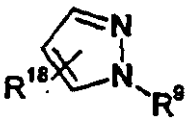
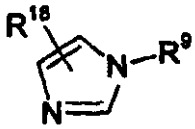
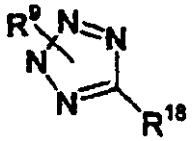
each R^4, R^5, R^6, R^7, R^8 and R^{13} is selected, independently, from hydrogen and (C_1 -C_6) alkyl, or R^5 and R^6, or R^7 and R^8 together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, piperizine, -N-(C_1-C_6)alkylpiperizine or thiomorpholine ring, or a thiomorpholine ring wherein the ring sulfur is replaced with a sulfoxide or sulfone; and

each X is, independently, (C_1-C_6)alkylene;

with the proviso that: (a) at least one of R^1, R^2 and R^3 must be the other than hydrogen, (b) when R^2 and R^3 are hydrogen, R^1 cannot be methyl or hydrogen; and (c) no fluorine atom in any of the fluoro substituted alkyl or alkoxy moieties of R^2 and R^3 can be attached to a carbon that is attached to a heteroatom;

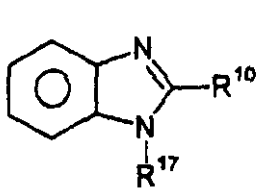
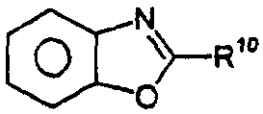
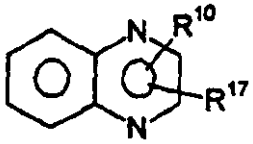
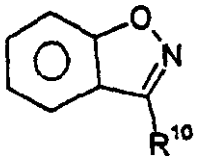
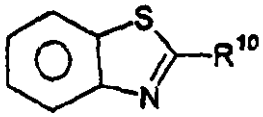
and the pharmaceutically acceptable salts of such compounds.

Examples of heteroaryl groups that each of R^2 and R^3 can be are the following: thienyl, oxazoyl, isoxazolyl, pyridyl, pyrimidyl, thiazolyl, tetrazolyl, isothiazolyl, triazolyl, imidazolyl, tetrazolyl, pyrroyl and the following groups:

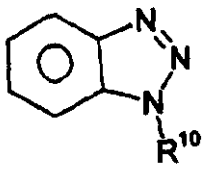
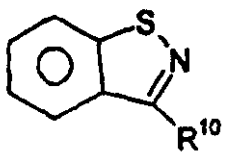
wherein one of R^9 and R^{18} is hydrogen or (C_1 -C_6) alkyl, and the other is a bond to the benzo ring of formula I.

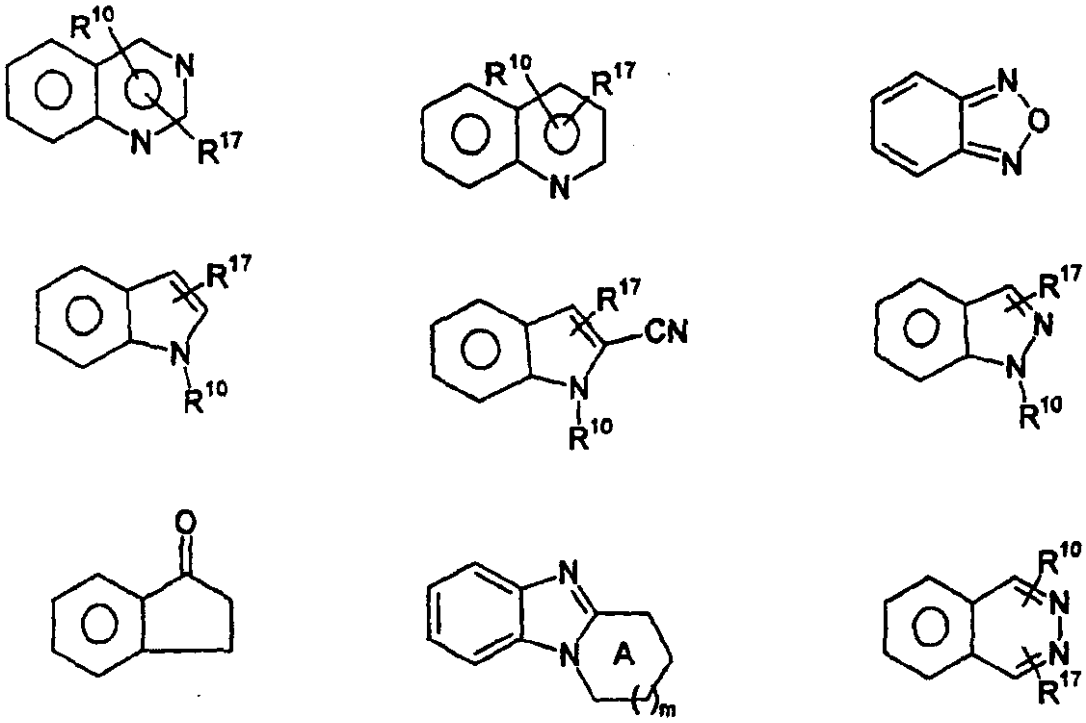
Examples of compounds of this invention are compounds of the formula I, and their pharmaceutically acceptable salts, wherein R^2 and R^3, together with the benzo ring of formula I, form a bicyclic ring system selected from the following:

wherein R^{10} and R^{17} are selected, independently, from (C_0 -C_6) alkoxy-(C_0-C_6)alkyl wherein the total number of carbon atoms does not exceed six and wherein any of the alkyl moieties may optionally be substituted with from one to seven fluorine atoms, (C_1 -C_6) alkoxy optionally substituted with from one to seven fluorine atoms, nitro, cyano, halo, amino, (C_1 -C_6)alkylamino, [(C_1 -C_6) alkyl]$_2$amino, phenyl and monocyclic heteroaryl wherein said heteroaryl is defined as in the definition of R^2 and R^3 above;

Other embodiments of this invention relate to compounds of the formula I, and their pharmaceutically acceptable salts, wherein R^2 and R^3, together with the benzo ring of formula I, form a bicyclic or tricyclic ring system selected from the following:



wherein R^{10} and R^{17} are defined as above and m is zero, one or two, and wherein one of the carbon atoms of ring A can optionally be replaced with oxygen or -N(C_1-C_6)alkyl.

Other embodiments of this invention relate to compounds of the formula I, and their pharmaceutically acceptable salts, wherein neither R^2 nor R^3 is attached to the benzo ring of formula I via an oxygen atom.

Other embodiments of this invention relate to compounds of the formula I wherein R^1 is not methyl.

Examples of specific compounds of the formula I are the following:

11-Azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-5-carbonitrile;

11-Azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-4-carbonitrile;

1-[11-Azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-yl]-1-ethanone;

1-[11-Azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-yl]-1-propanone;

4-Fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-5-carbonitrile;

5-Fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-4-carbonitrile;

1-[11-Azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-4-yl]-1-ethanone;

1-[11-Azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-4-yl]-1-propanone;

6-Methyl-7-thia-5,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;

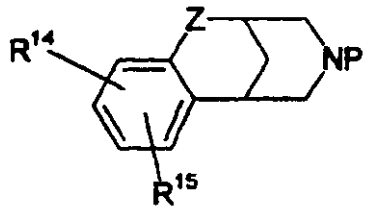
6-Methyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;

6,7-Dimethyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;

5,7,14-Triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
7-Methyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
5,11,18-Triazapentacyclo[14.3.1.$0^{2,14}$.$0^{4,12}$.$0^{6,11}$]icosa-2(14),3,5,12-tetraene;
7-Ethyl-6-methyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
6-Methyl-7-propyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
7-Ethyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
7-Butyl-6-methyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
7-Isobutyl-6-methyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
7-Butyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
7-Isobutyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
5,11,18-Triazapentacyclo[14.3.1.$0^{2,14}$.$0^{4,12}$.$0^{5,10}$]icosa-2(14),3,10,12-tetraene;
5,6-Dimethyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;
5-Ethyl-6-methyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;
5-Methyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;
5-Ethyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;
6-Methyl-5-propyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;
5-Isobutyl-6-methyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;
5-Propyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;
5-Isobutyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;
6-(Trifluoromethyl)-7-thia-5,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
5,8,15-Triazatetracyclo[11.3.1.$0^{2,11}$.$0^{4,9}$]heptadeca-2(11),3,5,7,9-pentaene;
7-Methyl-5,8,15-triazatetracyclo[11.3.1.$0^{2,11}$.$0^{4,9}$]heptadeca-2(11),3,5,7,9-pentaene;
6-Methyl-5,8,15-triazatetracyclo[11.3.1.$0^{2,11}$.$0^{4,9}$]heptadeca-2(11),3,5,7,9-pentaene;
6,7-Dimethyl-5,8,15-triazatetracyclo[11.3.1.$0^{2,11}$.$0^{4,9}$]heptadeca-2(11),3,5,7,9-pentaene;
7-Oxa-5,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
6-Methyl-7-oxa-5,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
6-Ethyl-7-oxa-5,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;

6-Propyl-7-oxa-5,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
5-Methyl-7-oxa-6,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
5-Oxa-7,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;
6-Methyl-5-oxa-7,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;
6-Ethyl-5-oxa-7,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;
6-Propyl-5-oxa-7,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;
7-Methyl-5-oxa-6,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;
4,5-Difluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene4-chloro-5-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;
5-Chloro-4-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;
4-(1-Ethynyl)-5-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;
5-(1-Ethynyl)-4-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene; and
4,5-Dichloro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene.

This invention also relates to compounds of the formula



(I)

wherein wherein Z is CH_2, C(=O) or CF_2; P is hydrogen, methyl, $COOR^{16}$ wherein R^{16} is allyl, 2,2,2-trichloroethyl or (C_1-C_6)alkyl; -C(=O)NR^5R^6 wherein R^5 and R^6 are defined as in formula I above; -C(=O)H, -C(=O)(C_1-C_6)alkyl wherein the alkyl moiety may optionally be substituted with from 1 to 3 halo atoms, preferably with from 1 to 3 fluoro or chloro atoms; benzyl or t-butoxycarbonyl (t-Boc); and R^{14} and R^{15} are selected, independently, from hydrogen, hydroxy, nitro, amino, -O(C_1-C_6)alkyl or halo; with the proviso that R^{14} and R^{15} can not both be hydrogen when P is hydrogen or methyl. Such compounds are useful as intermediates in the synthesis of compounds of the formula I.

Unless otherwise indicated, the term "halo", as used herein, includes fluoro, chloro, bromo and iodo.

Unless otherwise indicated, the term "alkyl", as used herein, includes straight, branched or cyclic, and may include straight and cyclic alkyl moieties as well as branched and cyclic moieties.

The term "alkoxy", as used herein, means "alkyl-O-", wherein "alkyl" is defined as above.

The term "alkylene, as used herein, means an alkyl radical having two available bonding sites (i.e., -alkyl-), wherein "alkyl" is defined as above.

Unless otherwise indicated, the term "one or more substituents", as used herein, refers to from one to the maximum number of substituents possible based on the number of available bonding sites.

The term "treatment", as used herein, refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such condition or disorder. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above.

The compounds of formula I may have optical centers and therefore may occur in different enantiomeric configurations. The invention includes all enantiomers, diastereomers, and other stereoisomers of such compounds of formula I, as well as racemic and other mixtures thereof.

The present invention also relates to all radiolabelled forms of the compounds of the formulae I. Preferred radiolabelled compounds of formula I are those wherein the radiolabels are selected from as ^{3}H, ^{11}C, ^{14}C, ^{18}F, ^{123}I and ^{125}I. Such radiolabelled compounds are useful as research and diagnostic tools in metabolism pharmacokinetics studies and in binding assays in both animals and man.

The present invention also relates to a pharmaceutical composition for use in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, including a human, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use and a pharmaceutically acceptable carrier.

The present invention also relates to a method for reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, including a human, comprising administering to said mammal an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use.

The present invention also relates to a method of treating a disorder or condition selected from inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyiotropic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supramuscular palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbituates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI), psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-

infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a mammal, comprising administering to a mammal in need of such treatment an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, that is effective in treating such disorder or condition.

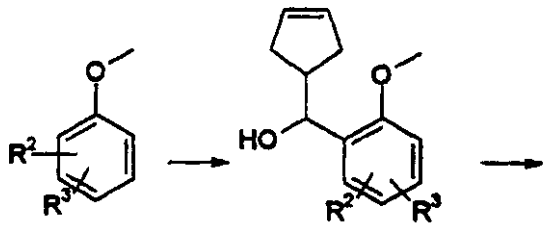
The present invention also relates to a pharmaceutical composition for treating a disorder or condition selected from inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amylotropic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supramuscular palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbituates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI), psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a mammal, comprising an amount of a compound of the formula I, or a pharmaceutically accepable salt thereof, and a pharmaceutically acceptable carrier.

This invention also relates to the pharmaceutically acceptable acid addition salts of the compounds of formula I. Examples of pharmaceutically acceptable acid addition salts of the compounds of formula I are the salts of hydrochloric acid, p-toluenesulfonic acid, fumaric acid, citric acid, succinic acid, salicylic acid, oxalic acid, hydrobromic acid, phosphoric acid, methanesulfonic acid, tartaric acid, malate, di-p-toluoyl tartaric acid, and mandelic acid.

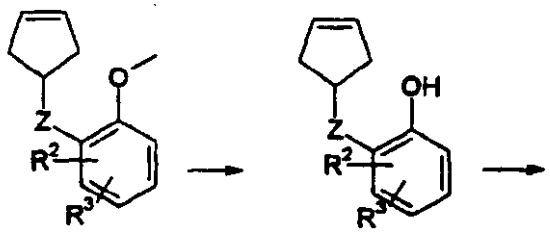
Detailed Description of the Invention

Except where otherwise stated, R^1 through R^{18}, m and P, and structural formula I in the reaction schemes and discussion that follow are defined as above.

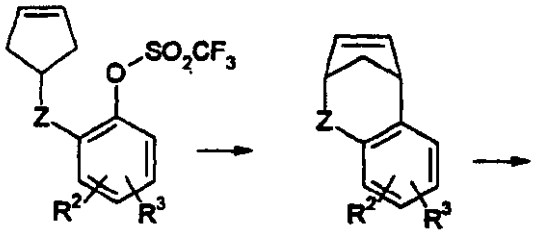
SCHEME 1



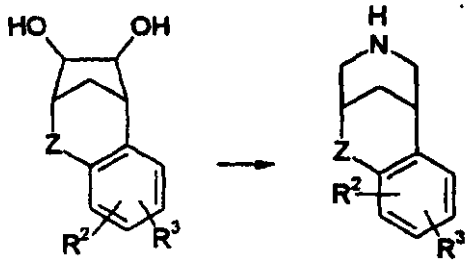
II III



IV V



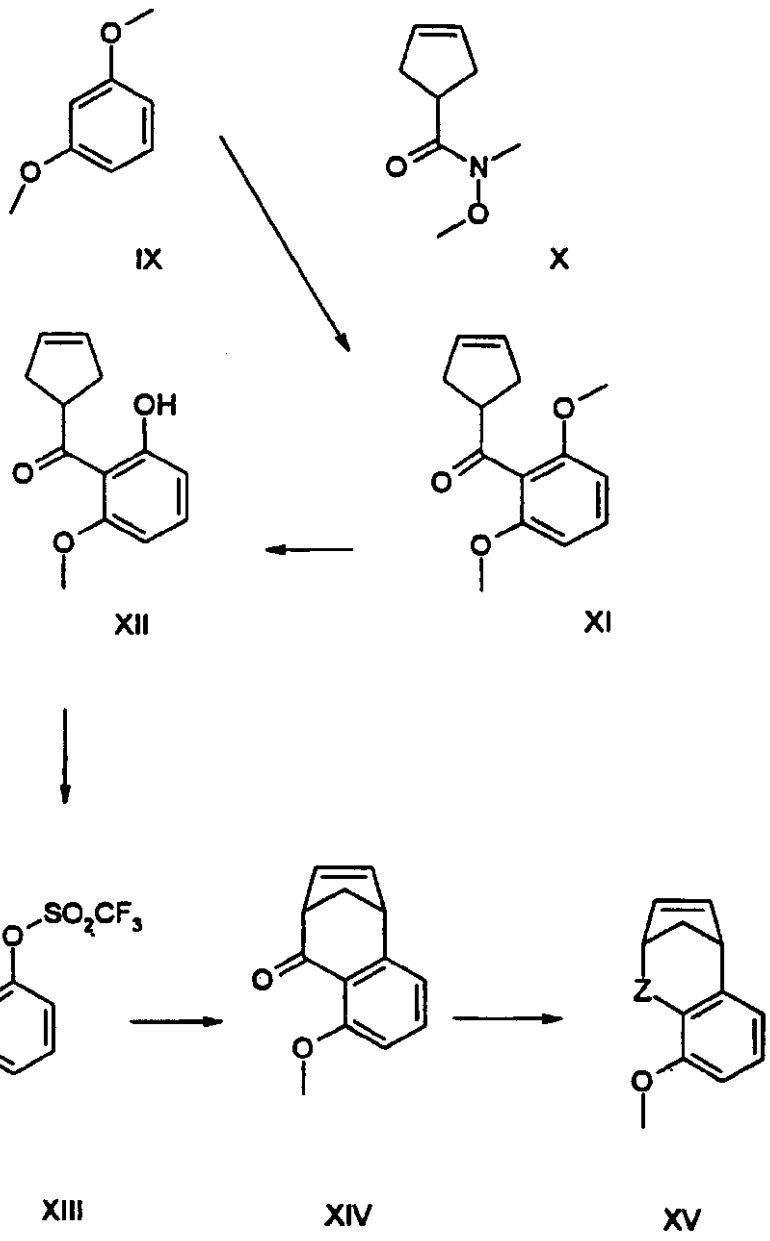
VI VII



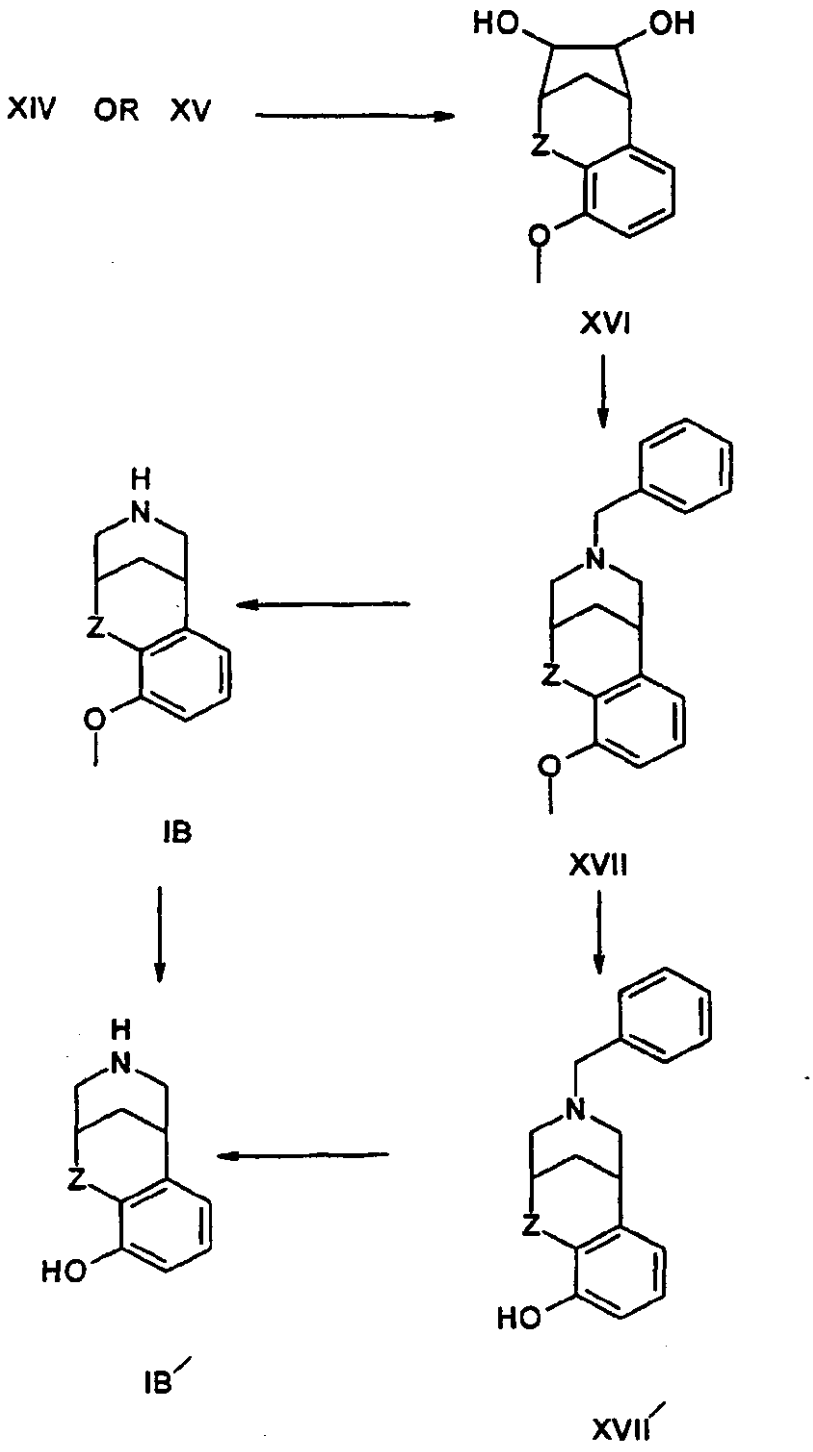
VIII IA

5

SCHEME 2



SCHEME 2 continued



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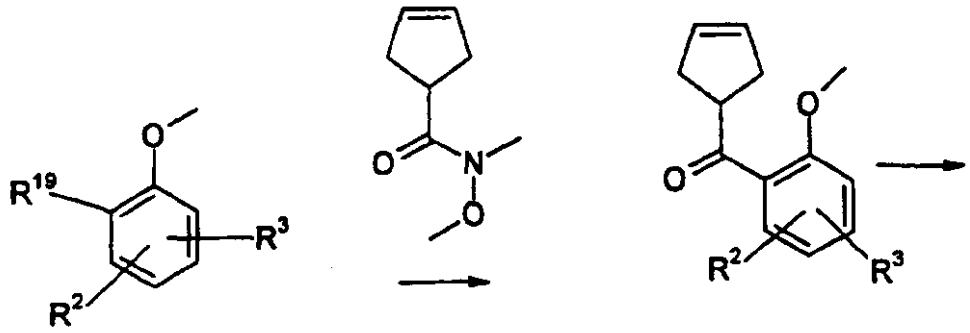
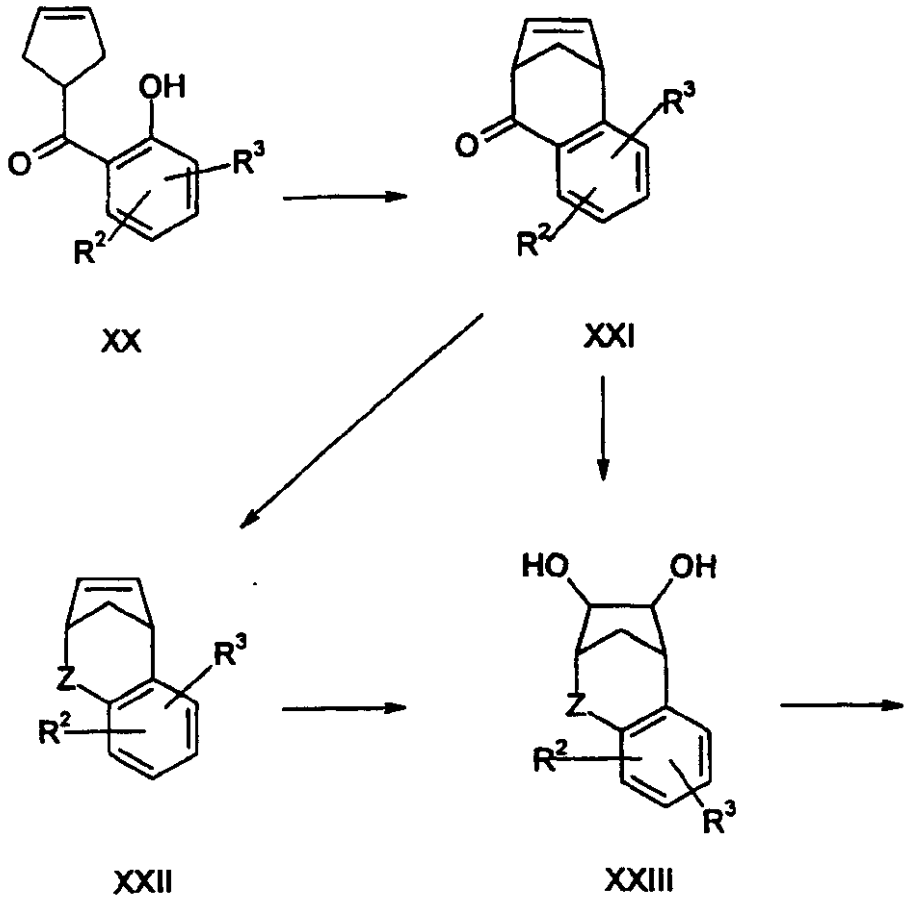
SCHEME 3



XVIII

XIX



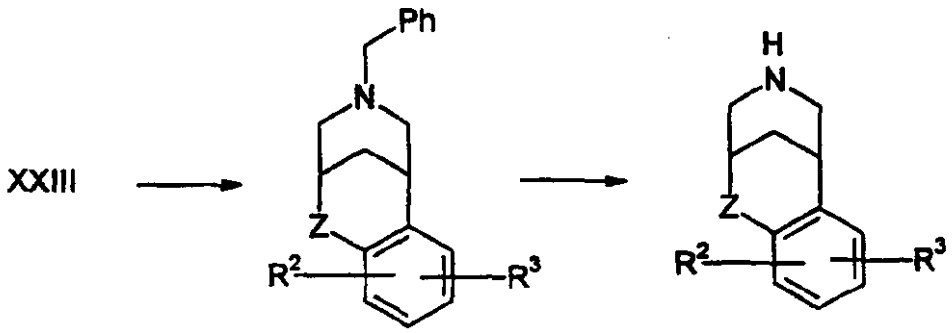
XX

XXI

XXII

XXIII

SCHEME 3 continued

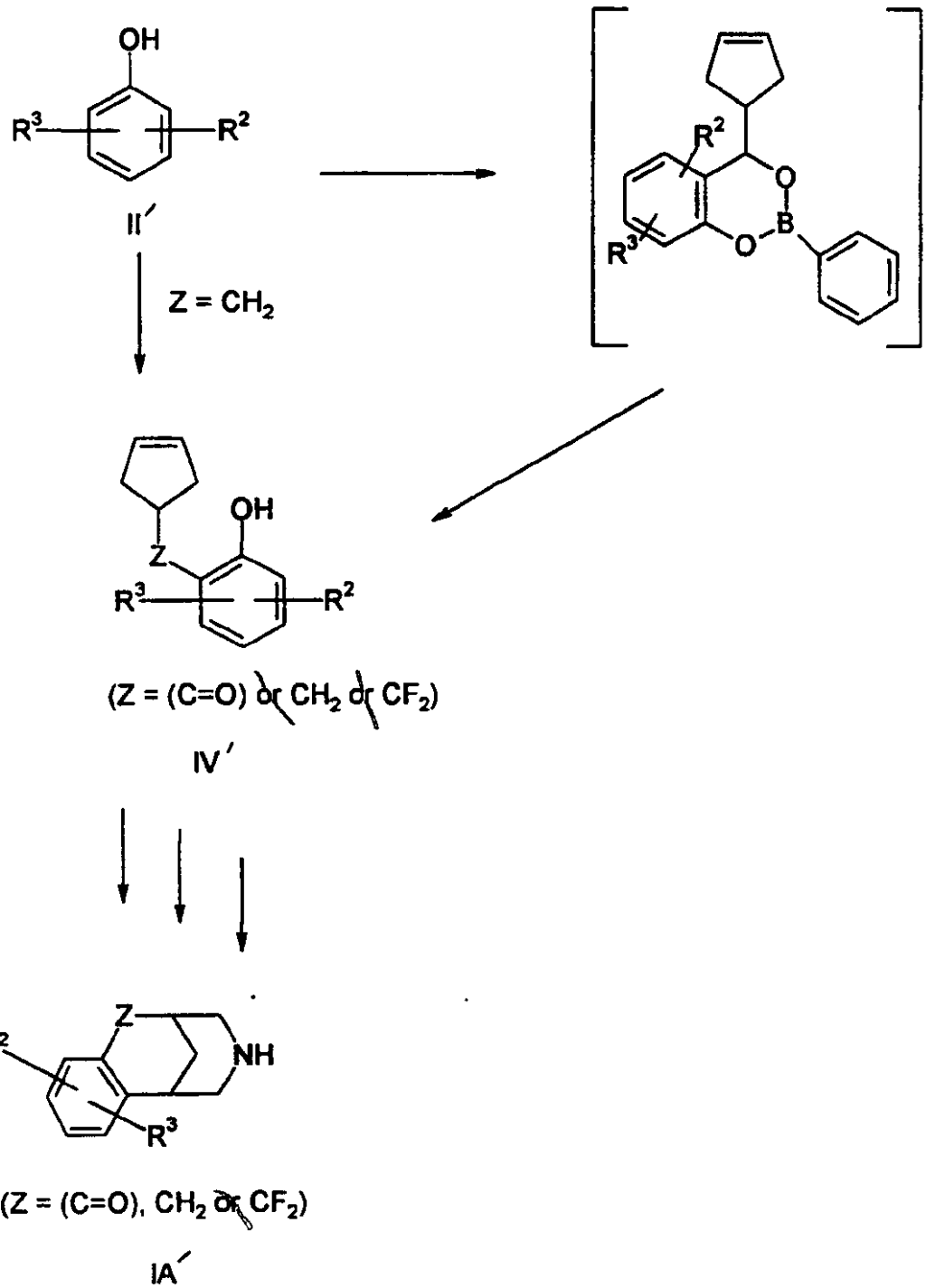


(Ph=phenyl)

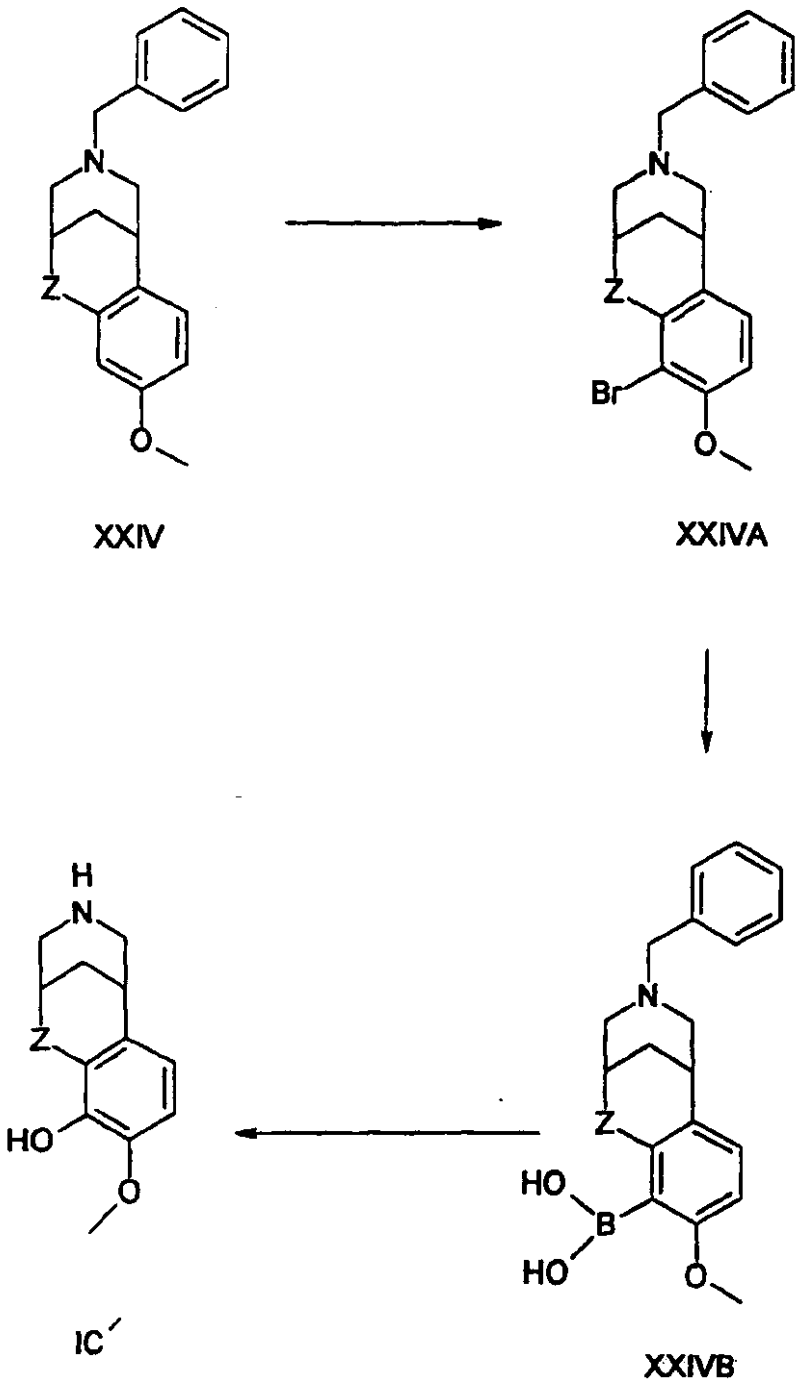
XXIV

IC

SCHEME 4


OH
R3
R2
II′
Z = CH2
R2
O
B
O
R3
OH
Z
R3
R2
(Z = (C=O) or CH2 or CF2)
IV′
Z
R2
NH
R3
(Z = (C=O), CH2 or CF2)
IA′

SCHEME 5

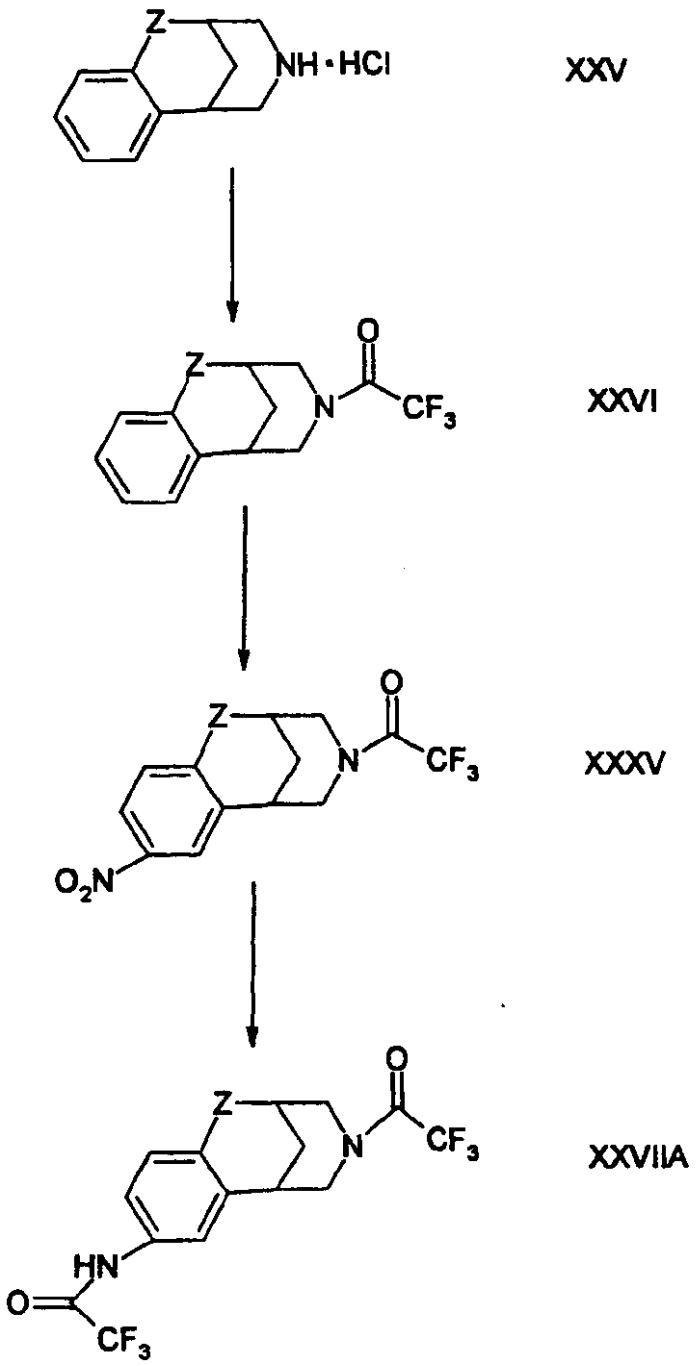


XXIV XXIVA

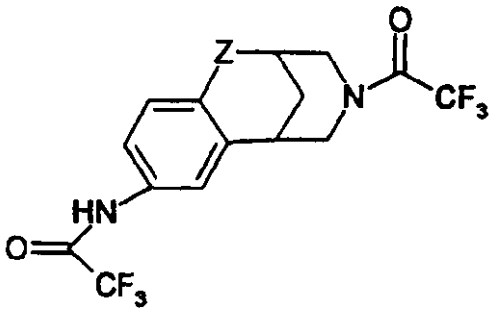
IC XXIVB

5

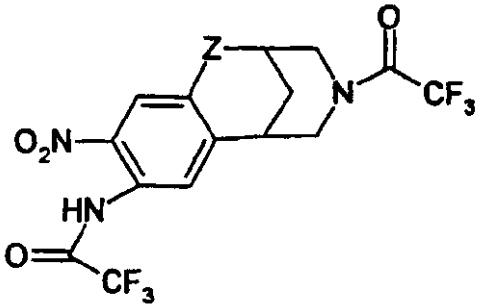
SCHEME 6



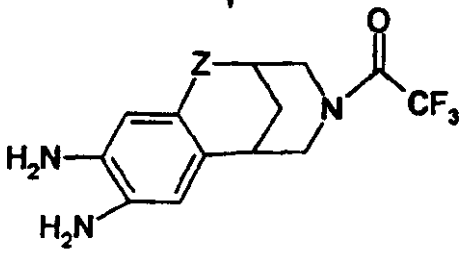
SCHEME 6 Continued



XXVIIA



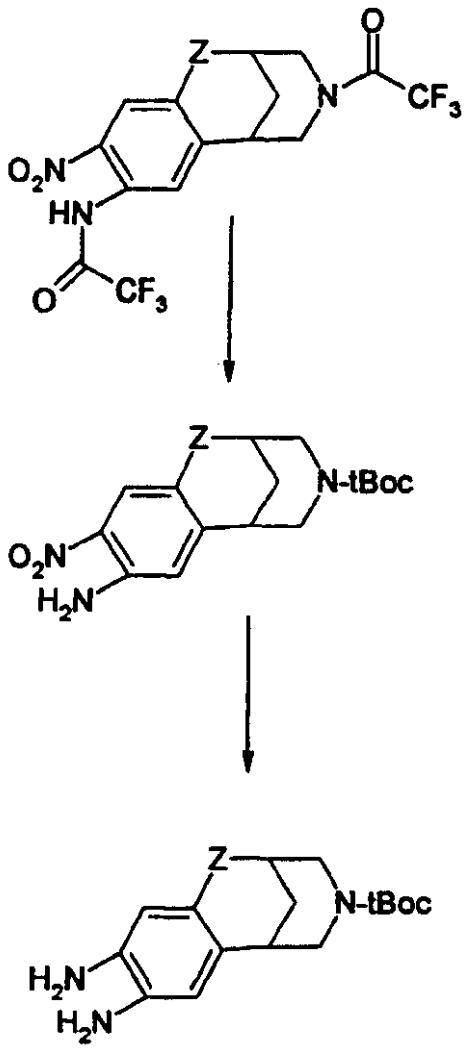
XXVIIA'



XXVIIB

5

SCHEME 7

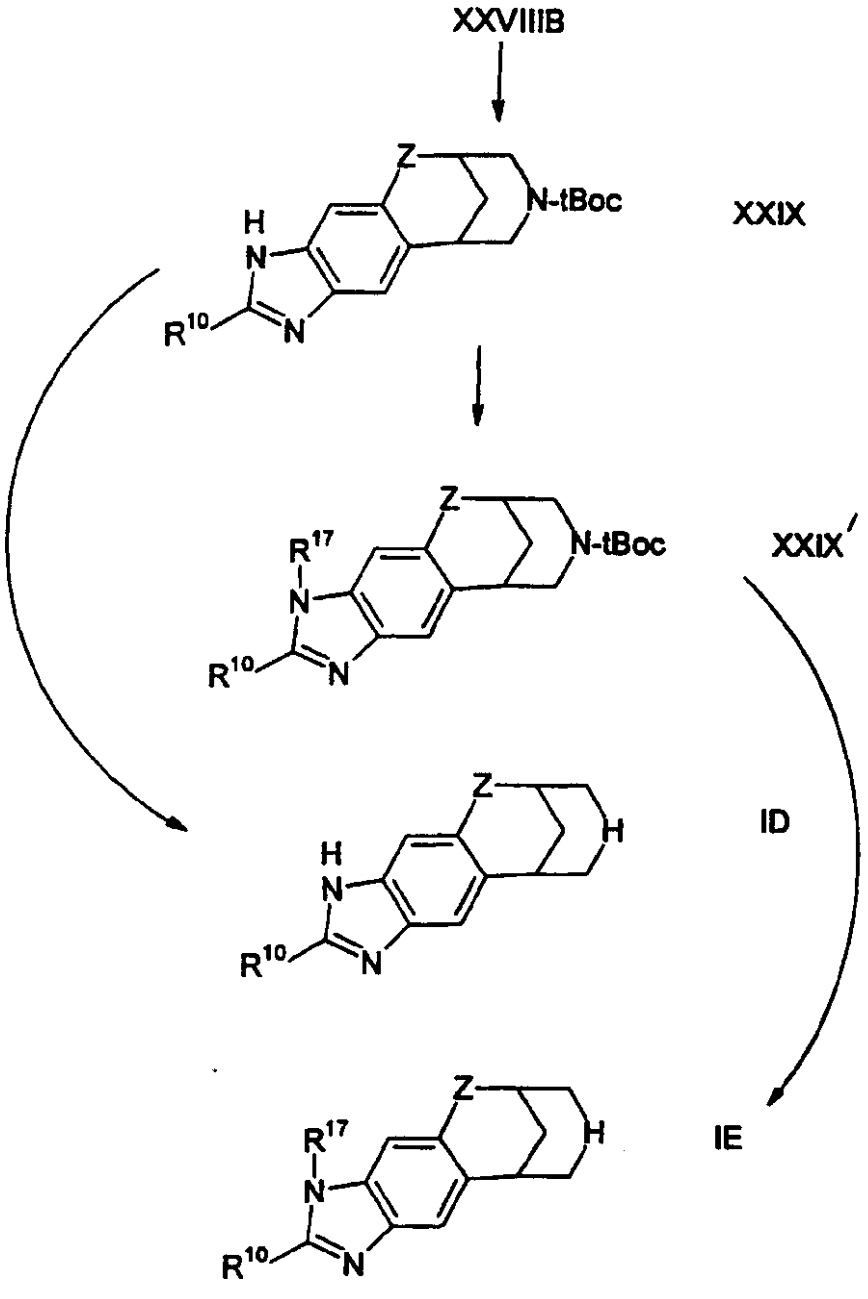


XXVIIA

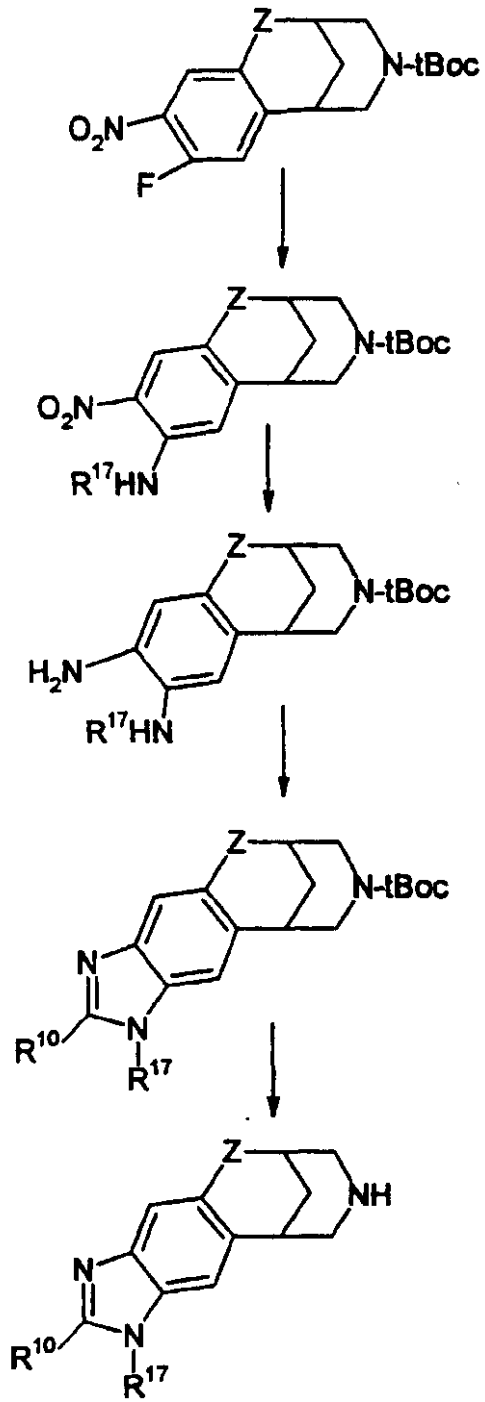
XXVIIIA

XXVIIIB

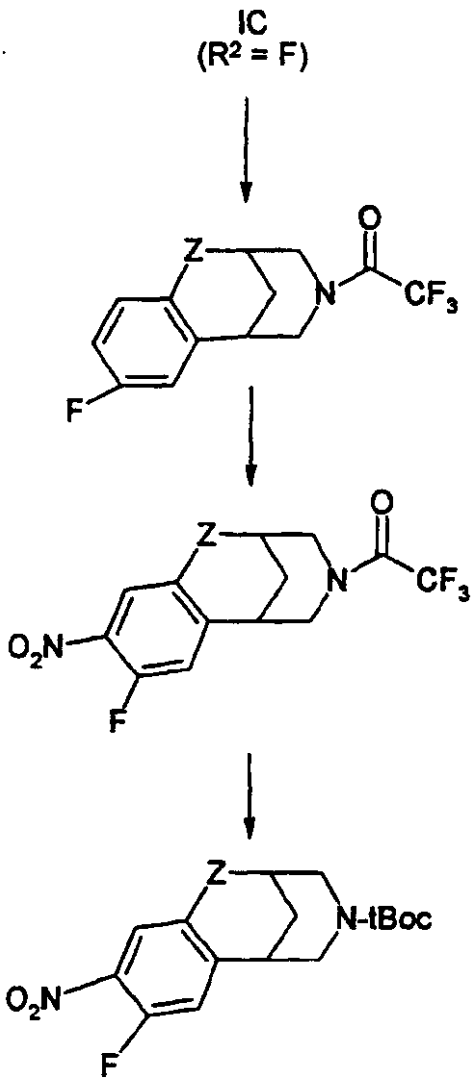
SCHEME 7 Continued



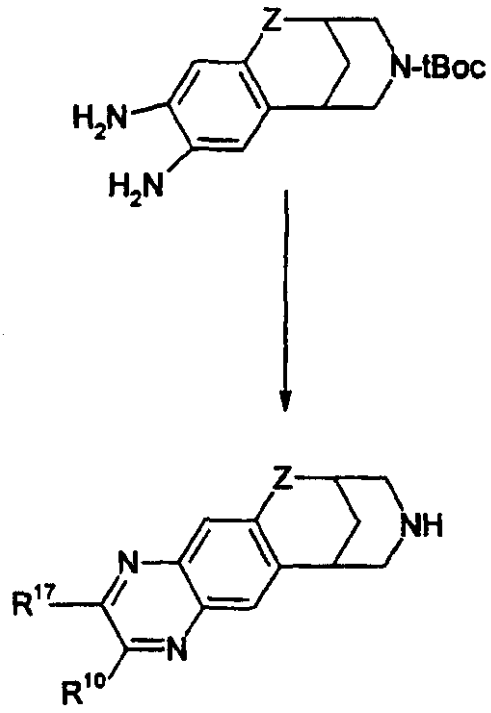
SCHEME 8


Z
N-tBoc
O_2N
F
XXVIIIA
Z
N-tBoc
O_2N
$R^{17}HN$
XXX
Z
N-tBoc
H_2N
$R^{17}HN$
XXXI
Z
N-tBoc
N
R^{10}
N
R^{17}
XXXII
Z
NH
N
R^{10}
N
R^{17}
IE

SCHEME 8A



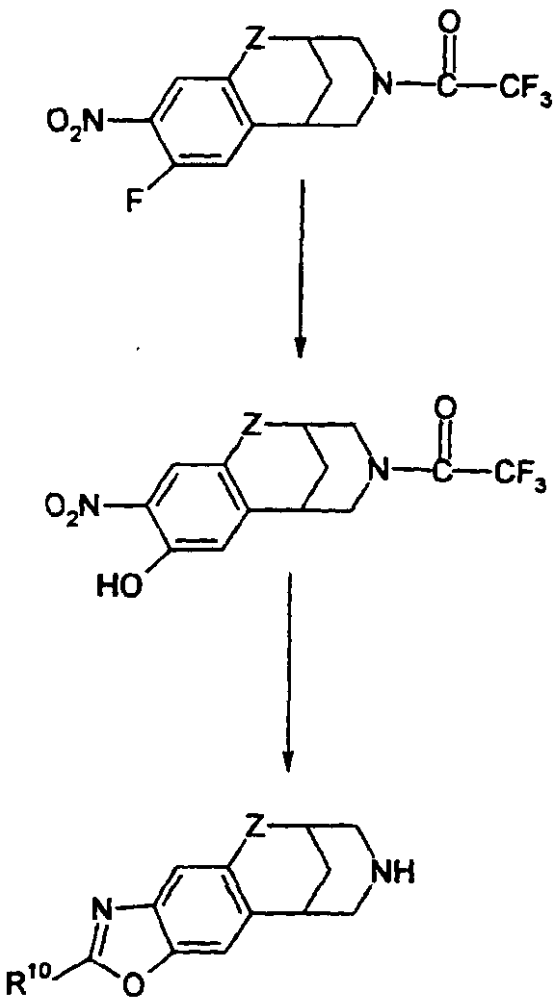
SCHEME 9



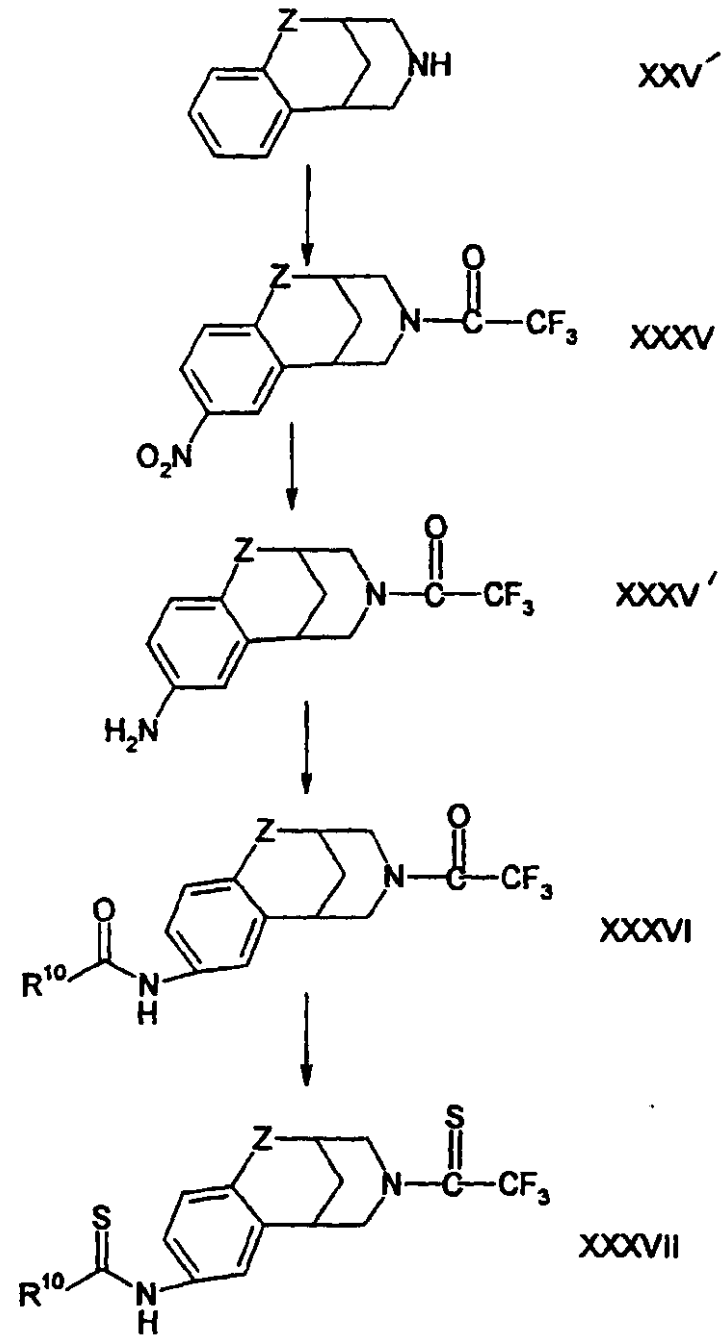
XXVIIIB

IF

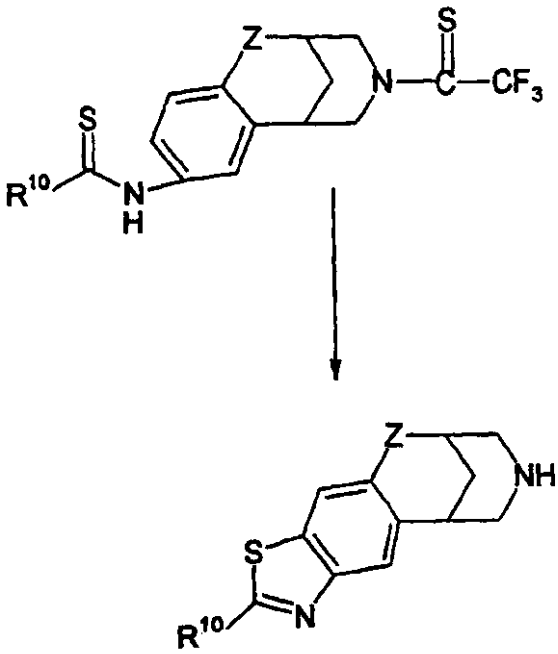
SCHEME 10



SCHEME 11



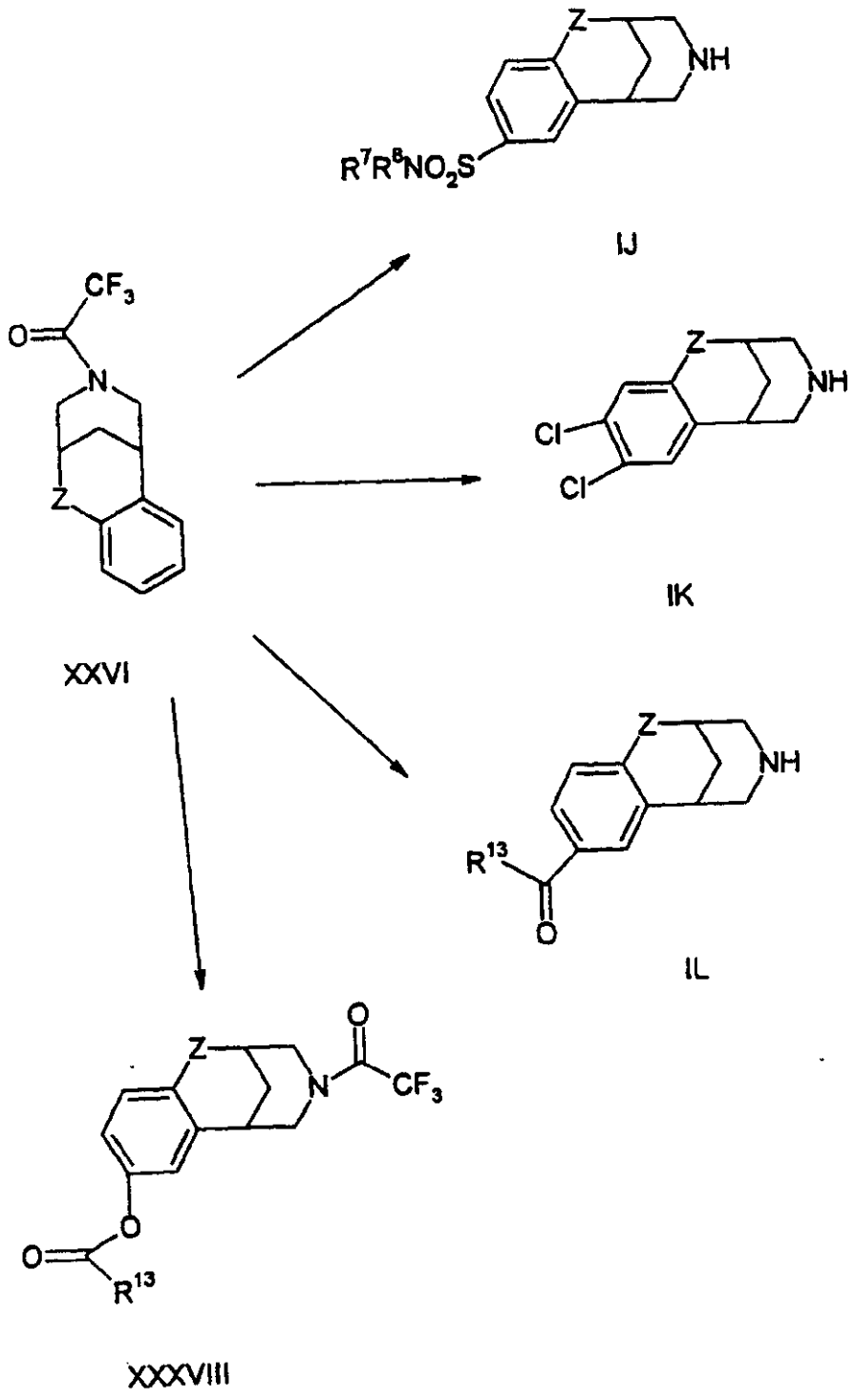
SCHEME 11 continued



XXXVII

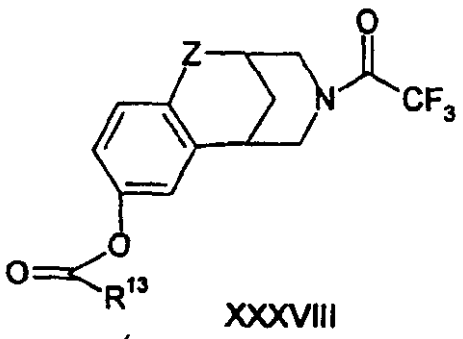
IH

SCHEME 12

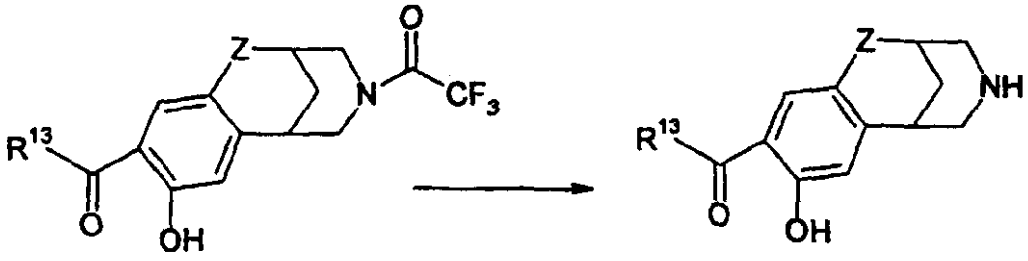

Z
NH
R7R8NO2S
IJ
CF3
O
N
Z
XXVI
Cl
Cl
IK
R13
O
IL
O
CF3
O
O
R13
XXXVIII

5

SCHEME 12 Continued

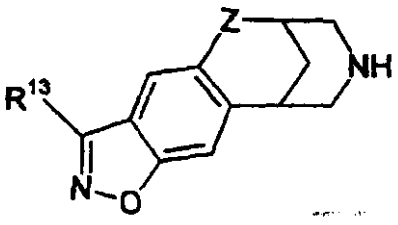


XXXVIII



XXXIX

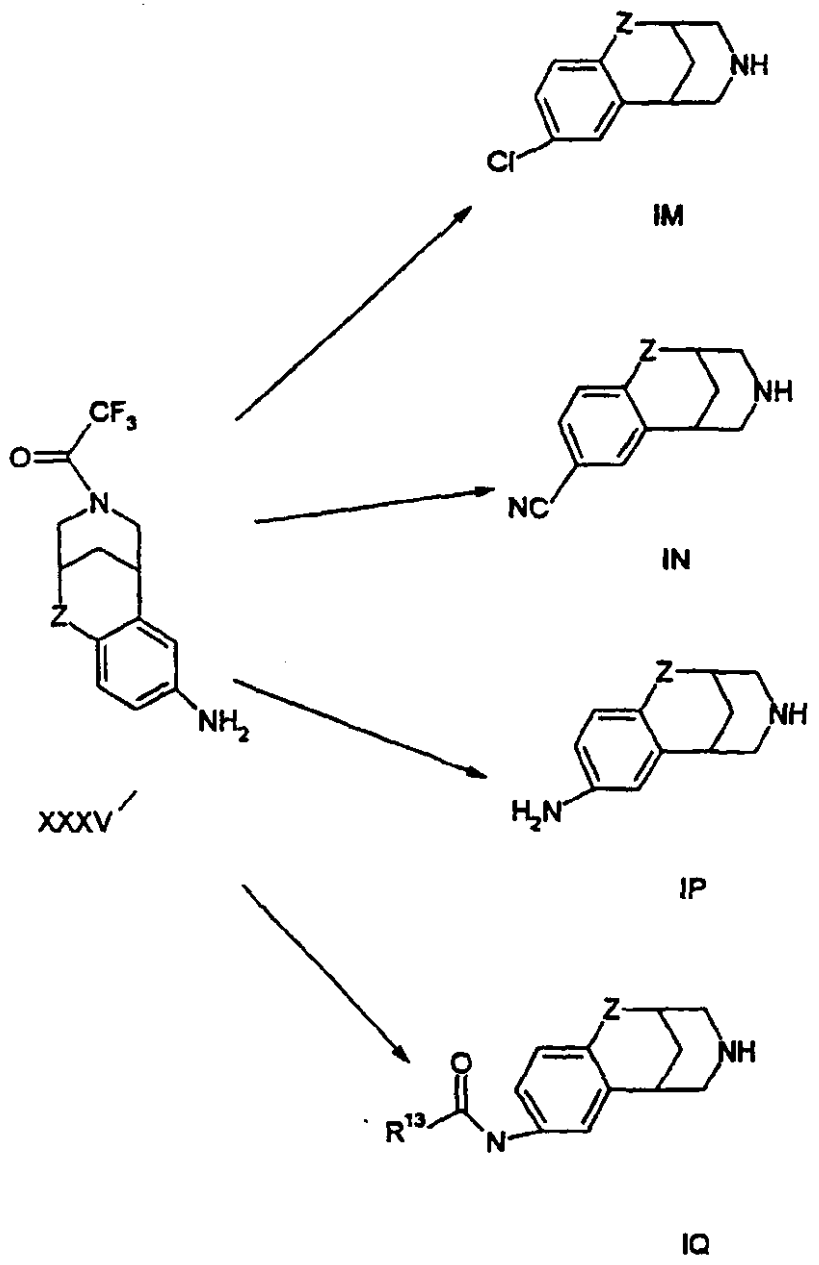
IS



IT

5

SCHEME 13



Scheme 1-13 illustrate methods of synthesizing compounds of the formula I. Schemes 1-4 illustrate such methods wherein the substituent groups R^2 and R^3 are attached prior to cyclization to form the tricyclic nucleus of formula I, which is represented by the free base of structural formula IA (Scheme 1) or IC (Scheme 3) wherein R^2 and R^3 are hydrogen. Schemes 5-13 illustrate methods of forming compounds of the formula I from starting materials that contain such nucleus.

Referring to Scheme 1, the starting material of formula II is converted to a compound of formula III by the following process. The starting material of formula II is reacted with approximately 1 equivalent of a strong base such as n-butyllithium in a solvent such as anhydrous THF, ether or methyl t-butyl ether, at a temperature from about -78°C to about -65°C. This metalation occurs over a period of from about ten minutes to five hours, typically in about two hours with the temperature maintained below -65°C. The anion, so-produced, is then treated with cyclopent-3-ene carboxaldehyde in the same solvent at such a rate so as to maintain the temperature below -65°C. The reaction is then quenched by addition of the reaction mixture to an aqueous acidic medium and worked up.

The compound of formula III, so-produced, is then reduced at the benzylic position by the action of trifluoroacetic acid and a reducing agent such as triethylsilane, to form the corresponding compound having formula IV. This reaction is generally conducted in a chlorinated hydrocarbon solvent, such as chloroform, dichoroethane (DCE) or methylene chloride, at about room temperature, for a period of about 6 to 24 hours, preferably for about 18 hours.

This compound of formula IV is then converted into the corresponding compound of formula V by treating it with equivalent amounts of tetrabutyl ammonium iodide and boron trichloride in a chlorinated hydrocarbon solvent, such as chloroform, dichoroethane (DCE) or methylene chloride. This reaction is typically conducted at a temperature of -78°C initially, and then allowed to react over a period of about two hours while warming to ambient temperature.

The resulting compound of formula V is then reacted with trifluoromethanesulfonic anhydride in a chlorinated hydrocarbon solvent, such as chloroform, dichoroethane (DCE) or methylene chloride, in the presence of a base such as pyridine or 3-methylpyridine, to form the corresponding trifluoromethanesulfonic acid ester of formula VI. Typically, the initial reaction temperature is about -78°C and the reaction is allowed to warm to room temperature to complete the reaction.

The trifluoromethanesulfonic acid ester of formula VI is then reacted under Heck cyclization conditions to produce the corresponding compound of formula VII. This reaction may be performed with or without a solvent. Suitable solvents include N,N-

dimethylformamide (DMF), N-methylpyrrolidone (NMP) and toluene. Temperatures ranging from about 60°C to about 130°C are suitable, and the reaction is generally run for a period of about 1 to 48 hours. Preferably, the reaction is conducted at a temperature of about 100°C for about 2-18 hours. Catalysts in this reaction are generated *in situ* by treatment with sources of palladium, such as palladium acetate ($Pd(OAc)_2$), palladium dichloride ($PdCl_2$) or palladium in the reduced zero oxidation state such as palladium on carbon (Pd/C) or tris(dibenzylidene acetone)dipalladium(O) ($Pd_2(dba)_3$). Analogous nickel catalysts can also be used. The amount of catalyst required is about 0.1 mole % to a stoichiometric amount. Preferably, about 2-10 mole % of the palladium or nickel catalyst is used. Often, conditions used in these reactions include ligands such as triphenylphosphine or tri-o-tolylphosphine, or bidentate ligands such as DPPF, DPPE, DPPB, DPPP (DPP=bis-diphenylphosphine, F=ferrocene, E=ethyl, P=propane, B=butane) or any of a variety of chiral ligands such as BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) or arsenate ligands, or bidentate combinations of these ligands with chiral directing groups, such as, for example, oxazolines, though the inclusion of ligands may not be necessary in all cases. If ligands are used in combination with palladium or nickel sources, they are typically used in amounts from about 0.5 to about 4 molar equivalents of the palladium or nickel catalyst.

The above reaction is conducted in the presence of a base, typically a tertiary amine base such as triethylamine or diisopropylethylamine. Other bases such as carbonates or acetates, (e.g., potassium carbonate, sodium carbonate, sodium acetate or potassium acetate) may also provide adequate or desirable results. In some cases, as exemplified in the experimental examples, it is beneficial to use a tertiary amine base, as described above, *in combination with* catalytic acetate or carbonate salt such as potassium acetate, in an amount equivalent to the phosphine ligand to accelerate the reaction. An additional additive that may be useful is an alkyl ammonium halide salt, such as tetrabutyl ammonium chloride. These conditions are common, and are based on the conditions described by Jeffrey T. in J. Chem. Soc., Chem. Commun., 1984, 1287 and Synthesis, 1987, 70. These reactions are generally performed under an atmosphere of nitrogen or argon, but may or may not require the presence of oxygen.

Reaction of the compound of formula VII with osmium tetroxide and a reoxidant such as N-methylmorpholine-N-oxide (NMO) in acetone and water at about room temperature yields the corresponding compound of formula VIII.

The compound having formula VIII is then converted into the desired corresponding compound of formula IA using the following procedure. First, the compound of formula VIII is reacted with sodium periodate in a mixture of a chlorinated hydrocarbon, preferably dichloroethane (DCE), and water, or with lead tetraacetate in a chlorinated hydrocarbon

solvent, at a temperature from about 0°C to about room temperature, to generate a dialdehyde or glycal intermediate. The product of this reaction is then reacted, with benzylamine (or ammonia) and sodium triacetoxyborohydride. Removal of the N-benzyl group yields the desired compound of formula IA. Removal of the benzyl group can be accomplished using methods well known to those of skill in the art, for example, by first optionally reacting the free base with one equivalent of acid, e.g., hydrochloric acid (to form the corresponding acid addition salt), and then with hydrogen and palladium hydroxide in methanol at about room temperature.

Alternatively, the reductive amination may be carried out in situ as follows. Oxidative cleavage of the diol of formula VIII performed using sodium periodate in aqueous THF or alcohol to form the dialdehyde/glycal intermediate referred to above. Treatment of this intermediate with excess benzylamine (or ammonia), palladium hydroxide and hydrogen at a temperature from about room temperature to about 70°C generates the desired compound of formula IA.

If the above method used leaves a benzyl group on the compound, removal of the benzyl group will yield the desired compound of formula IA. Removal of the benzyl group can be accomplished using methods well known to those of skill in the art, for example, optionally reacting the free base with one equivalent of acid, e.g., hydrochloric acid (to form the corresponding acid addition salt), followed by hydrogen and palladium hydroxide in methanol at about room temperature.

In the reductive animation step described above and throughout this document, alternatives to benzyl amine, such as ammonia, hydroxylamine, alkoxy amines, methyl amine, allyl amine, and substituted benzyl amines (e.g., diphenylmethyl amine and 2- and 4-alkoxy substituted benzyl amines) can also be used. They can be used as free bases, or as their salts, preferably their acetate salts, and can be subsequently removed by methods described for each by T. W. Greene and G.M. Wuts, "Protective Groups in Organic Synthesis", 1991, John Wiley & Sons, New York, NY.

The procedure described above and illustrated in Scheme 1 is preferred for making compounds of the formula I wherein R^2 or R^3 is susceptible to reacting to form an aryne or in another type of side reaction.

The procedure described above produces compounds of the formula IA wherein Z is CH_2. Compounds of the formula IA wherein Z is (C=O) can be formed using the procedure illustrated in Scheme 1, as described above, with the exception that the compound of formula III is oxidized, rather than reduced, at the benzylic position, to form a compound of the formula IV wherein Z is (C=O). This can be accomplished using methods well known to those of skill in the art such as by treatment with Jones reagent (chromic acid solution) in

ether or acetone at a temperature from about 0°C to about room temperature . Compounds of the formula IA wherein Z is CF_2 can be prepared in a similar manner by converting the oxidized compound of formula IV wherein Z is (C=O) into the corresponding compound of formula IV wherein Z is CF_2, and then continuing with the reaction sequence of Scheme 1. This conversion can be accomplished using methods well known in the art, such as by treatment with Lawesson's reagent. The reaction with Lawesson's reagent is generally carried out in a reaction inert solvent such as benzene or toluene, preferably toluene, at a temperature from about room temperature to about the reflux temperature of the reaction mixture, preferably at about the reflux temperature.

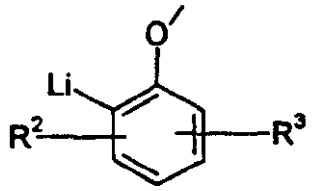
Scheme 2 illustrates an alternate method of preparing compounds of the formula I. This method is the preferred method for preparing such compounds wherein neither R^2 nor R^3 is susceptible to reacting in an undesireable side reaction. Referring to Scheme 2, the compound of formula IX is treated with a strong base such as n-butyllithium at a temperature from about room temperature to about the reflux temperature of the reaction mixture, in a solvent such as ether or t-butyl methyl ether. This metalation occurs over a period of from about 1 to 5 hours, typically in about 4 hours when the reaction is conducted at the reflux temperature in ether. The resulting anion is then cooled in the same solvent or in a solvent *mixture such as one containing tetrahydrofuran (THF), to a temperature of about -78°C. This* anion can then be reacted with cyclopent-3-enecarboxylic acid methoxy-methyl-amide (X) at about -78°C, for about a half hour, with completion of the reaction occurring upon warming to ambient temperature. This reaction yields the compound of formula XI. The compound of formula XI is then dissolved in a solvent such as methylene chloride and treated with boron trichloride at about -78°C. After a period of 20 about minutes, the reaction is allowed to warm to about 0°C and is worked up. The resulting phenol of formula XII is then converted into the trifluoromethanesulfonic ester by the methods described above for generating the *compound of formula XIII. The resulting ester can then be converted into a compound of* formula XIV under Heck conditions, as described above.

Reduction of the compound of formula XIV using standard Wolff-Kishner conditions yields the compound of formula XV. These conditions are well known to those skilled in the art, and include reacting the compound of formula XIV with hydrazine and potassium hydroxide, first at a temperature of approximately 100°C in a solvent, usually ethylene glycol or diglyme, and then increasing the temperature to about 180-200°C. Reductions that are known in the art to be equivalent to the standard Wolff-Kishner reduction may also be used. The compound of formula XV can be converted into the compound of formula IB by a procedure analogous to the conversion of compounds of the formula VII into those of the formula IA in Scheme 1.

Rather than reducing the ketone in the compound of formula XIV, the corresponding compound wherein the oxo group is replaced by CF_2 can be formed by treatment with Lawesson's reagent, or using other methods for effecting this conversion that are well known to those of skill in the art.

Methyl ethers may be converted to their corresponding phenols by methods well known to those skilled in the art. This can be accomplished by exposing the compound of formula IB or XVII to hydrobromic acid and warming the resulting mixture to the reflux temperature for a period of about 1 hour. This reaction produces the corresponding phenol of formula IB' or XVII', respectively.

An alternative to the methods described in Schemes 1 and 2 for generating aryl anions is to use halogen-metal exchange conditions. For example, a compound of the formula XVIII, illustrated in Scheme 3, wherein R^{19} is bromo or iodo, can be treated with an alkyllithium base such as n-butyllithium, at a temperature form about -78°C to 20°C, typically at about -78°C to produce an aryl anion of the formula



XVIII'

The anion produced in this reaction can then be reacted with an aldehyde, such as described in Scheme 1, or an appropriate disubstituted amide, as described in Scheme 2, to produce a compound of the formula XIX. (Rather than reacting the compound of formula XVIII with an alkyllithium base, as described immediately above, such compound can optionally first be converted into a Grignard reagent (R^{19}—⊱→ MgR^{19}) using standard methods, and then reacted as described above for compounds of the formula XVIII' to prepare a compound of the formula XIX).

The resulting compound of formula XIX can then be converted into a compound of the formula IC (Scheme 3) using the methods described above for the conversion of compounds of the formula XI into those of the formula IB (Scheme 2) and for the conversion of compounds of the formula IV into those of the formula IA (Scheme 1).

The generation of anions at the ortho position of the aromatic systems employed in the synthetic procedures described in this application is encompassed under a general

synthetic strategy known to those skilled in the art as Directed Ortho Metalation (DOM). Within this area, a number of functional groups known as Directed Metalation Groups (DMGs) have been studied for this purpose, and some are reviewed in Snieckus, V. *Chem Rev.* **1990**, 879. Where applicable, DMGs other than those utilized in this work may be equally applicable to the preparation of the compounds and intermediates described herein.

An alternative method for the generation of compounds similar to compounds of the formula V, XII or XX appears in Scheme 4. In this method, cyclopent-3-ene carboxaldehyde and a phenol are combined with an aryl boronic acid and an acid catalyst such as an acetic acid (optionally substituted with halo substitutents at the alpha position to modulate the acidity of the reaction), or with a aryl boron dihalide, which, by its nature, will generate a mineral acid under the conditions of the reaction, in a solvent such as benzene, toluene, dioxane or dichloromethane, preferably in benzene. The temperature of the reaction is typically the reflux temperaure, or at a temperature that allows any of the standard methods for removal of water generated in the reaction to be removed at a rate that allows the desired reaction to occur. A convenient method employs a Dean-Stark trap to remove water formed in the reaction. Typically, the reaction is conducted for a period of 3-48 hours, generally 10-24 hours, or until the theoretical amount of water has been collected. At this time the reaction is freed of solvent and then subjected to conditions as described above for reduction of benzylic hydroxyl groups or ethers, for example, treatment of this intermediate with trifluoroacetic acid and a reducing agent such as triethylsilane. This reaction is conducted in a chlorinated hydrocarbon solvent, such as chloroform, dichoroethane (DCE) or methylene chloride, at or about room temperature for a period of 6 to 24 hours, preferably 18 hours.

The above reaction produces a compound of the formula IV' wherein Z is CH_2. The corresponding compounds of the formula IV ' wherein Z is (C=O) and CF_2 can be formed using the methods described above for preparing compounds of the formula IV (Scheme 1) wherein Z is (C=O) or CF_2.

The resulting compounds of formula IV' (Z is (C = O), CH_2 or CF_2) are is then converted into the corresponding compound of formula IA' using the methods described above and depicted in Scheme 1 for the preparation of compounds of the formula IA.

Scheme 5 illustrates a method for the introduction of substituents, such as bromine and oxygen, into compounds of the invention. Treatment of a compound of formula XXIV with bromine, under standard conditions known to those of skill in the art, for example, in a chlorinated hydrocarbon solvent such as chloroform, dichoroethane (DCE) or methylene chloride, at a temperature of about 0°C to about room temperature, preferably at room temperature, in the presence of a base such as sodium acetate, generates the corresponding compound of formula XXIVA. The bromide so produced (XXIVA) can then be converted, by

the process of halogen-metal exchange described above, to a lithium anion derivative, which can then be treated with a variety of electrophiles, for example, trialkylborates, typically at temperatures ranging between -78 and 0°C to produce the corresponding boronic acid derivative of formula XXIVB.

This compound can then be converted to a variety of derivatives accessible through Suzuki coupling chemistry under standard conditions known to those of skill in the art. Alternatively these boronic acid compounds may be converted into the corresponding phenol derivatives, by reaction with hydrogen peroxide or N-methylmorpholine, in a solvent such as THF, or by any other standard methods known to those of skill in the art. Removal of the benzyl protecting group by methods described above yields the desired compound of formula IC'.

Phenols prepared as described above and in the experimental section can be converted to the corresponding trifluoromethanesulfonic esters. These derivatives, as well as the bromides formula XXIVA, can be used to access a variety of other substituents (i.e., other values of R^2 and R^3) such as aryl, acetylene and vinyl substituents, as well as the corresponding carbonyl esters and amides, by palladium and nickel catalyzed processes known to those of skill in the art, such as Heck, Suzuki and Stille couplings and Heck carbonylations. Additionally, phenols can be alkylated by a variety of common methods to prepare ethers. Additionally, esters may be treated with nucleophiles, such as Grignard reagents to prepare the corresponding tertiary alcohols. Examples of these transformations appear in the Experimental Examples.

Scheme 6 illustrates the preparation of certain intermediates used in the procedure of Scheme 7. Referring to Scheme 6, the starting material of formula XXV is reacted with trifluoroacetic anhydride, in the presence of pyridine, to form the compound of formula XXVI. This reaction is typically conducted in methylene chloride at a temperature from about 0°C to about room temperature.

The compound of formula XXVI, when Z is not (C=O), can then be converted into the nitro derivative of formula XXXV by the following process. The compound of the formula XXVI is added to a mixture of 2 or more equivalents of trifluoromethanesulfonic acid (CF_3SO_2OH) and 1 to 1.5 equivalents of nitric acid, in a chlorinated hydrocarbon solvent such as chloroform, dichoroethane (DCE) or methylene chloride. The resulting mixture is allowed to react for about 5 to 24 hours. Both of the foregoing reactions are generally conducted at a temperature ranging from about -78°C to about 0°C for about 2 hours, and then allowed to warm to room temperature for the remaining time.

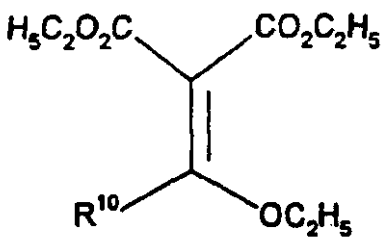
Compounds of the formula XXXV wherein Z is (C=O) can be prepared by oxidizing the analogous compounds wherein Z is CH_2 as described by Kapur et al., Can. J. Chem., 66, 1988, 2888-2893.

Reduction of the compound of formula XXXV, using methods well known to those of skill in the art, yields the corresponding aniline. This reduction can be accomplished, for example, using hydrogen and a palladium catalyst such as palladium hydroxide, and running the reaction in methanol or ethanol at about room temperature. The intermediate aniline is then converted into the trifluoroacetamide of formula XXVIIA as described above for the preparation of compounds of the formula XXVI.

Mononitration of the compound of formula XXVIIA, as described above for the preparation of compounds of the formula XXXV, yields the corresponding nitro derivative of formula XXVIIA'. Treatment of the nitro derivative of formula XXVIIA' with aqueous bicarbonate in methanol or THF, at a temperature from about 20°C to about 70°C, followed by reduction of the nitro group as described above, yields the corresponding compound of formula XXVIIB.

Referring to Scheme 7, the compound of formula XXVIIA' is converted into the corresponding compound wherein the trifluoroacetyl protecting group is replaced by a t-Boc protecting group (XXVIIIA) by reacting it first with an alkali metal or alkaline earth metal (or ammonium) hydroxide or carbonate, and then reacting the isolated product from the foregoing reaction with di-t-butyldicarbonate. The reaction with the alkali or alkaline earth metal (or ammonium) hydroxide or carbonate is generally carried out in an aqueous alcohol, dioxane or tetrahydrofuran (THF) at a temperature from about room temperature to about 70°C, preferably at about 70°C, for about one to about 24 hours. The reaction of the isolated, unprotected amine or an acid addition salt of such amine, from the above reaction with di-t-butyldicarbonate is preferably carried out in a solvent such as THF, dioxane or methylene chloride at a temperature from about 0°C to about room temperature. This reaction may or may not be conducted in the presence of a base. When the reactant is a salt of the amine, use of a base is preferred. The resulting compound of formula XXVIIIA can be converted into the corresponding diamino derivative of formula XXVIIIB using the procedure described above for converting compounds of the formula XXVIIA' into the corresponding diamino compounds of formula XXVIIB.

The conversion of the compound of formula XXVIIIB into the desired compound of the formula XXIX can be accomplished by reacting the compound of formula XXVIIIB with a compound of the formula



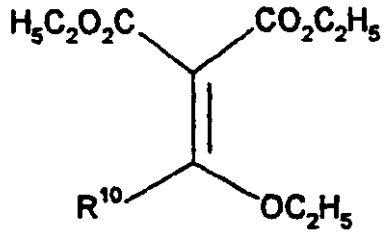
wherein R^{10} is hydrogen, (C_1-C_6) alkyl optionally substituted with from one to seven fluorine atoms, aryl-(C_0-C_3) alkyl wherein said aryl is selected from phenyl and naphthyl, or heteroaryl-(C_0-C_3) alkyl wherein said heteroaryl is selected from five to seven membered aromatic rings containing from one to four heteratoms selected from oxygen, nitrogen and sulfur, and wherein each of the foregoing aryl and heteroryl groups may optionally be substituted with one or more substituents, preferably from zero to two substituents, independently selected from (C_1-C_6) alkyl optionally substituted with from one to seven fluorine atoms, (C_1-C_6) alkoxy optionally substituted with from one to seven fluorine atoms and cyano. The preferred solvent for this reaction is a 10:1 mixture of ethanol:acetic acid. The reaction temperature can range from about 40°C to about 100°C. It is preferably about 60°C. Other appropriate solvents include acetic acid, ethanol and isopropanol.

Alternate methods of preparing compounds of the formula XXIX from the compound of formula XXVIIIB are described by Segelstein et al., Tetrahedron Lett., 1993, 34, 1897.

Removal of the t-Boc protecting group from the compound of formula XXIX yields the corresponding compound of formula ID. The protecting group can be removed using methods well known to those of skill in the art. For example, the compound of formula XXIX can be treated with an anhydrous acid such as hydrochloric acid, hydrobromic acid, methanesulfonic acid, or trifluoroacetic acid, preferably hydrochloric acid in ethyl acetate, at a temperature from about 0°C to about 100°C, preferably from about room temperature to about 70°C, for about one to 24 hours.

The compound of formula XXIX can be converted into the corresponding compound of formula IE by reacting it with a compound of the formula $R^{17}Z$, wherein R^{17} is defined as R^{10} is defined above, and Z is a leaving group such as a halo or sulfonate (e.g., chloro, bromo, iodo, mesylate or tosylate), in the presence of a base such as an alkali metal hydride, hydroxide or carbonate, preferably potassium hydroxide, in a polar solvent such as water, dimethylsulfoxide (DMSO), THF or DMF, preferably a mixture of DMSO and water, and then removing the protecting group as described above. The reaction with $R^{17}Z$ is generally carried out at a temperature from about room temperature to about 100°C, preferably at about 50°C, for about five hours. Subsequent removal of the protecting group, as described above, yields the desired compound of formula IE.

Scheme 8 illustrates an alternative method of preparing compounds of the formula IE from the compound of formula XXVIIIA'. This method is the preferred method of making compounds of the formula IE wherein R^{17} is a group such as an aryl or heteroaryl containing group, or when R^{17} can not be attached, as illustrated in Scheme 7, by alkylation or aryl substitution methods. Referring to Scheme 8, the compound of formula XXVIIIA' is reacted with the appropriate compound of formula $R^{17}NH_2$ in a polar solvent such as THF, DMF or DMSO, preferably THF, at a temperature from about room temperature to about 100°C, preferably at the reflux temperature, for about four to eighteen hours. This reaction produces a compound of the formula XXX. The resulting compound of formula XXX is then converted into the corresponding compound of the formula XXXI by reducing the nitro group to an amino group using methods well known to those of skill in the art. Such methods are referred to above for the conversion of the compounds of the formula XXVIIA' into a compound of the formula XXVIIB in Scheme 6. Closure of the imidazole ring to form the corresponding compound of formula XXXII can then be accomplished by reacting the compound of formula XXXI from the above reaction with a compound of the formula

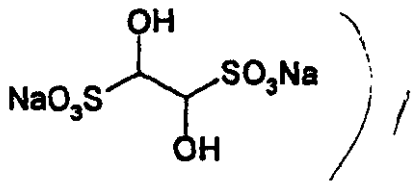


(wherein R^{10} is defined as above) as described above for converting compounds of the formula XXVIIIB into those of the formula XXIX.

Removal of the protecting group from the compound of formula XXXII yields the corresponding compound of formula IE. This can be accomplished using methods well known in the art, for example, as described above for forming compounds of the formula ID from the corresponding compounds of the formula XXIX.

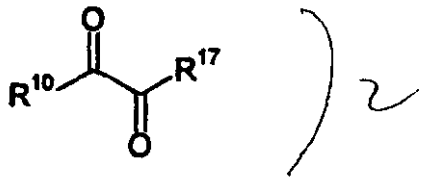
Compounds of the formula XXVIIIA', which are the starting materials used in the process of Scheme 8, can be synthesized as depicted in Scheme 8A and described below. The appropriate compound of formula IC (Scheme 3) wherein R^2 is fluoro is converted into its trifluoroacetamide derivative of the formula ICTFA, using methods described above. Such derivative is then nitrated, as described above or using other methods well known to those of skill in the art, to provide the corresponding nitro derivative of formula ICTFA'. Subsequent removal of the trifluoroacetamide group with an alkali metal carbonate or bicarbonate in methanol or THF, followed by protection with di-t-butyldicarbonate, as described above, yields the corresponding compound of formula XXVIIIA'.

Scheme 9 illustrates a method of preparing compounds of the formula IF, wherein R^{10} and R^{17} are as defined above. Referring to Scheme 9, the compound of formula XXVIIIB is reacted with a compound of the formula



(sodium bisulfite ethane dione addition adduct) in water or another polar solvent such as THF, DMF or DMSO, preferably a mixture of water and a water miscible solvent such as THF, for about one to four hours. The reaction temperature can range from about 40°C to about 100°C, and is preferably at about the reflux temperature.

Alternatively, the compound of formula XXVIIIB can be reacted with a compound of the formula



(double condensation reaction) in a polar solvent such as THF, water, or acetic acid, preferably a mixture of water and THF. This reaction is typically carried out at a temperature from about 40°C to about 100°C, preferably at the reflux temperature, for about two to four hours.

Both of the foregoing procedures can also be used to convert the corresponding compounds wherein the t-Boc protecting group is replaced by another protecting group such as TFA (e.g. , compounds of the formula XXVIIB) into quinoxolines.

The desired quinoxoline of formula IF can then be formed by deprotecting the compound formed in either of the foregoing reactions, using the method described above for converting a compound of the formula XXIX into one of the formula ID or the method described above for removing the TFA group from a compound of the formula XXVIIA'.

Scheme 10 illustrates a method of preparing compounds of the formula I wherein R^2 and R^3, together with the benzo ring to which they are attached, form a benzoxazole ring system. Such a compound, wherein R^1 is hydrogen, is depicted in Scheme 10 as chemical formula IG. Referring to Scheme 10, a compound of the formula ICTFA', wherein Y is nitro or fluoro, is reacted with potassium acetate or another alkali or alkaline earth metal carboxylate in a solvent such as dimethylsulfoxide (DMSO), DMF or acetonitrile, preferably DMSO. This reaction is generally allowed to run for about 12-24 hours. Appropriate reaction temperatures range from about 70°C to about 140°C. Approximately 100°C is preferred.

The above reaction yields the compound of formula XXXIV, which can then be converted into the desired compound having formula IG by the following procedure. First, the compound of formula XXXIV is reduced by reaction with hydrogen and a palladium or platinum catalyst such as palladium hydroxide in methanol at a temperature from about 0°C to about 70°C, preferably at about room temperature, to form the corresponding amino derivative. The product of this reaction is then reacted with an acid chloride of the formula $R^{10}COCl$ or an acid anhydride of the formula $(R^{10}CO)_2O$ wherein R^{10} is (C_1-C_8)alkyl, or a compound of the formula $R^{10}C(OC_2H_5)_3$, in an appropriate inert solvent such as decalin, chlorobenzene or xylenes. A mixture of xylenes is preferred. This reaction is typically conducted at a temperature from about 120-150°C, preferably at about 140°C. When $R^{10}COCl$ is used as a reactant, it is preferable to add a stoicheometric amount of triethylamine (TEA) or another organic tertiary amine base and a catalytic amount of pyridinium p-toluenesulfonic acid or pyridinum p-toluenesulfonate (PPTS) to the reaction mixture. When $R^{10}C(OC_2H_5)_3$ is used as a reactant, it is preferable to add a catalytic amount of PPTS to the reaction mixture.

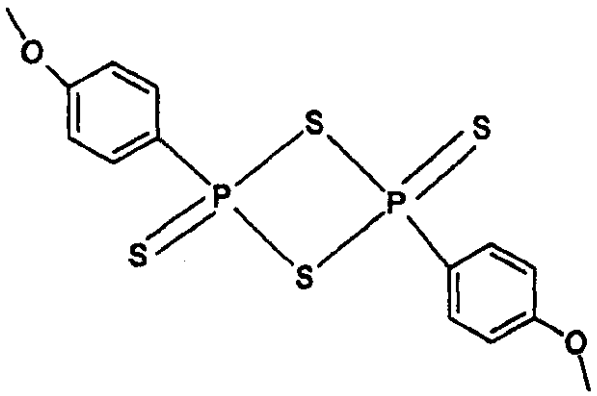
Removal of the trifluoroacetyl nitrogen protecting group yields the desired compound of the formula IG. This can be accomplished using methods well known to those of skill in the art, for example, reacting the protected compound with a lower alkanol and an aqueous alkali or alkaline earth metal (or ammonium) hydroxide or carbonate, aqueous sodium carbonate, at a temperature from about 50°C to about 100°C, preferably at about 70°C, for about two to six hours.

Scheme 11 illustrates the preparation of compounds of the formula I wherein R^1 is hydrogen and R^2 and R^3, together with the benzo ring to which they are attached, form a benzothiazole ring system. These compounds are referred to in Scheme 11 and hereinafter as "compounds of the formula IH". Referring to Scheme 11, the compound of formula XXV' is reacted with trifluoroacetic anhydride to form the corresponding compound wherein the ring nitrogen is protected by a trifluoroacetyl group, and the resulting nitrogen protected compound is then reacted with two equivalents of trifluoromethanesulfonic acid and one equivalent of nitric acid to form the corresponding compound of formula XXXV, wherein there is a single nitro substituent on the benzo ring. The reaction with trifluoroacetic acid is typically conducted in the presence of pyridine. Both of the above reactions are typically conducted in a reaction inert solvent such as a chlorinated hydrocarbon solvent, preferably methylene chloride, at a temperature from about 0°C to about room temperature, preferably at about room temperature.

The above transformation can also be accomplished using other nitration methods known to those skill in the art.

Reduction of the nitro group to an amine group can be accomplished as described above to provide a compound of the formula XXXV'.

The compound of formula XXXV' is then reacted with a carboxylic acid halide or anhydride of the formula $R^{10}COX$ or $(R^{10}CO)_2O$, wherein X is halo, and pyridine, TEA or another tertiary amine base, to form a compound of the formula XXXVI, which can then be converted to the desired compound having formula XXXVII by reacting it with Lawesson's reagent, which is depicted below.



The reaction with $R^{10}COX$, wherein X is halo, or $(R^{10}CO)_2O$ is generally carried out at a temperature from about 0°C to about room temperature, preferably at about room temperature. The reaction with Lawesson's reagent is generally carried out in a reaction inert solvent such as benzene or toluene, preferably toluene, at a temperature from about room temperature to about the reflux temperature of the reaction mixture, preferably at about the reflux temperature.

Closure to the benzothiazole ring and nitrogen deprotection to form the desired compound of formula IH can be accomplished by reacting the compound of formula XXXVII with potassium ferricyanide and sodium hydroxide in a mixture of water and methanol ($NaOH/H_2O/CH_3OH$), at a temperature from about 50°C to about 70°C, preferably at about 60°C for about 1.5 hours.

Schemes 12 and 13 illustrate methods of preparing compounds of the formula I wherein R^1 is hydrogen, and R^2 and R^3 represent a variety of different substituents, as defined above, but do not form a ring.

Scheme 12 illustrates methods of preparing compounds of the formula I wherein: (a) R^1 is hydrogen and R^2 is $R^7R^8NO_2S$-; (b) R^1 and R^2 are both chloro; and (c) R^1 is hydrogen and R^2 is $R^{13}C(=O)$-. These compounds are referred to in Scheme 12, respectively, as compounds of formulas IJ, IK and IL.

Referring to Scheme 12, compounds of the formula IJ can be prepared by reacting the compound of formula XXVI with two or more equivalents of a halosulfonic acid, preferably chlorosulfonic acid, at a temperature from about 0°C to about room temperature.

Reaction of the chlorosulfonic acid derivative so formed with an amine having the formula R^7R^8NH, wherein R^7 and R^8 are defined as above, followed by removal of the nitrogen protecting group, yields the desired compound having formula IJ.

Compounds of the formula IK can be prepared by reacting the compound of formula XXVI with iodine trichloride in a chlorinated hydrocarbon solvent, followed by removal of the nitrogen protecting group. The reaction with iodine trichloride is typically carried out at a temperature from about 0°C to about room temperature, and is preferably carried out at about room temperature. In a similar fashion, the analogous mono- or dibrominated or mono- or diiododinated compounds can be prepared by reacting the compound of XXVI with N-iodosuccinimide or N-bromosuccinimide in a trifluromethanesulfonic acid solvent, followed by removal of the nitrogen protecting group as described above.

Reaction of the compound of XXVI with an acid halide of the formula $R^{13}COCl$ or an acid anhydride of the formula $(R^{13}CO)_2O$, with or without a reaction inert solvent such as a chlorinated hydrocarbon solvent, preferably methylene chloride, in the presence of Lewis acid such as aluminum chloride, at a temperature from about 0°C to about 100°C, followed by nitrogen deprotection, yields the compound of formula IL. The reaction with the acid halide or anhydride can be carried out using other known Lewis acids or other Friedel-Crafts acylations methods that are known in the art.

The reactions described herein in which NO_2, $-SO_2NR^7R^8$, $-COR^{13}$, I, Br or Cl are introduced on the compound of formula XXVI, as depicted in Scheme 12 and described above, can be performed on any analogous compound wherein R^2 is hydrogen, (C_1-C_6)alkyl, halo, (C_1-C_6)alkoxy or $-NHCONR^7R^8$, producing compounds of the formula I wherein R^2 and R^3 are defined as in the definition of compounds of the formula I above.

Compounds that are identical to those of the formula IL, but which retain the nitrogen protecting group, can be converted into the corresponding O-acyl substituted compounds, i.e., those wherein the $-C(=O)R^{13}$ group of formula IL is replaced with a $-O-C(=O)R^{13}$ group, using Baeyer-Villiger processes well known to those skilled in the art. The resulting compounds can be partially hydrolyzed to yield the corresponding hydroxy substituted compounds, and then alkylated to form the corresponding alkoxy substituted compounds. Also, such O-acyl substituted compounds can be used to prepare variably substituted benzisoxazoles, using methods well known to those of skill in the art such as using, in sequence, a Fries rearrangement, oxime formation, acylation and treatment with base. Such a process involves performing a Fries rearrangement of a compound of the formula XXXIII by treatment with a Lewis acid such as aluminum chloride ($AlCl_3$) neat or in a solvent such as chlorobenzene, at a temperature from about 100°C to about 200°C, preferably at about 170°C for about 1 to 2 hours, preferably for about 2 hours, to produce a compound of the

formula XXXIX. Cleavage of the protecting group provides the corresponding compound of formula IS. Alternatively, the compound of formula XXXIX can be converted into its oxime using standard methods well known to those skilled in the art, such as treatment with hydroxylamine hydrochloride in an alcohol (e.g., methanol), in the presence of a base such as sodium acetate, at a temperature from about 20°C to about 70°C, preferably at about 50°C for about 5 to 20 hours. Acylation of the oxime using methods well known in the art, such as treatment with acetic anhydride and pyridine, followed by treatment of the isolated acyl oxime with a base such as sodium hydride, in a solvent such as DMF, NMP or DMSO, produces the corresponding protected benzisoxazole. Cleavage of the protecting group under standard conditions, as described above, yields the desired compound of formula IT.

Scheme 13 illustrates methods of making compounds of the formula I wherein: (a) R^1 is hydrogen and R^2 is chloro; (b) R^1 is hydrogen and R^2 is cyano; (c) R^1 is hydrogen and R^2 is amino; and (d) R^1 is hydrogen and R^2 is $R^{13}C(=O)N(H)$-. These compounds are referred to in Scheme 13, respectively, as compounds of the formula IM, IN, IP and IQ.

Compounds of formula IM can be prepared from compounds of the formula XXXV' by generation of a diazonium salt with, for instance, an alkali metal nitrite and strong mineral acid (e.g., hydrochloric acid, sulfuric acid, hydrobromic acid) in water, followed by reaction with a copper halide salt, such as copper (I) chloride. Nitrogen deprotection by the methods described above yields the desired compound of formula IM. Alternative methods for the generation of diazonium salts, as known and practiced by those of skill in the art, can also be used. The foregoing reaction is generally carried out at temperatures ranging from about 0°C to about 60°C, preferably about 60°C for about 15 minutes to one hour.

Reaction of the diazodium salt, prepared as described above, with potassium iodide in an aqueous medium provides the analogous iodide derivative. This reaction is generally carried out at a temperature from about 0°C to about room temperature, preferably at about room temperature. The resulting compound, or its analogous N-tert-butylcarbonate protected form, can be used to prepare the corresponding cyano derivative by reaction with copper (I) cyanide and sodium cyanide in DMF, N-methylpyrrolidone (NMP), N,N-dimethylpropylurea (DMPU) or DMSO, preferably NMP, at a temperature from about 50°C to about 180°C, preferably at about 175°C. Nitrogen deprotection as described above provides the corresponding desired compound of formula IN.

The above described iodide, bromide or diazonium salt derivative can also be used to access a variety of other substituents such as aryl, acetylene and vinyl substituents, as well as the corresponding carbonyl esters and amides, by palladium and nickel catalyzed processes known to those of skill in the art, such as Heck, Suzuki and Stille couplings and Heck carbonylations.

Nitrogen deprotection of the compound of formula XXXV' provides the compound of the formula IP.

The compound of formula XXXV' can be reacted with a acyl group having the formula $R^{13}COCl$ or $(R^{13}CO)_2O$ using the methods described above, followed by nitrogen deprotection to provide compounds of the formula IQ. In a similar fashion, treatment of the protected amine with a compound having the formula $R^{13}SO_2X$, when X is chloro or bromo, followed by nitrogen deprotection, provides the corresponding sulfonamide derivative.

Other suitable amine protecting groups that can be used, alternatively, in the procedures described throughout this document include $-COCF_3$, $-COCCl_3$, $-COOCH_2CCl_3$, $-COO(C_1-C_6)$alkyl and $-COOCH_2C_6H_5$. These groups are stable under the conditions described herein, and may be removed by methods described for each in Greene's "Protective Groups in Organic Chemistry", referred to above.

Compounds of the formula I wherein R^1 is other than hydrogen can be prepared as described above, such as the reductive amination ring formation by which compound XXIV in Scheme 3 (R^1=benzyl) is formed, and by the methods described below. Compounds of the formula I wherein R^1 is hydrogen can be converted into the corresponding compounds wherein R^1 is other than hydrogen by treating them with an equivalent amount of an aldehyde (R^1CHO) or ketone (R^1R^1CO wherein the two R^1's are the same or different) and a reducing agent, preferably a hydride reagent such as sodium traicetoxyborohydride or sodium cyanoborohydride, in a solvent such as methylene chloride, tetrahydrofuran or dioxane. The addition of acid to facilitate the reaction may be necessary in some cases, and acetic acid is commonly used. The temperature of this reaction is typically ambient for a period of about 0.5 to 24 hours. Commonly used methods are described in J. Org. Chem. 1996, 61, 3849.

Compounds of the formula I wherein R^1 is other than hydrogen can also be prepared by subjecting the corresponding compounds wherein R^1 is hydrogen to an alkylation reaction, using methods well known to those of skill in the art. For example, the compound wherein R^1 is hydrogen is treated with an equivalent amount or an excess of R^1X, wherein R^1 is other than hydrogen and X is halo, preferably bromo or iodo, or an O-sulfate ester of R^1OH. This reaction is typically performed neat or in polar solvent such as water, dimethylformamide or dimethylsulfoxide, usually in the presence of base, such as but not limited to an alkyli metal carbonate, for instance. The temperature of the reaction will generally range from about 20-120°C (preferably, it will be about 100°C) for a period of about 0.1 to 24 hours.

Compounds of the formula I wherein R^1 is other than hydrogen can also be prepared by converting the corresponding compounds wherein R^1 is hydrogen into amides by reacting them with a compound of the formula $R^1C(=O)X$, wherein X is defined as above, using methods well known to those of skill in the art, and then reducing the resulting amide with

borane or lithium aluminum hydride. The reduction step is usually carried out in an ethereal solvent such as ethyl ether or THF at a temperature from about 20°C to about 70°C for about one to twenty hours, to produce the desired amine.

In each of the reactions discussed above, or illustrated in Schemes 1-13, above, pressure is not critical unless otherwise indicated. Pressures from about 0.5 atmospheres to about 5 atmospheres are generally acceptable, with ambient pressure, i.e., about 1 atmosphere, being preferred as a matter of convenience.

The compounds of the formula I and their pharmaceutically acceptable salts (hereafter "the active compounds") can be administered via either the oral, transdermal (e.g., through the use of a patch), intranasal, sublingual, rectal, parenteral or topical routes. Transdermal and oral administration are preferred. These compounds are, most desirably, administered in dosages ranging from about 0.25 mg up to about 1500 mg per day, preferably from about 0.25 to about 300 mg per day in single or divided doses, although variations will necessarily occur depending upon the weight and condition of the subject being treated and the particular route of administration chosen. However, a dosage level that is in the range of about 0.01 mg to about 10 mg per kg of body weight per day is most desirably employed. Variations may nevertheless occur depending upon the weight and condition of the persons being treated and their individual responses to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval during which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effects, provided that such larger doses are first divided into several small doses for administration throughout the day.

The active compounds can be administered alone or in combination with pharmaceutically acceptable carriers or diluents by any of the several routes previously indicated. More particularly, the active compounds can be administered in a wide variety of different dosage forms, e.g., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, transdermal patches, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents. In addition, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the active compounds are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (preferably corn, potato or tapioca starch), alginic

acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc can be used for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar) as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration the active ingredient may be combined with various sweetening or flavoring agents, coloring matter and, if so desired, emulsifying and/or suspending agents, together with such diluents as water, ethanol, propylene glycol, glycerin and various combinations thereof.

For parenteral administration, a solution of an active compound in either sesame or peanut oil or in aqueous propylene glycol can be employed. The aqueous solutions should be suitably buffered (preferably pH greater than 8), if necessary, and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

It is also possible to administer the active compounds topically and this can be done by way of creams, a patch, jellies, gels, pastes, ointments and the like, in accordance with standard pharmaceutical practice.

Biological Assay

The effectiveness of the active compounds in suppressing nicotine binding to specific receptor sites is determined by the following procedure which is a modification of the methods of Lippiello, P. M. and Fernandes, K. G. (in The Binding of L-[^{3}H]Nicotine To A Single Class of High-Affinity Sites in Rat Brain Membranes, Molecular Pharm., 29, 448-54, (1986)) and Anderson, D. J. and Americ, S. P. (in Nicotinic Receptor Binding of ^{3}H-Cystisine, ^{3}H-Nicotine and ^{3}H-Methylcarmbamylcholine In Rat Brain, European J. Pharm., 253, 261-67 (1994)).

Procedure

Male Sprague-Dawley rats (200-300 g) from Charles River were housed in groups in hanging stainless steel wire cages and were maintained on a 12 hour light/dark cycle (7 a.m.-7 p.m. light period). They received standard Purina Rat Chow and water *ad libitum*.

The rats were killed by decapitation. Brains were removed immediately following decapitation. Membranes were prepared from brain tissue according to the methods of Lippiello and Fernandez (Molec Pharmacol, 29, 448-454, (1986) with some modifications. Whole brains were removed, rinsed with ice-cold buffer, and homogenized at 0° in 10 volumes of buffer (w/v) using a Brinkmann Polytron™, setting 6, for 30 seconds. The buffer consisted of 50 mM Tris HCl at a pH of 7.5 at room temperature. The homogenate was sedimented by centrifugation (10

minutes; 50,000 x g; 0 to 4°C. The supernatant was poured off and the membranes were gently resuspended with the Polytron and centrifuged again (10 minutes; 50,000 x g; 0 to 4°C. After the second centrifugation, the membranes were resuspended in assay buffer at a concentration of 1.0g/100mL. The composition of the standard assay buffer was 50 mM Tris HCl, 120 mM NaCl, 5 mM KCl, 2 mM $MgCl_2$, 2 mM $CaCl_2$ and has a pH of 7.4 at room temperature.

Routine assays were performed in borosilicate glass test tubes. The assay mixture typically consisted of 0.9 mg of membrane protein in a final incubation volume of 1.0 mL. Three sets of tubes were prepared wherein the tubes in each set contained 50µL of vehicle, blank, or test compound solution, respectively. To each tube was added 200 µL of [^{3}H]-nicotine in assay buffer followed by 750 µL of the membrane suspension. The final concentration of nicotine in each tube was 0.9 nM. The final concentration of cytisine in the blank was 1 µM. The vehicle consisted of deionized water containing 30 µL of 1 N acetic acid per 50 mL of water. The test compounds and cytisine were dissolved in vehicle. Assays were initiated by vortexing after addition of the membrane suspension to the tube. The samples were incubated at 0 to 4° C in an iced shaking water bath. Incubations were terminated by rapid filtration under vacuum through Whatman GF/B™ glass fiber filters using a Brandel™ multi-manifold tissue harvester. Following the initial filtration of the assay mixture, filters were washed two times with ice-cold assay buffer (5 m each). The filters were then placed in counting vials and mixed vigorously with 20 ml of Ready Safe™ (Beckman) before quantification of radioactivity. Samples were counted in a LKB Wallach Rackbeta™ liquid scintillation counter at 40-50% efficiency. All determinations were in triplicate.

Calculations

Specific binding (C) to the membrane is the difference between total binding in the samples containing vehicle only and membrane (A) and non-specific binding in the samples containing the membrane and cytisine (B), i.e.,

Specific binding = (C) = (A) - (B).

Specific binding in the presence of the test compound (E) is the difference between the total binding in the presence of the test compound (D) and non-specific binding (B), i.e., (E) = (D) - (B).

% Inhibition = (1-((E)/(C)) times 100.

The compounds of the invention that were tested in the above assay exhibited IC_{50} values of less than 10 µM.

The following experimental examples illustrate, but do not limit the scope of, this invention.

EXAMPLE 1

5,6-DIFLUORO-11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2,4,6-TRIENE HYDROCHLORIDE

A) Cyclopent-3-enyl-(2,3-difluoro-6-methoxy-phenyl)-methanol (For leading metalation references, see Example 6A. Cyclopent-3-enecarbaldehyde was derived from the lithium aluminum hydride reduction of cyclopent-3-enecarboxylic acid methoxy-methyl-amide, the preparation of which appears in Example 2A. For reduction conditions, see: Garigipati, R. S.; Tschaen, D. M.; Weinreb, S. M.; *J. Amer. Chem. Soc.* **1990**, *112*, 3475-3482.)

1,2-Difluoro-4-methoxy-benzene (10 g, 69.4 mmol) was stirred in anhydrous (anh.) THF (80 mL) in a dry 250 mL three neck round bottomed flask (3NRB flask) at -78 °C under nitrogen (N_2). To this was added n-butyllithium (n-BuLi) (28 mL, 2.5M/hexanes soln., 70 mmol) over 5 minutes. After stirring below -70 °C for 4.5 hours (h), a solution of cyclopent-3-enecarbaldehyde (5.7 g, 69.4 mmol) in anh. THF (30 mL) was added via addition funnel along the reaction vessel wall while keeping the internal temperature below -70 °C. After stirring for 1/2 hour (h), the reaction mixture was poured into a saturated aqueous ammonium chloride solution (sat. aq. NH_4Cl soln.) (100 mL), and the mixture was stirred and extracted with ethyl ether (Et_2O) (2 x 50 mL). The organic layer was washed with brine (50 mL), dried (Na_2SO_4), filtered, concentrated and chromatographed on silica gel to provide an oil (6.64 g, 40%). (Thin layer chromatography (TLC) 20%EtOAc/hexanes R_f 0.16). ^1H NMR ($CDCl_3$) δ 7.01 (ddd, J=9.0Hz, 1H), 6.58 (m, 1H), 5.72 (ddd, J=5.8,4.5,2.2 Hz, 1H), 5.62 (ddd, J=5.8,4.5,2.2 Hz, 1H), 4.79 (br d, J=9.5 Hz, 1H), 3.85 (s, 3H), 3.20 (br s, OH), 2.87 (m, 1H), 2.52 (AB m, 2H), 1.99 (AB m, 2H). GCMS m/e 240 (M^+).

B) 2-Cyclopent-3-enylmethyl-3,4-difluoro-1-methoxy-benzene (For related examples, see: Leeson, P. D.; Emmett, J. C.; Shah, V. P.; Showell, G. A.; Novelli, R. *J. Med. Chem.* **1989**, *32*, 320-336.)

Cyclopent-3-enyl-(2,3-difluoro-6-methoxy-phenyl)-methanol (6.64 g, 27.7 mmol) and triethylsilane (3.38 g, 29 mmol) were stirred in CH_2Cl_2 (40 mL) at 0°C. To this solution was added trifluoroacetic acid (17.3 mL, 224 mmol). The mixture was stirred at ambient temperature for 18 hours. The mixture was concentrated to an oil, which was dissolved in hexanes (100 mL), washed with water (H_2O) (2 x 50 mL) and a saturated aqueous sodium bicarbonate solution (sat. aq. $NaHCO_3$ soln.) (50 mL), and then dried (sodium sulfate (Na_2SO_4)), filtered, concentrated and chromatographed on Silica gel to provide an oil (3.67 g, 59%). (TLC hexanes R_f 0.38).

^{1}H NMR ($CDCl_3$) δ 6.92 (ddd, J=9.3 Hz, 1H), 6.49 (br d, J=9.3 Hz, 1H), 5.66 (br s, 2H), 3.78 (s, 3H), 2.72 (dd, J=7.5,2.0 Hz, 2H), 2.57 (m, 1H), 2.36 (AB m, 2H), 2.06 (AB dd, J=14.2,5.5 Hz, 2H). GCMS m/e 224 (M^+).

C) 2-Cyclopent-3-enylmethyl-3,4-difluoro-phenol

2-Cyclopent-3-enylmethyl-3,4-difluoro-1-methoxy-benzene (3.67 g, 16.38 mmol) and n-Bu_4NI (7.17 g, 19.4 mmol) were stirred in dry CH_2Cl_2 (50 mL) at -78 °C under nitrogen (N_2). To this was added boron trichloride (BCl_3) (22 mL, 1M CH_2Cl_2 soln., 22 mmol) over 2 minutes (min.). After 5 min., the solution was allowed to warm to room temperature (rt) and stirred for 2 hours. The reaction was quenched with H_2O (100 mL) and stirred for 1 hour. The layers were separated and the aq. layer extracted with methylene chloride (CH_2Cl_2) (2 x 30 mL). The combined organic layer was washed with H_2O (2 x 50 mL), and a sat. aq. $NaHCO_3$ soln. (50 mL), dried through a cotton plug, concentrated and chromatographed on silica gel to provide an oil (3.30 g, 96%). (TLC 50% ethyl acetate (EtOAc)/hexanes (hex) R_f 0.70). ^{1}H NMR ($CDCl_3$) δ 6.85 (ddd, J=9.0 Hz, 1H), 6.46 (m, 1H), 5.68 (br s, 2H), 4.76 (br s, 1H), 2.71 (d, J=8.0 Hz, 2H), 2.61 (m, 1H), 2.39 (AB m, 2H), 2.09 (AB dd, J=14.0,5.4 Hz, 2H). GSMS m/e 210 (M^+).

D) Trifluoro-methanesulfonic acid 2-cyclopent-3-enylmethyl-3,4-difluoro-phenyl ester

(For a leading reference, see: Su, T. M.; Sliwinski, W. F.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1969**, *91*, 5386.)

2-Cyclopent-3-enylmethyl-3,4-difluoro-phenol (3.30 g, 15.7 mmol) and pyridine (2.49 g, 31.5 mmol) were stirred in CH_2Cl_2 (50 mL) at -78 °C under N_2 and treated with trifluoromethane sulfonic anhydride (6.20 g, 22.0 mmol) dropwise over 20 min. The mixture was allowed to warm to rt and stirred for 1/2 hour then poured into 1N aq. HCl soln. and shaken. The layers were separated and the aq. layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layer was washed with H_2O (50 mL), and a sat. aq. $NaHCO_3$ soln. (50 mL), dried through a cotton plug, concentrated and chromatographed on silica gel to provide an oil (4.34 g, 81%). (TLC 30%EtOAc/Hex R_f 0.60). ^{1}H NMR ($CDCl_3$) δ 7.13-7.03 (2H), 5.67 (br s, 2H), 2.82 (dd, J=7.5,2.0 Hz, 2H), 2.58 (m, 1H), 2.40 (dd, J=14.0,8.0 Hz, 2H), 2.05 (dd, J=14.0,5.5 Hz, 2H). GCMS *m/e* 342 (M^+).

E) 5,6-Difluorotricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3,5,10-tetraene

Trifluoro-methanesulfonic acid 2-cyclopent-3-enylmethyl-3,4-difluoro-phenyl ester (340 mg, 0.99 mmol), was dissolved in DMF (5 mL) under a N_2 atmosphere and treated with diisopropylethylamine (0.26 mL, 1.5 mmol), potassium acetate (981 mg, 10.0 mmol) and tri-o-tolylphosphine (12 mg, 0.04 mmol). This mixture was stirred and degassed (3 vacuum/N_2 purge cycles) and then treated with palladium acetate (5 mg, 0.02 mmol). After 20 min. the mixture was warmed to 100 °C for 18 hours, cooled and poured into brine (50 mL). The

resulting mixture was extracted with hexanes (4 x 25 mL) and the combined organic layer was washed with a sat. aq. $NaHCO_3$ soln. (10 mL), water (H_2O) (10 mL), brine (10 mL), dried (magnesium sulfate ($MgSO_4$)), filtered and and chromatographed on silica gel to provide an oil (110 mg, 60%). (TLC hexanes R_f 0.58). ^1H NMR ($CDCl_3$) δ 6.80 (ddd, J=6.6,8.1,8.3 Hz, 1H), 6.68 (m, 1H), 6.17 (dd, J=5.5,2.8 Hz, 1H), 5.77 (dd, J=5.5,2.8 Hz, 1H), 3.29 (br s, 1H), 2.96 (br s, 1H), 2.84 (AB dd, J=17.9,5.0 Hz, 1H), 2.54 (AB d, J=17.9 Hz, 1H), 2.19 (m, 1H), 1.77 (d, J=10.5 Hz, 1H). GCMS m/e 192 (M^+).

F) 5,6-Difluoro-10,11-dihydroxytricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3,5-triene

5,6-Difluorotricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3,5,10-tetraene (714 mg, 3.72 mmol) and N-methyl morpholine N-oxide (553 mg, 4.10 mmol) were stirred in acetone (20 mL) and H_2O (3 mL). To this was added a solution of osmium tetraoxide (OsO_4) (0.2 mL, 2.5%wt. soln. in t-butanol (t-BuOH), 0.02 mmol). After 18 hours, the mixture was concentrated to an oil, dissolved in a minimum of CH_2Cl_2 and filtered through a silica pad (3 x 3 mm) eluting with 20% EtOAc/hexanes. Product containing fractions were concentrated to an oil (850 mg, 100%). (TLC 20% EtOAc/hexanes R_f 0.37). ^1H NMR ($CDCl_3$) δ 6.88 (ddd, J=9.3,8.5,7.6 Hz, 1H), 6.78 (m, 1H), 4.01 (AB d, 2H), 3.06 (br s, 1H), 2.92 (AB dd, J=17.9,5.0 Hz, 1H), 2.75 (br AB, J=17.9 Hz, 1H), 2.44 (br s, 1H), 2.32 (2-OH), 2.26 (m, 1H), 1.50 (d, J=7.8 Hz, 1H). GCMS m/e 226 (M^+).

G) 5,6-Difluoro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene hydrochloride

5,6-Difluoro-10,11-dihydroxytricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3,5-triene (840 mg, 3.72 mmol) was stirred in a parr bottle in ethanol (EtOH) (30 mL) and H_2O (10 mL). To this a soln. of sodium periodate ($NaIO_4$) (810 mg, 3.72 mmol) in H_2O (5 mL) was added. The resulting milky white dispersion was stirred 15 min., then treated with 37% aq. ammonium hydroxide (NH_4OH) soln. (25 mL) and palladium hydroxide ($Pd(OH)_2$) (360 mg, 20%wt/C) and shaken under 45 psi of H_2. After 18 hours, the mixture was filtered through a Celite pad and rinsed with EtOH and a 3:1 ethanol: water mixture. The filtrate was concentrated to an oily solid which was dissolved in EtOAc (50 mL) and washed with sat. aq. sodium carbonate (Na_2CO_3) soln. (2 x 20 mL). The organic layer was dried sodium sulfate (Na_2SO_4)), filtered, concentrated and chromatographed on Silica gel to provide an oil (330 mg, 42%). (TLC 5%MeOH/CH_2Cl_2 R_f 0.36). ^1H NMR ($CDCl_3$) δ 6.92 (ddd, J=8.1,8.5,10.0 Hz, 1H), 6.74 (m, 1H), 3.02-2.93 (4H), 2.83-2.71 (3H), 2.09 (br s, 1H), 1.98 (br d, J=12.5 Hz, 1H), 1.82 (br d, J=12.5 Hz, 1H). GSMS m/e 209 (M^+). APCI MS m/e 209.8 [$(M+1)^+$].

The product was dissolved in methanol (CH_3OH) and treated with 3M hydrochloric acid (HCl)/EtOAc (3 ml). The resulting slurry was concentrated, dissolved in a minimum of MeOH, saturated with Et_2O and stirred for 18 hours. The solids were filtered to give white solid (335 mg, 86%). mp 290-305 °C.

EXAMPLE 2

11-BENZYL-6-METHOXY-11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) Cyclopent-3-enecarboxylic acid methoxy-methyl-amide (For preparation of cyclopent-3-enecarboxylic acid, see: Depres, J-P.; Greene, A. E. *J. Org. Chem.* **1984**, *49*, 928-931, and for more recent approaches, see: a) Nugent, W. A.; Feldman, J.; Calabrese, J. C. *J. Am. Chem. Soc.* **1995**, *117*, 8992-8998, and b) Marinez, L. E.; Nugent, W. A.; Jacobsen, E. N. *J. Org. Chem.* **1996**, *61*, 7963-7966. For related methods for amide formation, see: Nitz, T. J.; Volkots, D. L.; Aldous, D. J.; Oglesby, R. C. *J. Org. Chem.* **1994**, *59*, 5828-5832.)

Cyclopent-3-enecarboxylic acid (65.6 g, 586 mmol) in CH_2Cl_2 (1 L) was treated with carbonyl diimidazole (100 g, 617 mmol) in portions. After ~3/4 h, the resulting solution was treated with N,O-dimethylhydroxylamine (60.8 g, 623 mmol) and the mixture was stirred for 40 h. The reaction was quenched with 1N aq. HCl soln. (600 mL), shaken and the layers were separated. The aq. layer was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layer was washed with 1N aq. HCl soln. (100 mL), H_2O (2 x 150 mL), 50% sat. aq. Na_2CO_3 soln./brine (200 mL) and dried through a cotton plug. The filtrate was diluted with EtOAc to ~10%EtOAc/CH_2Cl_2 and filtered through a silica pad (10 x 10 mm) eluting with 10%EtOAc/ CH_2Cl_2 to remove baseline color. Concentration affords a liquid (86 g, 95%). (TLC 10%EtOAc/ CH_2Cl_2 R_f 0.56). ^1H NMR ($CDCl_3$) δ 5.64 (br s, 2H), 3.69 (s, 3H), 3.47 (m, 1H), 3.19 (s, 3H), 2.61 (m, 4H). GSMS m/e 155 (M^+).

B) Cyclopent-3-enyl-(2,6-dimethoxy-phenyl)-methanone (For a leading reference, see: Koft, E. R.; Smith, A. B., III. *J. Am. Chem. Soc.* **1982**, *104*, 2659.)

1,3-Dimethoxybenzene (31.9 g, 231 mmol) was stirred in anh. Et_2O (200 mL) at 0°C under N_2 and treated with n-butyllithium (n-BuLi) (92.5 mL, 2.5M/hexanes soln., 231 mmol) over 5 minutes. The solution was brought to reflux for 4h, then cooled to -78 °C. The slurry was treated with cyclopent-3-enecarboxylic acid methoxy-methyl-amide (35.9 g, 231 mmol) dropwise over ~1 hour, then the mixture was stirred for 18 hours (the cooling bath evaporated overnight). The mixture was poured into 1N aq. HCl soln. (200 mL) and shaken. The layers were separated and the aq. layer extracted with Et_2O (2 x 100 mL). The organic layer was washed with H_2O (50 mL), and a sat. aq. $NaHCO_3$ soln. (100 mL), dried (Na_2SO_4), filtered through a silica plug and concentrated to an oil (52.6 g, 98%). (TLC 10%EtOAc/hexanes R_f 0.25). ^1H NMR ($CDCl_3$) δ 7.24 (t, J=8.4 Hz, 1H), 6.24 (d, J=8.4 Hz, 2H), 5.63 (br s, 2H), 3.76 (s, 6H), 3.68 (m, 1H), 2.75 (m, 2H), 2.48 (m, 2H). GSMS m/e 232 (M^+).

C) Cyclopent-3-enyl-(2-hydroxy-6-methoxy-phenyl)-methanone (For a leading reference, see: Nagaoka, H.; Schmid, G.; Iio, H.; Kishi, Y. *Tetrahedron Lett.* **1981**, *22*, 899.)

Cyclopent-3-enyl-(2,6-dimethoxy-phenyl)-methanone (52.6 g, 226 mmol) was stirred in CH_2Cl_2 (200 mL) at -78 °C under N_2 and treated with boron trichloride (BCl_3) (273 mL, 1M CH_2Cl_2 soln., 273 mmol) over 30 min. The mixture was allowed to warm to ambient temperature and was treated with additional BCl_3 (41.0 mL, 1M CH_2Cl_2 soln., 41.0 mmol). After the mixture was stirred 20 min., it was poured slowly into H_2O (300 mL) and stirred for 30 min. The layers were separated and the aq. layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layer was washed with H_2O (3 x 100 mL), sat. aq. $NaHCO_3$ soln. (100 mL), dried through a cotton plug and filtered through a Silica pad to remove baseline color. Concentration affords an amber oil (46.0 g, 93%). (TLC 10%EtOAc/hexanes R_f 0.50). ^1H NMR ($CDCl_3$) δ 7.32 (t, J=8.5 Hz, 1H), 6.57 (dd, J=8.5,1.0 Hz, 1H), 6.38 (dd, J=8.5,1.0 Hz, 1H), 5.66 (br s, 2H), 4.31 (m, 1H), 3.89 (s, 3H), 2.80-2.63 (4H). GSMS m/e 218 (M^+).

D) Trifluoro-methanesulfonic acid 2-(cyclopent-3-enecarbonyl)-3-methoxy-phenyl ester Cyclopent-3-enyl-(2-hydroxy-6-methoxy-phenyl)-methanone (45.0 g, 206 mmol) and pyridine (36.0 g, 453 mmol) were stirred in CH_2Cl_2 (250 mL) at -78 °C under N_2. To this a solution of trifluoromethane sulfonic anhydride (75.7 g, 268 mmol) in CH_2Cl_2 (100 mL) was added dropwise over 1/2 h. The mixture was allowed to warm to ambient temperature, stirred 1h, then poured into 1N aq. HCl soln. (250 mL). The mixture was shaken, the layers were separated, and the organic layer was washed with 1N aq. HCl soln. (3 x 150 mL), H_2O (2 x 100 mL), sat. aq. $NaHCO_3$ soln. (100 mL) and finally brine (100 mL). The organic layer was dried through a cotton plug and concentrated to an oil which was chromatographed through a Silica gel plug eluting with 10%EtOAc/hexanes to afford after concentration an oil (62.5 g, 87%). (TLC 10%EtOAc/hexanes R_f 0.14). ^1H NMR ($CDCl_3$) δ 7.41 (t, J=8.5 Hz, 1H), 6.95 (dd, J=8.5,1.0 Hz, 2H), 5.64 (br s, 2H), 3.86 (s, 3H), 3.73 (m, 1H), 2.70 (m, 2H), 2.57 (m, 2H). GSMS m/e 350 (M^+).

E) 6-Methoxytricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3,5,10-tetraene-8-one (For leading references, see: Heck, R. F. *Org. React.* (N.Y.) **1982**, *27*, 345, and Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2-7.)

Trifluoro-methanesulfonic acid 2-(cyclopent-3-enecarbonyl)-3-methoxy-phenyl ester (45.0 g, 129 mmol) was dissolved in DMF (100 mL) under a N_2 atmosphere and treated with triethylamine (19.5 g, 193 mmol), potassium acetate (1.89 g, 19.0 mmol) and 1,3-bis(diphenylphosphino)propane (5.30 g, 12.9 mmol). This mixture was stirred and degassed (3 vacuum/N_2 purge cycles) then treated with palladium acetate (1.16 g, 5.14 mmol). After 20 min. the mixture was warmed to 130 °C for 1 hour, cooled and poured into brine (300 mL). The resulting mixture was extracted with EtOAc (4 x 100 mL) and the combined organic layer

was washed with sat. aq. $NaHCO_3$ soln. (100 mL), H_2O (100 mL), and brine (100 mL), dried ($MgSO_4$), filtered and evaporated to an oil. (55 g). The oil was chromatographed on silica gel to provide product as a white solid (12.0 g, 47%). (TLC 25%EtOAc/ hexanes R_f 0.27). ^1H NMR ($CDCl_3$) δ 7.29 (t, J=8.0 Hz, 1H), 6.84 (d, J=8.0 Hz, 1H), 6.73 (d, J=8.0 Hz, 1H), 6.63 (dd, J=5.0,3.0 Hz, 1H), 6.15 (dd, J=5.0,3.0 Hz, 1H), 3.87 (s, 3H), 3.60 (br s, 1H), 3.39 (br s, 1H), 2.56 (AB m, 2H). ^{13}C NMR 195.38, 161.61, 149.82, 143.47, 133.77, 131.84, 131.80, 117.51, 111.46, 57.63, 55.96, 47.63, 47.51. GSMS m/e 200 (M^+). mp 135-136 °C.

F) 6-Methoxytricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3,5,10-tetraene (For a discussion, see: Fieser and Fieser, *Reagents for Organic Synthesis*, (N.Y.) 1967, *I*, p.435.)

6-Methoxytricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3,5,10-tetraene-8-one (3.0 g, 15 mmol) and pulverized KOH (5.05 g, 90 mmol) were warmed in ethylene glycol (40 mL) until solution occurred. The mixture was cooled to room temperature, treated with hydrazine hydrate (3.0 g, 60 mmol) and heated to reflux for 2 hours. The reflux condenser was replaced with a distilling head and distillates were collected from 120-190 °C. These distillates were diluted with H_2O (100 mL) and extracted with EtOAc (4 x 40 mL). The organic layer was washed with H_2O (4 x 30 mL), and brine (25 mL), dried ($MgSO_4$), filtered and concentrated to an oil (2.68 g, 96%). (TLC 50%EtOAc/ hexanes R_f 0.67). ^1H NMR ($CDCl_3$) δ 7.18 (t, J=8.0 Hz, 1H), 6.82 (d, J=8.0 Hz, 1H), 6.77 (d, J=8.0 Hz, 1H), 6.32 (dd, J=5.0,3.0 Hz, 1H), 5.93 (dd, J=5.0,3.0 Hz, 1H), 3.91 (s, 3H), 3.45 (dd, J=5.0,1.5 Hz, 1H), 3.11 (br s, 1H), 2.88 (AB dd, J=17.0,5.0 Hz, 1H), 2.58 (AB d, J=17.0 Hz, 1H), 2.31 (m, 1H), 1.96 (d, J=9.5 Hz, 1H).

G) 6-Methoxy-10,11-dihydroxytricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3,5,10-triene

6-Methoxytricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3,5,10-tetraene (1.5 g, 8.19 mmol) and N-methyl morpholine N-oxide (1.06 g, 9.03 mmol) were stirred in acetone (20 mL) and H_2O (0.16 mL). To this was added a solution of osmiom tetraoxide (OsO_4) (0.2 mL, 2.5%wt. soln. in t-butanol (t-BuOH), 0.02 mmol). After 2 hours, the mixture was diluted with EtOAc (50 mL) and washed with 10%aq. $NaHSO_3$ soln. (30 mL), H_2O (2 x 30 mL), sat. aq. $NaHCO_3$ soln. (30 mL) and brine (30 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to an oil (1.79 g, 99%). (TLC 50%EtOAc/hexanes R_f 0.20).

H) 11-Benzyl-6-methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene hydrochloride (For a discussion of oxidative cleavage with $Pb(OAc_4)$, see: Fieser and Fieser, *Reagents for Organic Synthesis*, (N.Y.) 1967, *I*, p.549. For reductive amination conditions and references, see Abdel-Magid et al., *J. Org. Chem.*, 1996, *61*, 3849; and Mazzocchi et al., *J. Med. Chem.*, 1979, 22, 455.)

1-Methoxy-6,7,8,9-tetrahydro-5H-5,8-methano-benzocycloheptene-6,7-diol (2.40 g, 11.0 mmol) was stirred at 0 °C in CH_2Cl_2 (70 mL) and treated with $Pb(OAc)_4$ (5.08 g, 11.5 mmol). After 2 hours the mixture was filtered through a Celite pad and rinsed with CH_2Cl_2

(10 mL). To the stirred filtrate was added acetic acid (AcOH) (1.97 g, 33.0 mmol) and benzyl amine (1.23 g, 11.5 mmol). After 15 min., the mixture was treated with sodium triacetoxyborohydride ($NaBH(OAc)_3$) (6.94 g, 33.0 mmol) and stirred for 18 hours. The mixture was poured into a sat. aq. $NaHCO_3$ soln. (100 mL) and stirred for 1/2 hour. The layers were separated and extracted with CH_2Cl_2 (2 x 50 mL). The organic layer was washed with a saturated (sat.) aqueous (aq.) sodium bicarbonate ($NaHCO_3$) soln. (2 x 50 mL), H_2O (50 mL), brine (50 mL), dried through a cotton plug, concentrated and purified by chromatography on Silica gel eluting with 10%EtOAc/hexanes to provide product as an oil (1.45 g, 45%). (TLC 25%EtOAc/hexanes R_f 0.76). ^1H NMR ($CDCl_3$) δ 7.12 (m, 4H), 6.89 (m, 2H), 6.74 (d, J=8.0 Hz, 1H), 6.64 (d, J=8.0 Hz, 1H), 3.87 (s, 3H), 3.41 (AB d, J=14.2 Hz, 1H), 3.38 (AB d, J=14.2 Hz, 1H), 2.87-2.70 (m, 5H), 2.36-2.23 (m, 3H), 1.85 (br AB d, J=12.1 Hz, 1H), 1.77 (br AB d, J=12.1 Hz, 1H). This oil was dissolved in a minimum of methanol (MeOH), stirred, and saturated with Et_2O. After 18 hours the white solids were filtered. ^1H NMR (CD_3OD) δ 7.44 (m, 5H), 7.15 (t, J=8.0 Hz, 1H), 6.85 (d, J=8.0 Hz, 1H), 6.68 (d, J=8.0 Hz, 1H), 4.27 (AB d, J=13.0 Hz, 1H), 4.15 (AB d, J=13.0 Hz, 1H), 3.84 (s, 3H), 3.47 (br d , J=12.3 Hz, 1H), 3.36-3.19 (m, 4H), 2.98 (AB dd, J=18.7,7.2 Hz, 1H), 2.85 (AB d, J=18.7 Hz, 1H), 2.60 (br s, 1H), 2.00 (AB d, J=13.0 Hz, 1H), 1.87 (AB d, J= 13.0 Hz, 1H). mp 210-212 °C

EXAMPLE 3

6-METHOXY-11-AZA-TRICYCLO[7.3.1.0^{2,7}]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

11-Benzyl-6-methoxy-11-aza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene hydrochloride (525 mg, 1.64 mmol), ammonium formate (2.07 g, 32.0 mmol) and 10% palladium hydroxide on carbon ($Pd(OH)_2/C$) (200 mg) were combined in MeOH (30 mL) and refluxed for 2 hours. The mixture was filtered hot through Celite and the filtrate concentrated then azeotroped from MeOH (5 x 50 mL) to yield a solid. This was recrystallized from MeOH/Et_2O to provide a white solid (306 mg, 81%). ^1H NMR (free base, $CDCl_3$) δ 7.15 (t, J=8.0 Hz, 1H), 6.74 (d, J=8.0 Hz, 1H), 6.63 (d, J=8.0 Hz, 1H), 3.82 (s, 3H), 3.34 (br d, J=13.0 Hz, 1H), 3.11-3.02 (m, 4H), 2.94 (AB d, J=18.3 Hz, 1H), 2.87 (AB dd, J=18.3,6.5 Hz, 1H), 2.41 (br s, 1H), 1.91 (AB q, 2H). GSMS m/e 203 (M^+). mp 272-274 °C.

EXAMPLE 4

11-AZA-TRICYCLO[7.3.1.0^{2,7}]TRIDECA-2(7),3,5-TRIEN-6-OL

6-Methoxy-11-aza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene hydrochloride (55 mg, 0.23 mmol) was brought to reflux in 48% aq. hydrobronic acid (HBr) (5 mL). After 1 hour the solution was cooled and poured into 1N aq. NaOH soln. adjusted to pH 10 and product was extracted with EtOAc (3 x 40 mL). The organic layer was washed with brine (50 mL), dried ($MgSO_4$) and concentrated to a white solid, which was recrystallized from EtOAc/hexanes (20

mg, 46%). ^{1}H NMR ($CDCl_3$) δ 6.95 (t, J=8.0 Hz, 1H), 6.68 (d, J=8.0 Hz, 1H), 6.53 (d, J=8.0 Hz, 1H), 3.27 (m, 1H), 3.11 (m, 2H), 3.02 (m, 2H), 2.77 (m, 1H), 2.57 (m,1H), 2.33 (br s, 1H), 1.90 (m, 2H). mp 106-108 °C.

EXAMPLE 5

6-FLUORO-11-AZA-TRICYCLO[7.3.1.0^{2,7}]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

3-Fluoromethoxybenzene (15.8 g, 125 mmol) was stirred at -78 °C in anh. THF (100 mL) and treated with n-BuLi (50 mL, 2.5M hexanes soln., 125 mmol) over 5 min. After stirring below –70 °C for 4 hours, the mixture was treated with cyclopent-3-enecarboxylic acid methoxy-methyl-amide (18.4 g, 119 mmol) dropwise over ~1/4 hour. The mixture was stirred below –70 °C for 1 hour, and then allowed to warm to ambient temperature over ~1 hour. The mixture was poured into 1N aq. HCl soln. (200 mL) and shaken. The layers were separated and the aq. layer extracted with EtOAc (3 x 100 mL). The organic layer was washed with H_2O (50 mL), sat. aq. $NaHCO_3$ soln. (100 mL), and brine (50 mL), dried (Na_2SO_4), filtered through a Silica plug and concentrated to an oil (21.0 g, 76%). (TLC 30%EtOAc/ hexanes R_f 0.43). GCMS *m/e* 220 (M^+). This material was converted to the title compound by the methods described in Example 2C-G and Example 1G. (TLC 10%MeOH/CH_2Cl_2 (NH_3) R_f 0.20). ^{1}H NMR (CD_3OD) δ 7.24 (m, 1H), 7.01 (m, 2H), 3.36 (d, J=13.0 Hz, 1H), 3.33-3.10 (m, 5H), 2.90 (d, J=18.5 Hz, 1H), 2.60 (m, 1H), 2.13 (AB d, J=13.0 Hz, 1H), 1.97 (AB d, J= 13.0 Hz, 1H). mp 240-241 °C.

EXAMPLE 6

11-BENZYL-5-METHOXY-11-AZA-TRICYCLO[7.3.1.0^{2,7}]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) Cyclopent-3-enyl-(2,5-dimethoxy-phenyl)-methanone (For a discussion of halogen-metal exchange, see: Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300.)

2-Bromo-1,4-dimethoxy-benzene (42.2 g, 195 mmol) was stirred in Et_2O (200 mL) under N_2 at -78 °C. The resulting precipitate was dissolved by the addition of THF (50 mL). To the resulting solution was added n-BuLi (78 mL, 2.5M in hexanes, 195 mmol) over 10 min. After stirring 10 min., the yellow solution was treated with cyclopent-3-enecarboxylic acid methoxy-methyl-amide (29.15 g, 188 mmol) in Et_2O (50 mL) over 10 min., then the mixture was stirred for 18 hours (the cooling bath evaporated overnight). The mixture was poured into 10% aq. HCl soln. (400 mL) and shaken. The layers were separated and the aq. layer extracted with Et_2O (3 x 50 mL). The organic layer was washed with H_2O (50 mL), a sat. aq. $NaHCO_3$ soln. (100 mL), dried (Na_2SO_4), filtered through a silica plug and concentrated to an oil (43.0 g, 99%). (In a separate experiment, THF was successfully

substituted for Et_2O in the reaction above.) (TLC 10%EtOAc/hexanes R_f 0.39). ^1H NMR ($CDCl_3$) δ 7.16 (d, J=3.0 Hz, 1H), 6.98 (dd, J=9.0,3.0 Hz, 1H), 6.88 (d, J=9.0 Hz, 1H), 5.64 (br s, 2H), 4.11 (m, 1H), 3.84 (s, 3H), 3.77 (s, 3H), 2.66 (m, 4H).

B) Cyclopent-3-enyl-(2-hydroxy-5-methoxy-phenyl)-methanone

Cyclopent-3-enyl-(2,5-dimethoxy-phenyl)-methanone (40.0 g, 172 mmol) was converted to the title compound as described in Example 2C to provide an oil (39.5 g, crude). (TLC 10%EtOAc/hexanes R_f 0.50). ^1H NMR ($CDCl_3$) δ 7.21 (m, 1H), 7.10 (m, 1H), 6.93 (br d, J=9.0 Hz, 1H), 5.69 (br s, 2H), 4.06 m, 1H), 3.79 (s, 3H), 2.76 (m, 4H). GCMS *m/e* 218 (M^+).

C) Trifluoro-methanesulfonic acid 2-(cyclopent-3-enecarbonyl)-4-methoxy-phenyl ester

Cyclopent-3-enyl-(2-hydroxy-5-methoxy-phenyl)-methanone (39.5 g crude, 172 mmol) and pyridine (28.7 g, 362 mmol) were stirred in CH_2Cl_2 (300 mL) at -78 °C under N_2. To this a solution trifluoromethane sulfonic anhydride (63.8 g, 226 mmol) in CH_2Cl_2 (100 mL) was added dropwise over 1/2 hour. The mixture was allowed to warm to ambient temperature and stirred 1h then poured into a 1N aq. HCl soln. (250 mL). The mixture was shaken, the layers were separated, and the organic layer was washed with a1N aq. HCl soln. (3 x 150 mL), H_2O (2 x 100 mL), a sat. aq. $NaHCO_3$ soln. (100 mL) and, finally, brine (100 mL). The organic layer was dried through a cotton plug and concentrated to an oil which was chromatographed through a Silica gel plug eluting with 10%EtOAc/hexanes to afford after concentration an oil (55.7 g, 93% over 2 steps). GCMS *m/e* 350 (M^+).

D) 5-Methoxytricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3,5,10-tetraene-8-one

Trifluoro-methanesulfonic acid 2-(cyclopent-3-enecarbonyl)-4-methoxy-phenyl ester (19.09 g, 54.5 mmol) was dissolved in DMF (100 mL) under a N_2 atmosphere and treated with diisopropylethylamine (10.6 g, 82.0 mmol), potassium acetate (1.07 g, 11.0 mmol) and 1,3-bis(diphenylphosphino)propane (2.25 g, 5.46 mmol). This mixture was stirred and degassed (3 vacuum/N_2 purge cycles) then treated with palladium acetate (0.49 g, 2.18 mmol). After stirring 20 min. the mixture was warmed to 120 °C for 18 hours, cooled and poured into brine (300 mL). The resulting mixture was extracted with EtOAc (4 x 100 mL) and the combined organic layer was washed with a sat. aq. $NaHCO_3$ soln. (100 mL), H_2O (100 mL), brine (100 mL), dried ($MgSO_4$), filtered, concentrated and chromatographed on silica gel to provide an oil (10.4 g, 95%). (elute w/ 7%EtOAc/hexanes). ^1H NMR ($CDCl_3$) δ 7.41 (d, J=2.8 Hz, 1H), 7.03 (d, J=8.0 Hz, 1H), 6.88 (dd, J=8.0,2.8 Hz, 1H), 6.72 (dd, J=5.2,3.0 Hz,1H), 6.06 (dd, J=5.2,3.2 Hz, 1H), 3.77 (s, 3H), 3.60 (dd, J=4.3,3.2 Hz, 1H), 3.44 (dd, J=5.0,3.4 Hz, 1H), 2.65 (AB m, 1H), 2.56 (br AB d, J=10.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) 196.11, 158.87, 145.90, 140.34, 130.295, 129.94, 126.14, 119.42, 111.90, 55.61, 55.48, 49.08, 45.97. GCMS *m/e* 200 (M^+).

E) 5-Methoxytricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3,5,10-tetraene

5-Methoxytricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3,5,10-tetraene-8-one (9.41 g, 47 mmol) and pulverized potassium hydroxide (KOH) (6.17 g, 110 mmol) were warmed in ethylene glycol (50 mL) until solution occurred. The mixture was cooled to rt, treated with hydrazine hydrate (6 mL, 190 mmol) and heated to reflux for 2 hours. The reflux condenser was replaced with a distilling head and distillates were collected from 120-190 °C. The distillates were diluted with H_2O (100 mL) and extracted with EtOAc (4 x 40 mL). The organic layer was washed with H_2O (4 x 30 mL), brine (25 mL), dried ($MgSO_4$), filtered and concentrated to an oil (8.2 g, 94%). (TLC 25%EtOAc/ hexanes R_f 0.68). ^{1}H NMR ($CDCl_3$) δ 6.92 (d, J=8.0 Hz, 1H), 6.88 (m, 2H), 6.25 (dd, J=5.1,2.5 Hz, 1H), 5.79 (dd, J=5.1,2.4 Hz, 1H), 3.77 (s, 3H), 3.31 (br s, 1H), 3.01-2.94 (2H), 2.56 (d, J=16.5 Hz, 1H), 2.22 (m, 1H), 1.85 (d, J=10.0 Hz, 1H). GCMS *m/e* 186 (M^+).

F) 5-Methoxy-10,11-dihydroxytricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3,5,10-triene

5-Methoxytricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3,5,10-tetraene (6.66 g, 35.7 mmol) was converted to the title compound as described in Example 2G to provide an oil (7.86 g, 100%). (TLC 10%MeOH/CH_2Cl_2 R_f 0.44). ^{1}H NMR ($CDCl_3$) δ 6.95 (d, J=8.0 Hz, 1H), 6.63 (dd, J=8.0,2.5 Hz, 1H), 6.56 (br s, 1H), 4.00 (s, 3H), 3.77 (m, 3H), 3.04-2.99 (m, 2H), 2.69 (d, J=13.0 Hz, 1H), 2.41 (br s, 1H), 2.33 (br s, 1H), 2.22 (m, 1H), 1.52 (d, J=11.5 Hz, 1H).

G) 11-Benzyl-5-methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene hydrochloride

5-Methoxy-10,11-dihydroxytricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3,5,10-triene (18.0 g, 79.0 mmol) was stirred at 0 °C in CH_2Cl_2 (150 mL) and treated with lead tetraacetate ($Pb(OAc)_4$) (35.0 g, 79.0 mmol). After 30 min. the mixture was filtered through a Celite pad and rinsed with CH_2Cl_2 (50 mL). To the stirred filtrate was added AcOH (23.7 g, 395 mmol) and benzyl amine (8.50 g, 79.0 mmol). After 15 min., the mixture was treated with $NaBH(OAc)_3$ (50.2 g, 237 mmol) and stirred for 18 hours. The mixture was poured into a sat. aq. Na_2CO_3 soln. (100 mL) stirred for 1/2 hour. The layers were separated and extracted with CH_2Cl_2 (2 x 100 mL). The organic layer was washed with a sat. aq. Na_2CO_3 soln. (2 x 50 mL), H_2O (50 mL), and then brine (50 mL), dried through a cotton plug and concentrated to an oil. Chromatography on silica gel eluting with 5%EtOAc/hexanes provided product as an oil (9.48 g, 41%). (TLC 25%EtOAc/hexanes R_f 0.69). ^{1}H NMR ($CDCl_3$) δ 7.15 (m, 3H), 6.92 (m, 3H), 6.71 (br s, 1H), 6.67 (dd, J=8.0,2.5 Hz, 1H), 3.83 (s, 3H), 3.99 (s, 2H), 3.07 (AB dd, J=17.5,7.0 Hz, 1H), 2.85 (br s, 1H), 2.83 (m, 1H), 2.79 (AB d, J=17.5 Hz, 1H), 2.70 (br d, J=10.5 Hz, 1H), 2.35 (dd, J=10.5,2.0 Hz, 1H), 2.27 (dd, J=10.2,2.0 Hz, 1H), 2.15 (br s, 1H), 1.86 (AB d, J=12.3 Hz, 1H), 1.78 (AB d, J=12.3 Hz, 1H). GCMS *m/e* 293 (M^+). This material was dissolved in excess 1N HCl-MeOH and concentrated. The solids were dissolved in a

minimum of MeOH, stirred, and saturated with Et_2O. After stirring 18h the white solids were filtered (900 mg, 58%). ^1H NMR (CD_3OD) δ 7.40 (m, 5H), 7.00 (d, J=8.0 Hz, 1H), 6.73 (m, 2H), 4.28 (AB d, J=13.5 Hz, 1H), 4.16 (AB d, J=13.5 Hz, 1H), 3.76 (s, 3H), 3.48 (br d , J=12.0 Hz, 1H), 3.35-3.20 (m, 5H), 2.98 (AB d, J=18.4 Hz, 1H), 2.54 (br s, 1H), 2.01 (AB d, J=12.0 Hz, 1H), 1.89 (AB d, J= 12.0 Hz, 1H). mp 233-234 °C.

EXAMPLE 7

11-BENZYL-11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5-TRIEN-5-OL HYDROCHLORIDE

11-Benzyl-5-methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene (203 mg, 0.62 mmol) was brought to reflux in 48%HBr (5 mL). After 1 hour the solution was cooled and poured into an aq. NH_4OH soln., the pH was adjusted to ~9 and the product was extracted with EtOAc (3 x 40 mL). The organic layer was washed with brine (50 mL), dried ($MgSO_4$) and concentrated to an oil. (TLC 25%EtOAc/hexanes (NH_3) R_f 0.37). This material was dissolved in excess 1N HCl in MeOH and concentrated. Recrystallization from MeOH/Et_2O provided a solid (154 mg, 80%). ^1H NMR ($CDCl_3$) δ 7.42 (m, 5H), 6.90 (d, J=8.0 Hz, 1H), 6.60 (m, 2H), 4.27 (AB d, J=13.0 Hz, 1H), 4.15 (AB d, J=13.0 Hz, 1H), 3.47 (d, J=12.2 Hz, 1H), 3.33-3.15 (5H), 2.86 (d, J=18.0 Hz, 1H), 2.52 (br s, 1H), 1.99 (AB d, J=12.5 Hz, 1H), 1.88 (AB d, J=12.5 Hz, 1H). mp 251-253 °C.

EXAMPLE 8

5-METHOXY-11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

11-Benzyl-5-methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene hydrochloride (206 mg, 0.63 mmol) was converted to the title compound by the method described in Example 3 to provide a white solid (122 mg, 81%). (TLC 10 %MeOH/CH_2Cl_2 (NH_3) R_f 0.48). ^1H NMR (CD_3OD) δ 7.08 (d, J=8.0 Hz, 1H), 6.77 (m, 2H), 3.76 (s, 3H), 3.31-3.12 (m, 6H), 2.98 (AB d, J=18.4 Hz, 1H), 2.43 (br s, 1H), 2.10 (AB d, J=13.0 Hz, 1H), 1.94 (AB d, J= 13.0 Hz, 1H). GSMS m/e 203 (M^+). mp 253.5-258 °C.

EXAMPLE 9

11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5-TRIEN-5-OL HYDROCHLORIDE

5-Methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene hydrochloride (187 mg, 0.78 mmol) was brought to reflux in 48%HBr (5 mL). After 1 hour the solution was cooled and poured into aq. NH_4OH soln., the pH was adjusted to ~9 and the product was extracted with EtOAc (3 x 40 mL). The organic layer was washed with brine (50 mL), dried ($MgSO_4$) and concentrated to a solid. (TLC 10 %MeOH/CH_2Cl_2 (NH_3) R_f 0.13). This material was dissolved in excess 1N HCl MeOH and concentrated. Recrystallization from MeOH/Et_2O provided a solid (70 mg, 40%). ^1H NMR (CD_3OD) δ 6.99 (d, J=8.0 Hz, 1H), 6.63 (m, 2H),

3.48-3.11 (6H), 2.83 (d, J=18.0 Hz, 1H), 2.42 (br s, 1H), 2.08 (AB d, J=12.5 Hz, 1H), 1.93 (AB d, J= 12.5 Hz, 1H). mp 295-298 °C.

EXAMPLE 10

11-BENZYL-5-DIFLUOROMETHOXY-11-AZA-TRICYCLO[7.3.1.0^{2,7}]TRIDECA-2(7),3,5-TRIENE (For leading references, see: Langlois, B. R. *J. Fluorine Chem.* **1988**, *41*, 247-262.)

11-Benzyl-11-aza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-trien-5-ol (572 mg, 2.05 mmol) was stirred in dioxane (5 mL) and H_2O (1 mL) at reflux under a balloon of freon (HCF_2Cl). To this was added 3N KOH dropwise so as to maintain a pH~12. The consumption of starting material was monitored by TLC for over 2 hours. The reaction was cooled, diluted with H_2O (40 mL) and extracted with EtOAc. The organic layer was washed with a sat. aq. Na_2CO_3 soln. (25 mL) and brine (25 mL), dried ($MgSO_2$), filtered and concentrated to an oil (620 mg, 92%). GCMS *m/e* 329 (M^+).

EXAMPLE 11

5-DIFLUOROMETHOXY-11-AZA-TRICYCLO[7.3.1.0^{2,7}]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

11-Benzyl-5-difluoromethoxy-11-aza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene (620 mg, 1.88 mmol) was converted to the title compound as described in Example 3. The HCl salt was generated as in Example 9 to provide product as a white powder (280 mg, 54%). ^{1}H NMR ($CDCl_3$) δ 7.42 (m, 5H), 7.01 (d, J=9.0 Hz, 1H), 6.92 (m, 2H), 6.48 (t, J=74 Hz, 1H), 3.37 (d, J=13.0 Hz, 1H), 3.18-3.04 (6H), 2.39 (br s, 1H), 1.95 (br s, 2H). GCMS *m/e* 239 (M^+). mp 230-234 °C.

EXAMPLE 12

11-BENZYL-5-ETHYL-11-AZA-TRICYCLO[7.3.1.0^{2,7}]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE (For a review, see: Mitsunobu, O. *Synthesis*, **1981**, 1.)

11-Benzyl-11-aza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-trien-5-ol (208 mg, 0.75 mmol), ethanol (69 mg, 1.49 mmol) and triphenylphosphine (391 mg, 1.49 mmol) were stirred under N_2 at 0°C in THF (2.5 mL). To this was added diethylazodicarboxylate (259 mg, 1.49 mmol) dropwise. After 18 hours, the reaction was concentrated, diluted with Et_2O (20 mL) and extracted with 1% aq. phosphoric acid (H_3PO_4) soln. (3 x 20 mL). The combined aq. layer was extracted with Et_2O (10 mL) and then basified to pH 10 with 1N NaOH soln. Product was extracted with EtOAc (3 x 20 mL) and the combined organic layer was washed with 1N NaOH soln. (20 mL) and brine (20 mL). The solution was dried ($MgSO_4$), filtered and evaporated to an oil (170 mg, 74%). (TLC 17%EtOAc/hexanes (NH_3) R_f 0.76). ^{1}H NMR ($CDCl_3$) δ 7.12 (m, 3H), 6.91 (m, 2H), 6.86 (d, J=8.0 Hz, 1H), 6.68 (br s, 1H), 6.63 (dd,

J=8.0,2.5 Hz, 1H), 4.03 (q, 2H), 3.37 (br s, 2H), 3.03 (dd, J=17.0,7.0 Hz, 1H), 2.82-2.68 (4H), 2.18 (2H), 2.12 (br s, 1H), 1.83 (AB d, J=12.0 Hz, 1H), 1.75 (AB d, J=12.0 Hz, 1H), 1.43 (t, J=7.0 Hz, 3H). GCMS *m/e* 307 (M^+). This material was dissolved in excess 1N HCl MeOH and concentrated. Recrystallization from CH_2Cl_2/Et_2O provided a solid (185 mg, 97%). mp 200-203 °C.

EXAMPLE 13

5-ETHYL-11-AZA-TRICYCLO[7.3.1.0^{2,7}]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

11-Benzyl-5-Ethyl-11-aza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene hydrochloride (160 mg, mmol), ammonium formate (220 mg, 3.49 mmol) and 10%$Pd(OH)_2$/C (100 mg) were combined in methanol (MeOH) (5 mL) and warmed to reflux for 15 min. The mixture was cooled, filtered, concentrated, diluted with sat. aq. Na_2CO_2 soln. and extracted with EtOAc (3 x 20 mL). The extracts were dried ($MgSO_4$), filtered and concentrated to an oil (94 mg, 83%). (TLC 50%EtOAc/hexanes (NH_3) R_f 0.20). ^{1}H NMR ($CDCl_3$) δ 6.90 (d, J=9.0 Hz, 1H), 6.66 (2H), 3.97 (m, 2H), 3.08 (dd, J=18.0,6.0 Hz, 1H), 2.94 (m, 3H), 2.76-2.65 (3H), 1.96 (m, 2H), 1.88 (d, J=11.0 Hz, 1H), 1.38 (t, J=7.0 Hz, 3H). This material was dissolved in excess 1N HCl MeOH and concentrated. Recrystallization from CH_2Cl_2/Et_2O provided a solid (74 mg, 68%). mp 243-245 °C.

EXAMPLE 14

5-ISOPROPOXY-11-AZA-TRICYCLO[7.3.1.0^{2,7}]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

11-Benzyl-11-aza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-trien-5-ol (208 mg, 0.75 mmol) and isopropyl alcohol (90 mg, 1.49 mmol) were converted to the title compound as described in Examples 12. (TLC of intermediate benzyl compound, 17%EtOAc/hexanes R_f 0.78). GCMS *m/e* 321 (M^+). Deprotection and conversion to the salt as described in Example 13 provided a solid (83 mg, 42% overall). (TLC of title compound, TLC 50%EtOAc/hexanes (NH_3) R_f 0.10). ^{1}H NMR ($CDCl_3$) δ ^{1}H NMR ($CDCl_3$) δ 6.89 (d, J=9.0 Hz, 1H), 6.66 (2H), 4.51 (m, 1H), 3.08 (dd, J=18.0,6.5 Hz, 1H), 2.98 (m, 3H), 2.78-2.68 (3H), 1.96 (m, 2H), 1.87 (d, J=11.0 Hz, 1H), 1.32 (t, J=5.5 Hz, 6H). mp 211-213 °C.

EXAMPLE 15

11-BENZYL-4-METHOXY-11-AZA-TRICYCLO[7.3.1.0^{2,7}]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 2-Cyclopent-3-enylmethyl-5-methoxy-phenol (For leading references, see: a) Nagata, W.; Okada, K.; Aoki, T. *Synthesis* **1979**, 365-366; b) Lau, C. K.; Williams, H. W. R.; Tardiff, S.; Dufresne, C.; Scheigetz, J.; Belanger, P, C. *Can. J. Chem.* **1989**, *67*, 1384-1387.)

3-Methoxyphenol (5.12 g, 42.0 mmol), cyclopent-3-enecarbaldehyde (8.00 g, 83.0 mmol), phenyl boronic acid (5.58 g, 46 mmol) and 1,1,1-trichloroacetic acid (2.04 g, 12.5 mmol) were refluxed in benzene (150 mL) for 18 hours. (TLC 5%CH_2Cl_2/hexanes R_f 0.47). The mixture was concentrated to an oil which was stirred at 0 °C in CH_2Cl_2 (100 mL) and treated with triethylsilane (8.67 g, 76.0 mmol) followed by trifluoroacetic acid (36.3 g, 318 mmol). The mixture was stirred for 1 hour then warmed to reflux for 24 hours. The mixture was concentrated, dissolved in CH_2Cl_2 (200 mL) and washed with a sat. aq. $NaHCO_3$ soln. (3 x 50 mL). The combined organic layer was dried through a cotton plug, concentrated and chromatographed on silica gel to provide an oil (3.85 g, 45%). (TLC 10%EtOAc/hexanes R_f 0.35). ^1H NMR ($CDCl_3$) δ 6.99 (d, J=8.0 Hz, 1H), 6.42 (dd, J=8.0,2.5 Hz, 1H), 6.36 (d, J=2.5 Hz, 1H), 5.67 (br s, 2H), 3.75 (s, 3H), 2.58 (m, 3H), 2.40 (m, 2H), 2.08 (m, 2H). GCMS *m/e* 204 (M^+).

B) Trifluoro-methanesulfonic acid 2-cyclopent-3-enylmethyl-5-methoxy-phenyl ester

2-Cyclopent-3-enylmethyl-5-methoxy-phenol (3.85 g, 19.0 mmol) was converted to the title compound (4.92 g, 77%) by the method described in Example 1D. (TLC 10%CH_2Cl_2/hexanes R_f 0.52). ^1H NMR ($CDCl_3$) δ 7.21 (d, J=8.0 Hz, 1H), 6.86 (dd, J=8.0,2.5 Hz, 1H), 6.79 (d, J=2.5 Hz, 1H), 5.67 (br s, 2H), 3.79 (s, 3H), 2.70 (d, J=7.5 Hz, 2H), 2.59 (m, 1H), 2.43 (m, 2H), 2.03 (m, 2H).

C) 4-Methoxytricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3,5,10-tetraene

Trifluoro-methanesulfonic acid 2-cyclopent-3-enylmethyl-5-methoxy-phenyl ester (2.00 g, 5.95 mmol) was dissolved in DMF (10 mL) under a N_2 atmosphere and treated with triethylamine (0.91 g, 8.92 mmol) and 1,3-bis(diphenylphosphino)propane (0.37 g, 0.89 mmol). This mixture was stirred and degassed (3 vacuum/N_2 purge cycles), and then treated with palladium acetate (93 mg, 0.42 mmol). After stirring for 20 min. the mixture was warmed to 100 °C for 18 hours, cooled and poured into brine (30 mL). The resulting mixture was extracted with EtOAc (4 x 10 mL) and the combined organic layer was washed with sat. aq. $NaHCO_3$ soln. (10 mL), H_2O (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and evaporated to an oil. The oil was chromatographed on Silica gel (2%CH_2Cl_2/hexanes) to provide product as an oil (1.05 g, 95%). (TLC 10%EtOAc/ hexanes R_f 0.52). ^1H NMR ($CDCl_3$) δ 6.94 (d, J=8.0 Hz, 1H), 6.68 (dd, J=8.0,2.8 Hz, 1H), 6.59 (d, J=2.8 Hz, 1H), 6.23 (dd, J=5.5,2.8 Hz,1H), 5.79 (dd, J=5.5,2.6 Hz, 1H), 3.77 (s, 3H), 3.28 (m, 1H), 2.96-2.89 (m, 2H), 2.49 (d, J=15.5 Hz, 1H), 2.19 (m, 1H), 1.85 (d, J=10.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) 156.94, 144.07, 138.95, 131.24, 131.21, 126.34, 111.73, 111.45, 55.22, 45.10, 40.18, 38.47, 29.49. GCMS *m/e* 186 (M^+).

D) 11-Benzyl-4-methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene hydrochloride

4-Methoxytricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3,5,10-tetraene (1.0 g, 5.37 mmol) was converted to 4-methoxy-10,11-dihydroxytricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3,5,10-triene (0.95 g, 80%) (TLC 50%EtOAc/CH_2Cl_2 R_f 0.48) according to the procedure described in Example 2G. This material was converted to the title compound according to the procedures described in Example 2H with final recrystallization from Et_2O/hexanes (650 mg, 46%). (TLC 50%EtOAc/CH_2Cl_2 R_f 0.67). ^1H NMR (CD_3OD) δ 7.42 (m, 5H), 7.12 (d, J=8.0 Hz, 1H), 6.84 (dd, J=8.0,2.5 Hz, 1H), 6.67 (d, J=2.5 Hz, 1H), 4.27 (AB d, J=13.0 Hz, 1H), 4.17 (AB d, J=13.0 Hz, 1H), 3.72 (s, 3H), 3.48 (br d , J=12.5 Hz, 1H), 3.34-3.16 (m, 5H), 2.86 (AB d, J=18.0 Hz, 1H), 2.55 (br s, 1H), 2.00 (AB d, J=13.0 Hz, 1H), 1.90 (AB d, J= 13.0 Hz, 1H). mp 245-246 °C. 1

EXAMPLE 16

4-METHOXY-11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

11-Benzyl-4-methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene hydrochloride (525 mg, 1.60 mmol) was converted to the title compound by the methods described in Example 3 to provide a white solid (336 mg, 88%). (TLC 40%EtOAc/CH_2Cl_2 (NH_3) R_f 0.22). ^1H NMR (CD_3OD) δ 7.11 (d, J=8.5 Hz, 1H), 6.82 (dd, J=8.5,2.5 Hz, 1H), 6.75 (d, J=2.5 Hz, 1H), 3.76 (s, 3H), 3.34-3.16 (m, 6H), 2.86 (AB d, J=17.7Hz, 1H), 2.45 (m, 1H), 2.11 (AB d, J=13.5 Hz, 1H), 1.94 (AB d, J= 13.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) 158.47, 136.58, 130.15, 127.71, 114.11, 112.61, 54.32, 49.99, 49.47, 32.16, 31.97, 27.15, 25.70. mp 259-261 °C. 2

EXAMPLE 17

11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5-TRIEN-4-OL

4-Methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene hydrochloride (120 mg, 0.50 mmol) was brought to reflux in 48%HBr (2 mL). After 1 hour the solution was cooled and poured into a 1N aq. NaOH soln. adjusted to pH 10 and product was extracted with EtOAc (3 x 40 mL). The organic layer was washed with brine (50 mL), dried ($MgSO_4$) and concentrated to a white solid which was recrystallized from Et_2O/hexanes (40 mg, 42%). (TLC 50%EtOAc/CH_2Cl_2 R_f 0.15). ^1H NMR ($CDCl_3$) δ 6.96 (d, J=8.0 Hz, 1H), 6.60 (dd, J=8.0,2.5 Hz, 1H), 6.46 (d, J=2.5 Hz, 1H), 3.31 (m, 1H), 3.03 (dd, J=17.0,6.0 Hz, 1H), 2.95 (m, 2H,NH), 2.73 (m, 3H), 1.99 (m, 2H), 1.87 (AB d, J= 12.5 Hz, 1H). mp 215-217 °C. 3

EXAMPLE 18

11-BENZYL-11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

The title compound was prepared from phenol according to the procedures described in Example 15. (TLC 10%EtOAc/ hexanes (NH_3) R_f 0.76). ^1H NMR (CD_3OD) δ 7.42 (m, 5H), 7.22 (m, 2H), 7.15 (t, J=7.5 Hz, 1H), 7.10 (t, J=7.5 Hz, 1H), 4.28 (AB d, J=13.0 Hz, 1H), 4.18 4

(AB d, J=13.0 Hz, 1H), 3.51 (d, J=12.8 Hz, 1H), 3.36 (d, J=13.2 Hz, 1H), 3.34-3.23 (m, 4H), 2.95 (d, J=12.2 Hz, 1H), 2.58 (m, 1H), 2.03 (AB d, J=13.0 Hz, 1H), 1.92 (AB d, J=13.0 Hz, 1H). mp 125-127 °C.

EXAMPLE 19

11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

11-Benzyl-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene hydrochloride (150 mg, 0.50 mmol) was converted to the title compound as described in Example 3. (TLC 20%EtOAc/hexanes (NH_3) R_f 0.20). ^1H NMR (CD_3OD) δ 7.26-7.17 (m, 4H), 3.37-3.18 (m, 6H), 2.92 (d, J=18.2 Hz, 1H), 2.48 (m, 1H), 2.13 (AB d, J=13.0 Hz, 1H), 1.97 (AB d, J= 13.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 136.08, 135.67, 129.43, 128.78, 127.30, 126.42, 49.90, 49.05, 32.67, 31. 86, 27.15, 25.60. mp 227-228 °C.

EXAMPLE 20

4-NITRO-11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 1-(11-Aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-11-yl)-2,2,2-trifluoro-ethanone

11-Aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene (1.22 g, 7.08 mmol) was stirred at 0 °C in CH_2Cl_2 (10 mL) and treated with triethylamine (0.94 mL, 10.6 mmol) followed by TFAA (1.90 mL, 14.2 mmol). After ~1 hour, the solution was poured into 0.5 N HCl (200 mL) and the layers separated. The aq. layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layer was washed with 0.5 N HCl (50 mL), H_2O (2 x 50 mL) and sat. aq. $NaHCO_3$ soln. (50 mL). This solution was dried through a cotton plug, then diluted with ~3% EtOAc and filtered through a 2 inch silica pad eluted with ~3% EtOAc/CH_2Cl_2. Concentration afforded a clear oil (1.90 g, 99%). ^1H NMR ($CDCl_3$) δ 7.15-7.02 (4H), 4.67 (d, J=13.0 Hz, 1/2H), 4.42 (d, J=13.0 Hz, 1/2H), 4.03 (d, J=13.0 Hz, 1/2H), 3.81 (d, J=13.0 Hz, 1/2H), 3.44 (d, J=13.0 Hz, 1H), 3.29-2.99 (3H), (d, J=18.0 Hz, 1H), 2.37 (br s, 1/2H), 2.30 (br s, 1/2H), 2.04 (AB d, 2H). GCMS *m/e* 269 (M^+).

B) ~Nitro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene hydrochloride

The title compound was prepared as follows, based on the method described by Coon et al., *J. Org. Chem.*, **1973**, *25*, 4243. To a solution of trifluoromethanesulfonic acid (0.94 ml, 10.6 mmol) in CH_2Cl_2 (10 ml) stirred at 0 °C was slowly added nitric acid (0.60 ml, 14.1 mmol) generating a white precipitate. After 10 minutes the resulting mixture was cooled to -78 °C and treated with 1-(11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-11-yl)-2,2,2-trifluoro-ethanone (1.9 g, 7.06 mmol) in CH_2Cl_2 (15 ml) dropwise over 5 minutes. The reaction was stirred at -78 °C for 2h then warmed to 0 °C for 1/2 hour. The reaction mixture was poured into a stirred ice (50 g). The layers were separated and the aq. layer back extracted with CH_2Cl_2 (3 x 30 ml). The organic layer was combined and washed with H_2O (3

x 30 ml). The combined organic layer was washed with sat. aq. $NaHCO_3$ soln. (20 mL) and H_2O (20 mL) then dried through a cotton plug and concentrated to a yellow solid (1.58 g) which contained four products (TLC). The solids were slurried in Et_2O and filtered to provide a solid (900 mg, 41%). (TLC 30% EtOAc/hexanes, R_f 0.21). The filtrate was chromatographed on Silica gel eluting with 30% EtOAc/hexanes to provide three materials. R_f 0.32 (50 mg, 2%), R_f 0.21 (as solids above) and R_f 0.13 (50 mg, 2%). GCMS *m/e* 314 (M^+).

C) 4-Nitro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene hydrochloride

NOE (Nuclear Overhauser Effect) experiments elucidated the primary product, (TLC 30%EtOAc/hexanes, R_f 0.21) as 2,2,2-trifluoro-1-(4-nitro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-11-yl)-ethanone, by a 4% NOE between H-3 and H-1. This solid (780 mg, 2.48 mmol) was stirred in MeOH (20 mL) and treated with Na_2CO_3 (650 mg, 4.96 mmol) in H_2O (10 mL). The stirred mixture was warmed to 70°C for 6 hours, concentrated to solids, diluted with H_2O and extracted with CH_2Cl_2 (3 x 40 mL). The product was extracted into 1N aq. HCl soln. (3 x 40 mL) which was washed with EtOAc then neutralized with a sat. aq. Na_2CO_3 soln. to pH~10. Product was extracted with CH_2Cl_2 (3 x 40 mL), dried through a cotton plug, concentrated to an oil. The oil was dissolved in MeOH and treated with 3N HCl EtOAc (4 mL) and concentrated, then dissolved in a minimum of CH_2Cl_2 and the solution was saturated with hexanes and stirred 18 hours. The product was collected by filtration (145 mg, 23%). ^{1}H NMR ($DMSO_{d-6}$) d 8.12 (d, J=2.5 Hz, 1H), 8.09 (d, J=8.0 Hz, 1H), 7.50 (dd, J=8.0,2.5 Hz, 1H), 3.25 (m, 3H), 3.08 (m, 3H), 2.88 (m, 2H), 2.27 (m,1H), 1.99 (d, J=11.0 Hz, 1H). GCMS *m/e* 218 (M^+). mp 215-220 °C.

EXAMPLE 21

5-NITRO-11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

The other meta substituted isomer from above, 2,2,2-trifluoro-1-(5-nitro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-11-yl)-ethanone (TLC 30%EtOAc/hexanes, R_f 0.13) was converted to the title compound by the method in Example 20C. ^{1}H NMR free base ($CDCl_3$) δ 8.01 (d, J=2.0 Hz, 1H), 7.95 (dd, J=8.0,2.0 Hz, 1H), 7.17 (d, J=8.0 Hz, 1H), 3.16 (dd, J=18.0,6.5 Hz, 1H), 3.10-2.97 (4H), 2.89 (d, J=18.0 Hz, 1H), 2.79 (d, J=12.0 Hz, 1H), 2.12 (m, 1H), 2.02 (d, J=12.5 Hz, 1H), 1.88 (d, J=12.5 Hz, 1H). Conversion to the salt as in Example 20C provides a solid mp 245-255 °C.

EXAMPLE 22

3-NITRO-11-AZA-TRICYCLO[7.3.1.0^{2,7}]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

The remaining isolated isomer from above, 2,2,2-trifluoro-1-(3-nitro-11-aza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-trien-11-yl)-ethanone (TLC 30%EtOAc/hexanes, R_f 0.32) (50 mg) was converted to the title compound by the method in Example 20C to give 25 mg, 64%). The regiochemistry of this nitro isomer was established by HMQC (heteronuclear multiple-quantum correlation) between C-3 and H-1. ^{1}H NMR ($DMSO_{d-6}$) δ 7.80 (d, J=8.0 Hz, 1H), 7.53 (d, J=8.0 Hz, 1H), 7.45 (t, J=8.0 Hz, 1H), 3.71-3.15 (m, 6H), 2.95 (d, J=18.5 Hz, 1H), 2.40 (br s, 1H), 2.04 (d, J=12.5 Hz, 1H), 1.70 (d, J=12.5 Hz, 1H).

EXAMPLE 23

11-BENZYL-5-FLUORO-11-AZA-TRICYCLO[7.3.1.0^{2,7}]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

The title compound was prepared from 2-bromo-4-fluoro-1-methoxy-benzene by the methods described in Example 6. ^{1}H NMR (CD_3OD) δ 7.15 (m, 3H), 6.94-6.76 (m, 5H), 3.40 (AB d, 2H), 3.06 (dd, J=17.5,7.0 Hz, 1H), 2.87-2.73 (3H), 2.69 (d, J=10.5 Hz, 1H), 2.37 (d, J=10.5 Hz, 1H), 2.28 (d, J=10.5 Hz, 1H), 2.17 (br s, 1H), 1.83 (AB d, 2H). GCMS *m/e* 281 (M^+). mp 202-203 °C.

EXAMPLE 24

5-FLUORO-11-AZA-TRICYCLO[7.3.1.0^{2,7}]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

11-Benzyl-5-fluoro-11-aza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene hydrochloride (310 mg, 0.94 mmol) was converted to the title compound by the methods described in Example 3 to yield a white solid (140 mg, 65%). ^{1}H NMR (CD_3OD) δ 7.22 (m, 1H), 6.93 (m, 2H), 3.38-3.14 (6H), 2.93 (d, J=18.5 Hz, 1H), 2.45 (m, 1H), 2.17 (AB d, J=13.0 Hz, 1H), 1.94 (AB d, J= 13.0 Hz, 1H). mp 286-287 °C.

EXAMPLE 25

5,7-DIOXA-14-AZATETRACYCLO[10.3.1.0^{2,10}.0^{4,8}]HEXADECA-2(10),3,8-TRIENE HYDROCHLORIDE

5-Bromo-6-methoxy-benzo[1,3]dioxole (Preparation described previously, see; Getahun, Z.; Jurd, L.; Chu, P. S.; Lin, C. M.; Hamel, E. *J. Med. Chem.* **1992**, *35*, 1058-1067.) was converted to the title compound using methods described in Example 3 and Example 6 to yield a white solid (110 mg). ^{1}H NMR (CD_3OD) δ 6.65 (s, 2H), 5.88 (s, 2H), 3.33-3.12 (6H), 2.81 (d, J=18.0 Hz, 1H), 2.42 (m, 1H), 2.09 (AB d, J=12.5 Hz, 1H), 1.90 (AB d, J= 12.5 Hz, 1H). GCMS *m/e* 217 (M^+). APCI MS *m/e* 218.1 [(M + 1)$^+$]. mp 241-243 °C.

EXAMPLE 26

11-BENZYL-6-BROMO-5-METHOXY-11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5 -TRIENE

11-Benzyl-5-methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5 -triene (3.00 g, 10.2 mmol) was stirred at 0°C in CH_2Cl_2 (10 mL) and AcOH (5 mL) and treated with bromine (3.21 g, 20 mmol) in CH_2Cl_2 (10 mL) and AcOH (5 mL). After 18 hours the reaction was quenched with 20% aq. $NaHSO_3$ soln. (100 mL). The product was extracted with CH_2Cl_2 (3 x 40 mL) and washed with sat. aq. $NaHCO_3$ soln. (3 x 50 mL). The combined organic layer was dried through a cotton plug, concentrated and chromatographed on Silica gel to provide an oil (1.05 g, 28%). (TLC 30%EtOAc/hexanes R_f 0.48). ^1H NMR ($CDCl_3$) δ 7.13 (m, 3H), 6.91 (m, 3H), 6.68 (d, J=8.0 Hz, 1H), 3.90 (s, 3H), 3.36 (s, 2H), 2.86-2.79 (4H), 2.67 (br d, J=9.0 Hz, 1H), 2.31 (br s, 1H), 2.28 (br s, 1H), 2.22 (br s, 1H), 1.78 (AB d, J=13.0 Hz, 2H). GCMS *m/e* 373,371 (M^+).

EXAMPLE 27

11-BENZYL-6-HYDROXY-5-METHOXY-11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5 -TRIENE

11-Benzyl-6-bromo-5-methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5 -triene (1.05 g, 2.70 mmol) was stirred at -78 °C in anh. THF (10 mL) and treated with n-BuLi (1.08 mL 2.5M soln. in hexanes, 2.70 mmol) dropwise over 1 min. After 10 min., triisopropyl borate (559 mg, 2.97 mmol) was added and the mixture was allowed to warm to ambient temperature. The reaction was quenched with with sat. aq. $NaHCO_3$ soln. (50 mL) and the product was extracted with EtOAc (3 x 20 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to give an oil (640 mg, 67%). (TLC 30%EtOAc/hexanes R_f 0.18). This material (640 mg, 1.81 mmol) was stirred in THF (10 mL) with 30% aq. hydrogen peroxide soln. (205 mg, 1.81 mmol). After 18 hours the reaction was quenched with 20% aq. $NaHSO_3$ soln. (10 mL). The mixture was diluted with sat. aq. $NaHCO_3$ soln. (50 mL) and product was extracted with CH_2Cl_2 (3 x 40 mL). The organic layer washed with sat. aq. $NaHCO_3$ soln. (3 x 50 mL), dried through a cotton plug, concentrated and chromatographed on Silica gel to provide an oil (360 mg, 64%). (TLC 40%EtOAc/hexanes R_f 0.44). ^1H NMR ($CDCl_3$) δ 7.14 (3H), 6.95 (2H), 6.67 (d, J=8.0 Hz, 1H), 6.52 (d, J=8.0 Hz, 1H), 3.89 (s, 3H), 3.40 (AB d, 2H), 2.88-2.63 (5H), 2.34-2.22 (3H), 1.79 (AB d, 2H). GCMS *m/e* 309 (M^+).

EXAMPLE 28

6-HYDROXY-5-METHOXY-11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5 -TRIENE HYDROCHLORIDE

11-Benzyl-6-hydroxy-5-methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5 -triene (58 mg, 0.18 mmol) was converted to the title compound according to the procedure described in

Example 3 followed by conversion to the salt as described in Example 9 to provide a white solid (15 mg, 32%). (TLC 10%MeOH/CH_2Cl_2 (NH_3) R_f 0.26). ^1H NMR (CD_3OD) δ 6.84 (d, J=8.0 Hz, 1H), 6.68 (d, J=8.0 Hz, 1H), 3.82 (s, 3H), 3.29 (3H), 3.13 (m, 2H), 3.00 (dd, J=18.0,6.0 Hz, 1H), 2.85 (d, J=18.0 Hz, 1H), 2.42 (m, 1H), 2.09 (AB d, J=12.5 Hz, 1H), 1.82 (AB d, J= 12.5 Hz, 1H). mp 285-290 °C.

EXAMPLE 29

TRIFLUORO-METHANESULFONIC ACID-11-BENZYL-11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5-TRIEN-5-YL ESTER

11-Benzyl-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-ol (850 mg, 3.03 mmol) was converted to the title compound (1.18 g, 94%) by the method described in Example 1D. (TLC 30%EtOAc/hexanes R_f 0.47). ^1H NMR ($CDCl_3$) δ 7.10 (3H), 6.97 (3H), 6.78 (2H), 3.40 (AB d, J=14.0 Hz, 1H), 3.30 (AB d, J=14.0 Hz, 1H), 3.05 (AB dd, J=17.5,7.0 Hz, 1H), 2.89-2.79 (3H), 2.62 (d, J=10.0 Hz, 1H), 2.40 (d, J=10.5 Hz, 1H), 2.28 (d, J=12.0 Hz, 1H), 2.17 (br s, 1H), 1.83 (AB d, 2H). APCI MS *m/e* 412.1 [(M + 1)$^+$].

EXAMPLE 30

5-(4-TRIFLUOROMETHYL-PHENYL)-11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 11-Benzyl-5-(4-trifluoromethyl-phenyl)-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene (For a discussion, see: Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483.)

Trifluoro-methanesulfonic acid-11-benzyl-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-yl ester (258 mg, 0.63 mmol), potassium acetate (493 mg, 5.02 mmol) and 4-trifluoromethylphenyl boronic acid (141 mg, 0.94 mmol) were combined in 10/1 EtOH/H_2O (5 mL). The mixture was degassed (3 vacuum/N_2 cycles), treated with tetrakis(triphenylphosphine)palladium(0) (36.0 mg, 0.032 mmol) and warmed to 90 °C for 18h. The reaction was cooled, diluted with H_2O and extracted with Et_2O (3 x 50 mL). The organic layer was washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated to provide an oil (60 mg, 23%). (TLC hexanes R_f 0.16). ^1H NMR ($CDCl_3$) δ 7.73 (d, J=8.5 Hz, 2H), 7.68 (d, J=8.5 Hz, 2H), 7.38 (d, J=2.0 Hz, 1H), 7.32 (dd, J=8.0,2.0 Hz, 1H), 7.10 (4H), 6.88 (m, 2H), 3.40 (s, 2H), 3.14 (dd, J= 17.5, 7.0 Hz, 1H), 2.94-2.87 (3H), 2.76 (d, J=10.5 Hz, 1H), 2.40 (dd, J=10.5,2.0 Hz, 1H), 2.33 (dd, J=10.5,2.0 Hz, 1H), 2.22 (br s, 1H), 1.91 (AB d, J=12.5 Hz, 1H), 1.83 (AB d, J=12.5 Hz, 1H). GCMS *m/e* 407 (M)$^+$.

B) 5-(4-Trifluoromethyl-phenyl)-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene hydrochloride

11-Benzyl-5-(4-Trifluoromethyl-phenyl)-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene was converted to the title compound as described in Example 3. (TLC

50%EtOAc/hexanes R_f 0.81). ^{1}H NMR ($CDCl_3$) δ 7.62 (m, 4H), 7.15-6.98 (3H) 3.50-2.97 (6H), 2.92 (d, J=18.0 Hz, 1H), 2.38 (br s, 1H), 2.02 (AB d, 2H).

EXAMPLE 31

5-(4-METHOXY-PHENYL)-11-AZA-TRICYCLO[7.3.1.0^{2,7}]TRIDECA-2(7),3,5-TRIENE HYDROCHLORIDE

Trifluoro-methanesulfonic acid-11-benzyl-11-aza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-trien-5-yl ester and 4-methoxyphenyl boronic acid were converted to the title compound by the methods described in Example 30. ^{1}H NMR (CD_3OD) δ 7.57 (d, J=8.0 Hz, 2H), 7.42 (d, J=2.0 Hz, 1H), 7.38 (dd, J=8.0,2.0 Hz, 1H), 7.18 (d, J=8.0 Hz, 1H), 6.97 (d, J=8.0 Hz, 2H), 3.81 (s, 3H), 3.48-3.08 (6H), 2.95 (d, J=18.0 Hz, 1H), 2.30 (br s, 1H), 2.10 (AB d, J=11.5 Hz, 1H), 1.97 (AB d, J=11.5 Hz, 1H).

EXAMPLE 32

11-AZA-TRICYCLO[7.3.1.0^{2,7}]TRIDECA-2(7),3,5-TRIENE-5-CARBOXYLIC ACID METHYL ESTER HYDROCHLORIDE (Based on Dolle, R. E.; Schmidt, S. J.; Kruse, L. I. *J. Chem. Soc., Chem. Commun.* **1987**, 904-905.)

Trifluoro-methanesulfonic acid-11-benzyl-11-aza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-trien-5-yl ester (1.0 g, 2.26 mmol) was dissolved in DMSO (15 mL) and MeOH (2 mL) and treated with triethylamine (505 mg, 4.99 mmol), potassium acetate (22.0 mg, 0.23 mmol) and 1,3-bis(diphenylphosphino)propane (94.0 mg, 0.23 mmol). This mixture was stirred and degassed (3 vacuum/N_2 purge cycles) then treated with palladium acetate (51 mg, 0.23 mmol). The system was purged with carbon monoxide gas (CO(g)) at balloon pressure, stirred 20 min., warmed to 100°C for 3 hours, cooled and then poured into brine (50 mL). The resulting mixture was extracted with EtOAc (4 x 40 mL) and the combined organic layer was washed with a sat. aq. $NaHCO_3$ soln. (100 mL), H_2O (100 mL), brine (100 mL), dried ($MgSO_4$), filtered and evaporated to an oil. The oil, 11-benzyl-11-aza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-5-carboxylic acid methyl ester, was chromatographed on silica gel to provide an oil (280 mg, 38%). (TLC 10%EtOAc/ hexanes R_f 0.21). APCI MS *m/e* 322.2 [(M + 1)$^+$]. This oil was converted into the title compound by the methods described in Example 3. (TLC 10%CH_2Cl_2/MeOH (NH_3) R_f 0.21). ^{1}H NMR (CD_3OD) δ 7.87 (d, J=2.0 Hz, 1H), 7.83 (dd, J=8.0,2.0 Hz,1H), 7.35 (d, J=8.0 Hz, 1H), 3.87 (s, 3H), 3.49-3.12 (6H), 2.97 (d, J=18.5 Hz, 1H), 2.52 (br s, 1H), 2.18 (AB d, J=11.5 Hz, 1H), 1.97 (AB d, J=11.5 Hz, 1H). mp 255-256 °C.

EXAMPLE 33

2-(11-AZA-TRICYCLO[7.3.1.$0^{2,7}$]TRIDECA-2(7),3,5-TRIEN-5-YL)-PROPAN-2-OL HYDROCHLORIDE

11-Benzyl-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-5-carboxylic acid methyl ester (180 mg, 0.62 mmol) was stirred under N_2 at -78 °C in anh. THF (15 mL) and treated with excess methyl magnesiumbromide (~1 mL, 3M in THF). The resulting mixture was allowed to warm to ambient temperature and quenched with a sat. aq. NH_4Cl soln. (25 mL). The product was extracted with EtOAc (3 x 50 mL), washed with brine (50 mL), dried ($MgSO_4$), filtered and evaporated to an oil (100 mg, 50%). GCMS *m/e* 321 (M^+). This material was converted to the title compound by the methods described in Example 3. ^1H NMR (CD_3OD) δ 7.32 (OH), 7.24 (s, 1H), 7.16 (d, J=8.0 Hz, 1H), 7.08 (m, 1H), 3.50-3.12 (6H), 2.91 (d, J=18.5 Hz, 1H), 2.47 (br, s, 1H), 2.11 (AB d, J=11.5 Hz, 1H), 1.97 (AB d, J=11.5 Hz, 1H), 1.15 (s, 6H). mp 80-81°C.

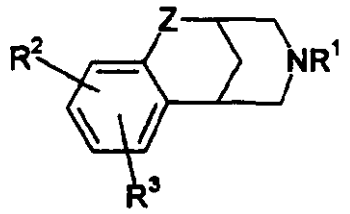
EXAMPLE 34

5-Pyridin-3-yl-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene hydrochloride

Trifluoro-methanesulfonic acid 11-benzyl-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-yl ester and diethyl-pyridin-3-yl-borane were converted to the title compound by the methods described in Example 30. ^1H NMR (CD_3OD) δ 9.14 (br s, 1H), 8.78 (m, 2H), 8.08 (m, 1H), 7.69 (d, J=2.0 Hz, 1H), 7.62 (dd, J=8.0,2.0 Hz,1H), 7.43 (d, J=8.0 Hz, 1H), 3.43-3.18 (6H), 3.05 (d, J=18.5 Hz, 1H), 2.56 (br s, 1H), 2.18 (AB d, J=11.5 Hz, 1H), 2.02 (AB d, J=11.5 Hz, 1H). GCMS *m/e* 250 (M^+). mp 240-242 °C.

CLAIMS

1. A compound of the formula



(I)

wherein Z is CH_2, C(=O) or CF_2;

R^1 is hydrogen, $(C_1$-$C_6)$alkyl, unconjugated $(C_3$-$C_6)$alkenyl, benzyl, $XC(=O)R^{13}$ or $-CH_2CH_2$-O-$(C_1$-$C_4)$alkyl;

R^2 and R^3 are selected independently, from hydrogen, $(C_2$-$C_6)$ alkenyl, $(C_2$-$C_6)$ alkynyl, hydroxy, nitro, amino, halo, cyano, $-SO_q(C_1$-$C_6)$alkyl wherein q is zero, one or two, $(C_1$-$C_6)$alkylamino, $[(C_1$-$C_6)$alkyl$]_2$amino, CO_2R^4, $CONR^5R^6$, $SO_2NR^7R^8$, $C(=O)R^{13}$, $XC(=O)R^{13}$, aryl-$(C_0$-$C_3)$ alkyl or aryl-$(C_0$-$C_3)$alkyl-O- wherein said aryl is selected from phenyl and naphthyl, heteroaryl-$(C_0$-$C_3)$alkyl or heteroaryl-$(C_0$-$C_3)$alkyl-O-, wherein said heteroaryl is selected from five to seven membered aromatic rings containing from one to four heteroatoms selected from oxygen, nitrogen and sulfur, and $X^2(C_0$-$C_6)$alkoxy-$(C_0$-$C_6)$alkyl, wherein X^2 is absent or X^2 is $(C_1$-$C_6)$alkylamino or $[(C_1$-$C_6)$alkyl$]_2$amino, and wherein the $(C_0$-$C_6)$alkoxy-$(C_0$-$C_6)$alkyl moiety of said $X^2(C_0$-$C_6)$alkoxy-$(C_0$-$C_6)$alkyl contains at least one carbon atom, and wherein from one to three of the carbon atoms of said $(C_0$-$C_6)$alkoxy-$(C_0$-$C_6)$alkyl moiety may optionally be replaced by an oxygen, nitrogen or sulfur atom, with the proviso that any two such heteroatoms must be separated by at least two carbon atoms, and wherein any of the alkyl moieties of said $(C_0$-$C_6)$alkoxy-$(C_0$-$C_6)$alkyl may be optionally substituted with from two to seven fluorine atoms, and wherein one of the carbon atoms of each of the alkyl moieties of said aryl-$(C_0$-$C_3)$alkyl and said heteroaryl-$(C_0$-$C_3)$alkyl may optionally be replaced by an oxygen, nitrogen or sulfur atom, and wherein each of the foregoing aryl and heteroaryl groups may optionally be substituted with one or more substituents, preferably from zero to two substituents, independently selected from $(C_1$-$C_6)$ alkyl optionally substituted with from one to seven fluorine atoms, $(C_1$-$C_6)$ alkoxy optionally substituted with from two to seven fluorine atoms, halo (e.g., chloro, fluoro, bromo or iodo), hydroxy, nitro, cyano, amino, $(C_1$-$C_6)$ alkylamino and $[(C_1$-$C_6)$ alkyl$]_2$ amino;

or R^2 and R^3, together with the carbons to which they are attached, form a four to seven membered monocyclic, or a ten to fourteen membered bicyclic, carbocyclic ring that can be saturated or unsaturated, wherein from one to three of the nonfused carbon atoms of said monocyclic rings, and from one to five of the carbon atoms of said bicyclic rings that are not part of the benzo ring shown in formula I, may optionally and independently be replaced by a nitrogen, oxygen or sulfur, and wherein said monocyclic and bicyclic rings may optionally be substituted with

one or more substituents, preferably from zero to two substituents for the monocyclic rings and from zero to three substituents for the bicyclic rings, that are selected, independently, from (C_0-C_6) alkoxy-(C_0-C_6)alkyl-, wherein the total number of carbon atoms does not exceed six and wherein any of the alkyl moieties may optionally be substituted with from one to seven fluorine atoms; nitro, oxo, cyano, halo, hydroxy, amino, (C_1 -C_6)alkylamino, [(C_1 -C_6) alkyl]$_2$amino, phenyl and monocyclic heteroaryl wherein said heteroaryl is defined as in the definition of R^2 and R^3 above;

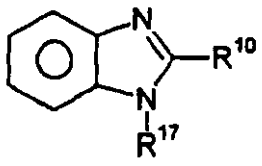
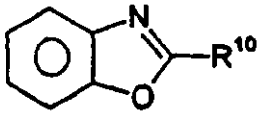
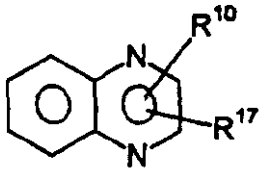
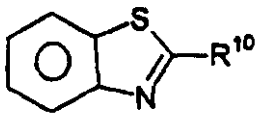
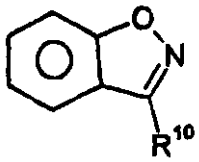
each R^4, R^5, R^6, R^7, R^8 and R^{13} is selected, independently, from hydrogen and (C_1 -C_6) alkyl, or R^5 and R^6, or R^7 and R^8 together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, piperizine, -N-(C_1-C_6)alkylpiperizine or thiomorpholine ring, or a thiomorpholine ring wherein the ring sulfur is replaced with a sulfoxide or sulfone; and

each X is, independently, (C_1-C_6)alkylene;

with the proviso that: (a) at least one of R^1, R^2 and R^3 must be the other than hydrogen, (b) when R^2 and R^3 are hydrogen, R^1 cannot be methyl or hydrogen; and (c) no fluorine atom in any of the fluoro substituted alkyl or alkoxy moieties of R^2 and R^3 can be attached to a carbon that is attached to a heteroatom;

or a pharmaceutically acceptable salt thereof;

2. A compound according to claim 1, wherein R^2 and R^3, together with the benzo ring of formula I, form a bicyclic ring system selected from the following:

wherein R^{10} and R^{17} are selected, independently, from hydrogen and (C_1-C_6)alkyl.

3. A compound according to claim 1, wherein R^2 and R^3 do not, together with the benzo ring of formula I, form a bicyclic or tricyclic ring system.

4. A compound according to claim 1, wherein one or both of R^2 and R^3 are $-C(=O)R^{13}$ wherein R^{13} is (C_1-C_6)alkyl.

5. A compound according to claim 1, wherein one of R^2 and R^3 is $-COR^{13}$ wherein R^{13} is (C_1-C_6)alkyl or (C_1-C_3)alkyl optionally substituted with from one to seven fluorine atoms.

6. A compound according to claim 1, wherein one of R^2 and R^3 is CF_3 , fluoro, cyano or C_2F_5.

7. A pharmaceutical composition for use in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, comprising an amount of a compound according to claim 1 that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use and a pharmaceutically acceptable carrier.

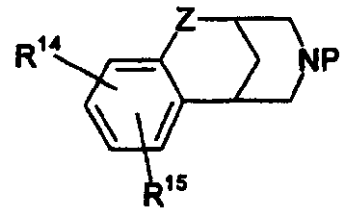
8. A method for reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, comprising administering to said mammal an amount of a compound according to claim 1 that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use.

9. A pharmaceutical composition for treating a disorder or condition selected from inflammatory bowel disease, irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyiotropic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supramuscular palsy, chemical dependencies and addictions, headache, stroke, TBI, psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a mammal, comprising an amount of a compound according to claim 1 that is effective in treating such disorder or condition and a pharmaceutically acceptable carrier.

10. A method for treating a disorder or condition selected from inflammatory bowel disease, irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyiotropic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supramuscular palsy, chemical dependencies and addictions, headache, stroke, TBI, psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a mammal, comprising administering

to a mammal in need of such treatment an amount of a compound according to claim 1 that is effective in treating such disorder or condition.

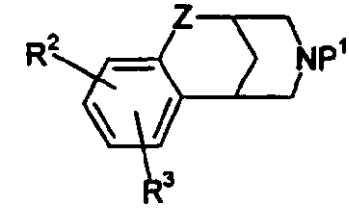
11. A compound of the formula



(I)

wherein Z is CH_2, CF_3 or C(=O); P is hydrogen, methyl, $COOR^{16}$ wherein R^{16} is $(C_1\text{-}C_6)$alkyl, allyl or 2,2,2-trichloroethyl; $-C(=O)NR^5R^6$ wherein R^5 and R^6 are defined as in formula I above; -C(=O)H, $-C(=O)(C_1\text{-}C_6)$alkyl wherein the alkyl moiety may optionally be substituted with from 1 to 3 halo atoms, preferably with from 1 to 3 fluoro or chloro atoms; benzyl or t-butoxycarbonyl (t-Boc), and R^{14} and R^{15} are selected, independently, from hydroxy, nitro, amino, $-O(C_1\text{-}C_6)$alkyl and halo; with the proviso that R^{14} and R^{15} cannot both be hydrogen when P is hydrogen or methyl.

12. A compound of the formula



(I)

wherein Z is CH_2, CF_3 or C(=O); R^2 and R^3 are defined as in claim 2; and P^1 is $COOR^{16}$ wherein R^{16} is allyl, 2,2,2-trichloroethyl or $(C_1\text{-}C_6)$alkyl; $-C(=O)NR^5R^6$ wherein R^5 and R^6 are defined as in formula I above; -C(=O)H, $-C(=O)(C_1\text{-}C_6)$alkyl wherein the alkyl moiety may optionally be substituted with from 1 to 3 halo atoms, preferably with from 1 to 3 fluoro or chloro atoms; benzyl, t-butoxycarbonyl (t-Boc), or trifluoroacetyl.

INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/IB 99/00617

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D221/22 A61K31/435

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

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

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WEI K. CHANG ET AL.: JOURNAL OF MEDICINAL CHEMISTRY, vol. 14, no. 10, 1971, pages 1011-3, XP002108896 see table I, compounds no. 1-4 ---	1,3,11
A	K. KITAHONOKI ET AL.: TETRAHEDRON, vol. 25, no. 2, 1969, pages 335-53, XP002108897 see page 341, compound XXXVa ---	1,3,11
A	T. KOMETANI ET AL.: CHEM. PHARM. BULL., vol. 24, no. 3, 1976, pages 541-4, XP002108898 see page 542, chart 2, compounds X and XIb ---	1,3,11

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[X] Further documents are listed in the continuation of box C. [ ] Patent family members are listed in annex.

° Special categories of cited documents :

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

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 July 1999	29/07/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hass, C

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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/IB 99/00617

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	K. KITAHONOKI ET AL.: TETRAHEDRON LETTERS, no. 13, 1968, pages 1651-5, XP002108899 see page 1652, compound Xa	1,3,11
A	CHEMICAL ABSTRACTS, vol. 81, no. 13, 30 September 1974 (1974-09-30) Columbus, Ohio, US; abstract no. 77812w, page 452; XP002108900 & JP 49 024968 A (TAKEDA CHEMICAL INDUSTRIES, LTD.) 5 March 1974 (1974-03-05)	1,3,9,11
A	CHEMICAL ABSTRACTS, vol. 80, no. 19, 13 May 1974 (1974-05-13) Columbus, Ohio, US; abstract no. 108399c, page 407; XP002108901 & JP 49 014473 A (TAKEDA CHEMICAL INDUSTRIES, LTD.) 7 February 1974 (1974-02-07)	1,3,9,11

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C07D221/22
A61K 31/435

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[71]申请人 辉瑞产品公司
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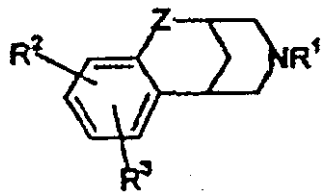
[74]专利代理机构 中国国际贸易促进委员会专利商标事务所
代理人 周中琦

权利要求书5页 说明书78页 附图页数0页

[54]发明名称 芳基稠合氮杂多元环化合物

[57]摘要

本发明请求保护式(Ⅰ)的化合物及其药学上可接受的盐,其中R^1、R^2、R^3和Z如说明书中定义;合成上述化合物的中间体,含有所述化合物的药物组合物和所述化合物在治疗神经病学和心理学疾病中应用的方法。



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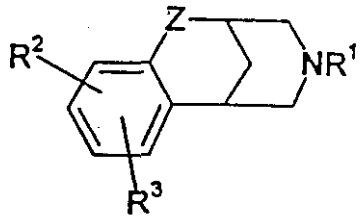
权 利 要 求 书

1. 式(I)的化合物:



(I)

其中 Z 是 CH_2、C(=O)或 CF_2;

R^1是氢、(C_1-C_6)烷基、非共轭(C_3-C_6)链烯基、苄基、$XC(=O)R^{13}$或$-CH_2CH_2-O-(C_1-C_4)$烷基;

R^2和R^3独立地选自氢、(C_2-C_6)链烯基、(C_2-C_6)炔基、羟基、硝基、氨基、卤素、氰基,$-SO_q(C_1-C_6)$烷基,其中 q 是 0、1 或 2,(C_1-C_6)烷基氨基、$[(C_1-C_6)烷基]_2$氨基、CO_2R^4、$CONR^5R^6$、$SO_2NR^7R^8$、$C(=O)R^{13}$、$XC(=O)R^{13}$,芳基-(C_0-C_3)烷基或芳基-(C_0-C_3)烷基-O-,其中所述芳基选自苯基和萘基,杂芳基-(C_0-C_3)烷基或杂芳基-(C_0-C_3)烷基-O-,其中所述杂芳基选自含有 1-4 个选自氧、氮和硫的杂原子的 5-7 元芳香环,和$X^2(C_0-C_6)$烷氧基-(C_0-C_6)烷基,其中X^2不存在或X^2是(C_1-C_6)烷基氨基或$[(C_1-C_6)烷基]_2$氨基,和其中所述$X^2(C_0-C_6)$烷氧基-(C_0-C_6)烷基的(C_0-C_6)烷氧基-(C_0-C_6)烷基部分含有至少一个碳原子,和其中所述(C_0-C_6)烷氧基-(C_0-C_6)烷基部分的 1-3 个碳原子可以被氧、氮或硫原子任选地置换,条件是任何两个所述杂原子必须被至少两个碳原子分隔开,和其中所述(C_0-C_6)烷氧基-(C_0-C_6)烷基的任何烷基部分可以被 2-7 个氟原子任选取代,和其中所述芳基-(C_0-C_3)烷基和所述杂芳基-(C_0-C_3)烷基的各烷基部分中的一个碳原子可以被氧、氮或硫原子任选地置换,和其中上述各个芳基和杂芳基可以被一个或多个取代基,优选 0-2 个取代基任选取代,所述取代基独立地选自:被 1-7 个氟原子任选取代的(C_1-C_6)烷基、被 2-7 个氟原子任选取代的(C_1-C_6)烷氧基、卤素(例如氯、氟、溴或碘)、羟基、硝基、氰基、氨基、(C_1-C_6)烷基氨基和$[(C_1-C_6)$

烷基]$_2$氨基；

或 R^2 和 R^3 与其所连接的碳原子一起构成 4-7 元单环或 10-14 元双环，碳环，其可以是饱和或不饱和，其中所述的单环中 1-3 个非稠合碳原子，和所述双环中不构成式 I 所示苯并环部分的 1-5 个碳原子，可以被氮、氧或硫任选地和独立地置换，和其中所述单环和双环可以被一个或多个取代基任选取代，对于该单环优选被 0-2 个取代基任选取代，对于所述双环优选被 0-3 个取代基任选取代，所述取代基独立地选自：(C_0-C_6)烷氧基-(C_0-C_6)烷基-，其中碳原子的总数不超过 6 个且其中任何烷基部分可以被 1-7 个氟原子任选取代；硝基、氧代、氰基、卤素、羟基、氨基、(C_1-C_6)烷基氨基、[(C_1-C_6)烷基]$_2$氨基、苯基和单环杂芳基，其中所述杂芳基如上述 R^2 和 R^3 定义中所定义；

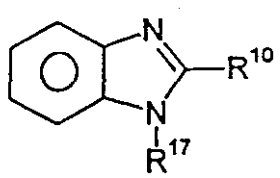
各个 R^4、R^5、R^6、R^7、R^8 和 R^{13} 独立地选自氢和(C_1-C_6)烷基，或 R^5 和 R^6，或 R^7 和 R^8 与其所连接的氮一起构成吡咯烷、哌啶、吗啉、氮杂环丁烷、哌嗪、-N-(C_1-C_6)烷基哌嗪或硫代吗啉环，或是其中环硫被亚砜或砜置换的硫代吗啉环；和

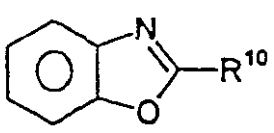
各个 X 独立地是(C_1-C_6)亚烷基；

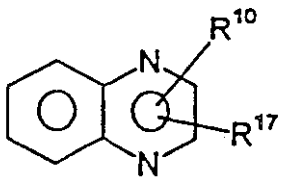
条件是：(a)至少一个 R^1、R^2 和 R^3 一定不是氢，(b)当 R^2 和 R^3 是氢时，R^1 不是甲基或氢；和(c)R^2 和 R^3 中的任何氟取代烷基或烷氧基部分中没有氟原子可以连接在与杂原子相连的碳原子上；

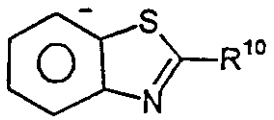
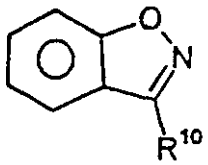
或所述化合物的药学上可接受的盐。

2. 按照权利要求 1 所述的化合物，其中 R^2 和 R^3 与式 I 的苯并环共同构成选自如下的双环体系：







其中 R^{10} 和 R^{17} 独立地选自氢和 (C_1-C_6) 烷基。

3. 按照权利要求 1 所述的化合物，其中 R^2 和 R^3 不与式 I 的苯并环构成双环或三环体系。

4. 按照权利要求 1 所述的化合物，其中 R^2 和 R^3 之一或两者是 $-C(=O)R^{13}$，其中 R^{13} 是 (C_1-C_6) 烷基。

5. 按照权利要求 1 所述的化合物，其中 R^2 和 R^3 中的一个是 $-COR^{13}$，其中 R^{13} 是 (C_1-C_6) 烷基或 (C_1-C_3) 烷基，任选地被 1 - 7 个氟原子取代。

6. 按照权利要求 1 所述的化合物，其中 R^2 和 R^3 之一是 CF_3、氟、氰基或 C_2F_5。

7. 一种用于在哺乳动物中减轻烟瘾或有助于停止或减少烟草使用的药物组合物，该组合物含有有效减轻烟瘾或有助于停止或减少烟草使用的量的式 I 化合物以及药学上可接受的载体。

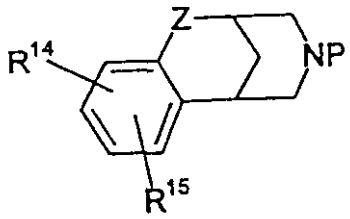
8. 一种用于在哺乳动物中减轻烟瘾或有助于停止或减少烟草使用的方法，该方法包括给该哺乳动物施用可以有效减轻烟瘾或有助于停止或减少烟草使用的量的式 I 化合物。

9. 一种用于治疗选自下列疾病或病症的药物组合物，所述疾病或病症选自：炎性肠病、过敏性肠综合征、痉挛性张力障碍、慢性疼痛、急性疼痛、腹腔口炎性腹泻、囊炎、血管收缩、焦虑、恐慌症、抑郁症、双相精神障碍、孤独症、睡眠障碍、时差综合征、肌萎缩性脊髓

侧索硬化症(ALS)、认知机能障碍、高血压、食欲过盛、厌食、肥胖、心律失常、胃酸分泌过多、溃疡病、嗜铬细胞瘤、进行性肌肉上部麻痹、化学品依赖性和癖嗜、头痛、中风、TBI、精神病、杭廷顿氏舞蹈病、迟发性运动障碍、运动机能亢进、诵读困难、精神分裂症、多梗塞性痴呆、衰老相关性认知衰退、癫痫，包括癫痫失神小发作、阿耳茨海默氏型的老年性痴呆(AD)、帕金森氏病(PD)、注意力缺乏活动过强症(ADHD)和图雷特氏病，所述组合物含有有效治疗上述疾病或病症量的如权利要求 1 所述的化合物和药学上可接受的载体。

10. 一种用于治疗选自下列疾病或病症的方法，所述疾病或病症选自：炎性肠病、过敏性肠综合征、痉挛性张力障碍、慢性疼痛、急性疼痛、腹腔口炎性腹泻、囊炎、血管收缩、焦虑、恐慌症、抑郁症、双相精神障碍、孤独症、睡眠障碍、时差综合征、肌萎缩性脊髓侧索硬化症(ALS)、认知机能障碍、高血压、食欲过盛、厌食、肥胖、心律失常、胃酸分泌过多、溃疡病、嗜铬细胞瘤、进行性肌肉上部麻痹、化学品依赖性和癖嗜、头痛、中风、TBI、精神病、杭廷顿氏舞蹈病、迟发性运动障碍、运动机能亢进、诵读困难、精神分裂症、多梗塞性痴呆、衰老相关性认知衰退、癫痫，包括癫痫失神小发作、阿耳茨海默氏型的老年性痴呆(AD)、帕金森氏病(PD)、注意力缺乏活动过强症(ADHD)和图雷特氏病，所述方法包括给需此治疗的哺乳动物施用有效治疗上述疾病或病症量的如权利要求 1 所述的化合物。

11. 下式的化合物：

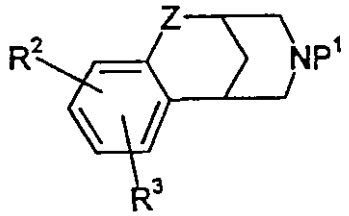


(I)

其中 Z 是 CH_2、CF_3 或 C(=O)；P 是氢，甲基，$COOR^{16}$，其中 R^{16} 是(C_1-C_6)烷基、烯丙基或 2,2,2-三氯乙基；$-C(=O)NR^5R^6$，其中 R^5 和 R^6 如上述

式 I 定义；-C(=O)H、-C(=O)(C_1-C_6)烷基，其中烷基部分可以被 1-3 个卤素原子，优选 1-3 个氟原子或氯原子任选取代；苄基或叔丁氧基羰基(t-Boc)；和 R^{14} 和 R^{15} 独立地选自羟基、硝基、氨基、-O(C_1-C_6)烷基或卤素；条件是当 P 是氢或甲基时，R^{14} 和 R^{15} 不同时为氢。

12. 下式的化合物:



(I)

其中 Z 是 CH_2、CF_3 或 C(=O)；R^2 和 R^3 如权利要求 2 定义；和 P^1 是 $COOR^{16}$，其中 R^{16} 是烯丙基、2,2,2-三氯乙基或(C_1-C_6)烷基；-C(=O)NR^5R^6，其中 R^5 和 R^6 如上述式 I 定义；-C(=O)H、-C(=O)(C_1-C_6)烷基，其中烷基部分可以被 1-3 个卤素原子，优选 1-3 个氟原子或氯原子任选取代；苄基或叔丁氧基羰基(t-Boc)，或三氟乙酰基。

说　明　书

芳基稠合氮杂多元环化合物

发明背景

本发明涉及芳基稠合氮杂多元环类化合物，更具体地如下式 I 定义的化合物。式 I 的化合物结合在神经烟碱性乙酰胆碱特异性受体位点上且有效调节胆碱能功能。此类化合物适用于治疗：炎性肠病(包括但不限于溃疡性结肠炎、坏疽性脓皮病和局限性回肠炎)、过敏性肠综合征、痉挛性张力障碍、慢性疼痛、急性疼痛、腹腔口炎性腹泻(celiac sprue)、囊炎、血管收缩、焦虑、恐慌症、抑郁症、双相性精神障碍、孤独症、睡眠障碍、时差综合征、肌萎缩性脊髓侧索硬化症(ALS)、认知机能障碍、高血压、食欲过盛、厌食、肥胖、心律失常、胃酸分泌过多、溃疡病、嗜铬细胞瘤、进行性肌肉上部麻痹(progressive supramuscular palsy)、化学品依赖性和癖嗜(例如对烟碱(和/或烟草产品)、醇、苯并二氮䓬类、巴比妥类、阿片样物质类或可卡因依赖或成瘾)，头痛、中风、创伤性脑损伤(TBI)、强迫观念与行为障碍、精神病、杭廷顿氏舞蹈病、迟发性运动障碍、运动机能亢进、诵读困难、精神分裂症、多梗塞性痴呆、衰老相关性认知衰退、癫痫(包括癫痫失神小发作(petit mal absence epilepsy))、阿耳茨海默氏类的老年性痴呆(AD)、帕金森氏病(PD)、注意力缺乏活动过强症(ADHD)和图雷特氏病。

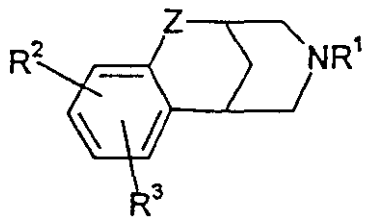
本发明的化合物还适合：与抗抑郁药，例如三环类抗抑郁药或 5-羟色胺重摄取抑制抗抑郁药(SRI)联合应用，用于治疗与 AD、PD、休克、杭廷顿氏舞蹈病或创伤性脑损伤(TBI)有关的认知衰退和抑郁；与毒蕈碱性激动剂联合应用于刺激中枢毒蕈碱性和烟碱性受体，以治疗如 ALS、认知机能障碍、衰老相关性认知衰退、AD、PD、中风、杭廷顿氏舞蹈病和 TBI；与神经营养因子如 NGF 联合应用以最大化胆碱能增强以治疗如 ALS、认知机能障碍、衰老相关性认知衰退、AD、PD、

中风、杭廷顿氏舞蹈病和TBI；或与减缓或阻止AD的药物如认识增强剂、淀粉样蛋白聚集抑制剂、分泌酶(secretase)抑制剂、taukinase抑制剂、神经元抗炎剂和雌激素类治疗剂联合应用。

其他可与神经元烟碱性受体位点结合的化合物参见美国专利申请08/963852(提交于1997年11月4日)和美国临时专利申请60/070245(提交于1997年12月31日)。上述两个专利申请皆属于本申请人，并且在此全文引入作为参考。

发明概述

本发明涉及下式的芳基稠合氮杂多元环类化合物：



(I)

其中Z是CH_2、C(=O)或CF_2；

R^1是氢、(C_1-C_6)烷基、非共轭(C_3-C_6)链烯基、苄基、$XC(=O)R^{13}$或$-CH_2CH_2-O-(C_1-C_4)$烷基；

R^2和R^3独立地选自氢、(C_2-C_6)链烯基、(C_2-C_6)炔基、羟基、硝基、氨基、卤素、氰基，$-SO_q(C_1-C_6)$烷基，其中q是0、1或2，(C_1-C_6)烷基氨基、$[(C_1-C_6)烷基]_2$氨基、CO_2R^4、$CONR^5R^6$、$SO_2NR^7R^8$、$C(=O)R^{13}$、$XC(=O)R^{13}$，芳基$-(C_0-C_3)$烷基或芳基$-(C_0-C_3)$烷基-O-，其中所述芳基选自苯基和萘基，杂芳基$-(C_0-C_3)$烷基或杂芳基$-(C_0-C_3)$烷基-O-，其中所述杂芳基选自含有1-4个选自氧、氮和硫的杂原子的5-7元芳香环；和$X^2(C_0-C_6)$烷氧基$-(C_0-C_6)$烷基，其中X^2不存在或X^2是(C_1-C_6)烷基氨基或$[(C_1-C_6)烷基]_2$氨基，和其中所述$X^2(C_0-C_6)$烷氧基$-(C_0-C_6)$烷基的(C_0-C_6)烷氧基$-(C_0-C_6)$烷基部分含有至少一个碳原子，和其中所述(C_0-C_6)烷氧基$-(C_0-C_6)$烷基部分的1-3个碳原子可以被氧、氮或硫原子任选地置换，条件是任何两个所述杂原子必须被至少两个碳原子分隔开，和其中所述(C_0-C_6)烷氧基$-(C_0-C_6)$烷基的任何烷基部分可以被2-7

个氟原子任选取代，和其中所述芳基-(C_0-C_3)烷基和所述杂芳基-(C_0-C_3)烷基的各烷基部分中的一个碳原子可以被氧、氮或硫原子任选地置换，和其中上述各个芳基和杂芳基可以被一个或多个取代基，优选被 0-2 个取代基任选地取代，所述取代基独立地选自：被 1-7 个氟原子任选取代的(C_1-C_6)烷基、被 2-7 个氟原子任选取代的(C_1-C_6)烷氧基、卤素(例如氯、氟、溴或碘)、羟基、硝基、氰基、氨基、(C_1-C_6)烷基氨基和[(C_1-C_6)烷基]$_2$氨基；

或 R^2和 R^3与其所连接的碳原子一起构成 4-7 元单环或 10-14 元双环，碳环，可以是饱和或不饱和，其中所述的单环中 1-3 个非稠合碳原子，和所述双环中不构成式 I 所示苯并环部分的 1-5 个碳原子，可以被氮、氧或硫任选地和独立地置换，和其中所述单环和双环可以被一个或多个取代基任选取代，对于所述单环优选被 0-2 个取代基任选取代，对于所述双环优选被 0-3 个取代基任选取代，所述取代基独立地选自：(C_0-C_6)烷氧基-(C_0-C_6)烷基-，其中碳原子的总数不超过 6 个且其中任何烷基部分可以被 1-7 个氟原子任选取代；硝基、氧代、氰基、卤素、羟基、氨基、(C_1-C_6)烷基氨基、[(C_1-C_6)烷基]$_2$氨基、苯基和单环杂芳基，其中所述杂芳基如上述 R^2和 R^3定义中所定义；

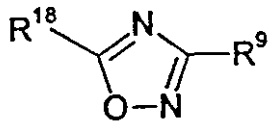
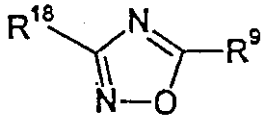
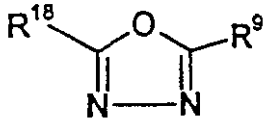
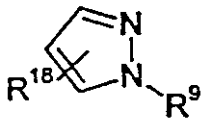
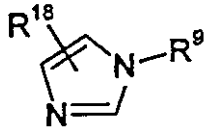
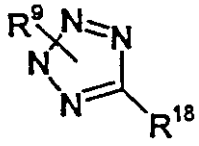
各个 R^4、R^5、R^6、R^7、R^8和 R^{13}独立地选自氢和(C_1-C_6)烷基，或 R^5和 R^6，或 R^7和 R^8与其所连接的氮一起构成吡咯烷、哌啶、吗啉、氮杂环丁烷、哌嗪（piperizine）、-N-(C_1-C_6)烷基哌嗪（piperizine）或硫代吗啉环，或是其中环硫被亚砜或砜置换的硫代吗啉环；和

各个 X 独立地是(C_1-C_6)亚烷基；

条件是：(a)至少一个 R^1、R^2和 R^3一定不是氢，(b)当 R^2和 R^3是氢时，R^1不是甲基或氢；和(c)R^2和 R^3中的任何氟取代烷基或烷氧基部分中无氟原子可以连接在与杂原子相连的碳原子上；

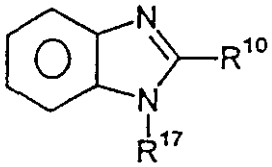
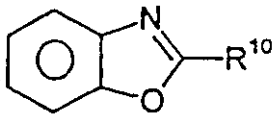
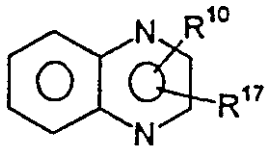
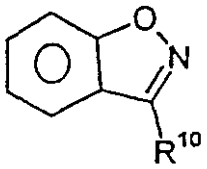
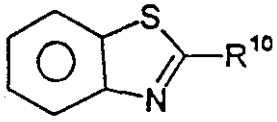
和所述化合物的药学上可接受的盐。

各个可作为 R^2和 R^3的杂芳基的实例可以是下列基团：噻吩基、噁唑基、异噁唑基、吡啶基、嘧啶基、噻唑基、四唑基、异噻唑基、三唑基、咪唑基、四唑基、吡咯基和以下基团：

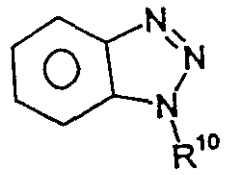
其中 R^9 和 R^{18} 之一是氢或 (C_1-C_6) 烷基，并且另一个是与式 I 的苯并环相连的键。

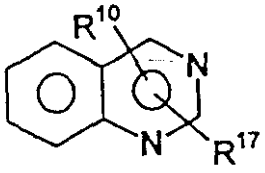
本发明的化合物的实例是式 I 的化合物及其药学上可接受的盐，其中 R^2 和 R^3 与式 I 的苯并环一起构成选自如下的双环体系：

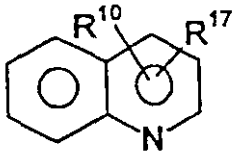






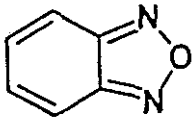
其中 R^{10} 和 R^{17} 独立地选自 (C_0-C_6) 烷氧基-(C_0-C_6) 烷基，其中碳原子的总数不超过 6 且其中任何的烷基部分可以被 1-7 个氟原子、被 1-7 个氟原子任选取代的 (C_1-C_6) 烷氧基、硝基、氰基、卤素、氨基、(C_1-C_6) 烷基氨基、$[(C_1-C_6)$ 烷基$]_2$ 氨基、苯基和单环杂芳基，其中所述杂芳基如上述 R^2 和 R^3 定义中的定义；

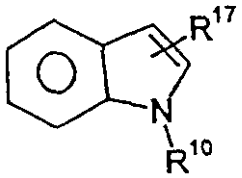
本发明的其它实施方案涉及式 I 的化合物及其药学上可接受的盐，其中 R^2 和 R^3 连同与式 I 的苯并环形成选自如下的双环或三环体系：

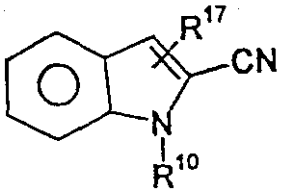


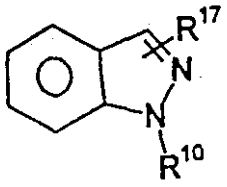


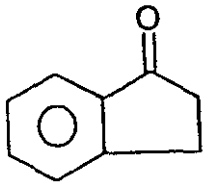


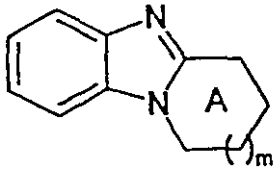


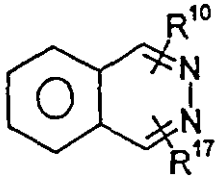












其中 R^{10} 和 R^{17} 定义如上和 m 是 0、1 或 2，和其中 A 环的一个碳原子可以被氧或-N(C_1-C_6)烷基任选地置换。

本发明的其它实施方案涉及式 I 的化合物及其药学上可接受的盐，其中既无 R^2 也无 R^3 通过氧原子与式 I 的苯并环相连。

本发明的其它实施方案涉及其中 R^1 不是甲基的式 I 化合物。

式 I 的具体化合物的实例如下所示：

11-氮杂三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯-5-甲腈；

11-氮杂三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯-4-甲腈；

1-[11-氮杂三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯-5-基]-1-乙酮;

1-[11-氮杂三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯-5-基]-1-丙酮;

4-氟-11-氮杂三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯-5-甲腈;

5-氟-11-氮杂三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯-4-甲腈;

1-[11-氮杂三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯-4-基]-1-乙酮;

1-[11-氮杂三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯-4-基]-1-丙酮;

6-甲基-7-硫杂-5,14-二氮杂四环[10.3.1.$0^{2,10}$.$0^{4,8}$]十六碳-2(10),3,5,8-四烯;

6-甲基-5,7,14-三氮杂四环[10.3.1.$0^{2,10}$.$0^{4,8}$]十六碳-2(10),3,5,8-四烯;

6,7-二甲基-5,7,14-三氮杂四环[10.3.1.$0^{2,10}$.$0^{4,8}$]十六碳-2(10),3,5,8-四烯;

5,7,14-三氮杂四环[10.3.1.$0^{2,10}$.$0^{4,8}$]十六碳-2(10),3,5,8-四烯;

7-甲基-5,7,14-三氮杂四环[10.3.1.$0^{2,10}$.$0^{4,8}$]十六碳-2(10),3,5,8-四烯;

5,11,18-三氮杂五环[14.3.1.$0^{2,14}$.$0^{4,12}$.$0^{6,11}$]二十碳-2(14),3,5,12-四烯;

7-乙基-6-甲基-5,7,14-三氮杂四环[10.3.1.$0^{2,10}$.$0^{4,8}$]十六碳-2(10),3,5,8-四烯;

6-甲基-7-丙基-5,7,14-三氮杂四环[10.3.1.$0^{2,10}$.$0^{4,8}$]十六碳-2(10),3,5,8-四烯;

7-乙基-5,7,14-三氮杂四环[10.3.1.$0^{2,10}$.$0^{4,8}$]十六碳-2(10),3,5,8-四烯;

7-丁基-6-甲基-5,7,14-三氮杂四环[10.3.1.$0^{2,10}$.$0^{4,8}$]十六碳

-2(10),3,5,8-四烯;

7-异丁基-6-甲基-5,7,14-三氮杂四环[10.3.1.$0^{2,10}$.$0^{4,8}$]十六碳-2(10),3,5,8-四烯;

7-丁基-5,7,14-三氮杂四环[10.3.1.$0^{2,10}$.$0^{4,8}$]十六碳-2(10),3,5,8-四烯;

7-异丁基-5,7,14-三氮杂四环[10.3.1.$0^{2,10}$.$0^{4,8}$]十六碳-2(10),3,5,8-四烯;

5,11,18-三氮杂五环[14.3.1.$0^{2,14}$.$0^{4,12}$.$0^{5,10}$]二十碳-2(14),3,10,12-四烯、

5,6-二甲基-5,7,14-三氮杂四环[10.3.1.$0^{2,10}$.$0^{4,8}$]十六碳-2(10),3,6,8-四烯;

5-乙基-6-甲基-5,7,14-三氮杂四环[10.3.1.$0^{2,10}$.$0^{4,8}$]十六碳-2(10),3,6,8-四烯;

5-甲基-5,7,14-三氮杂四环[10.3.1.$0^{2,10}$.$0^{4,8}$]十六碳-2(10),3,6,8-四烯;

5-乙基-5,7,14-三氮杂四环[10.3.1.$0^{2,10}$.$0^{4,8}$]十六碳-2(10),3,6,8-四烯;

6-甲基-5-丙基-5,7,14-三氮杂四环[10.3.1.$0^{2,10}$.$0^{4,8}$]十六碳-2(10),3,6,8-四烯;

5-异丁基-6-甲基-5,7,14-三氮杂四环[10.3.1.$0^{2,10}$.$0^{4,8}$]十六碳-2(10),3,6,8-四烯;

5-丙基-5,7,14-三氮杂四环[10.3.1.$0^{2,10}$.$0^{4,8}$]十六碳-2(10),3,6,8-四烯;

5-异丁基-5,7,14-三氮杂四环[10.3.1.$0^{2,10}$.$0^{4,8}$]十六碳-2(10),3,6,8-四烯;

6-(三氟甲基)-7-硫杂-5,14-二氮杂四环[10.3.1.$0^{2,10}$.$0^{4,8}$]十六碳-2(10),3,5,8-四烯;

5,8,15-三氮杂四环[11.3.1.$0^{2,11}$.$0^{4,9}$]十七碳-2(11),3,5,7,9-五烯;

7-甲基-5,8,15-三氮杂四环[11.3.1.$0^{2,11}$.$0^{4,9}$]十七碳-2(11),3,5,7,9-五烯;

6-甲基-5,8,15-三氮杂四环[11.3.1.$0^{2,11}$.$0^{4,9}$]十七碳-2(11),3,5,7,9-五烯;

6,7-二甲基-5,8,15-三氮杂四环[11.3.1.$0^{2,11}$.$0^{4,9}$]十七碳-2(11),3,5,7,9-五烯;

7-氧杂-5,14-二氮杂四环[10.3.1.$0^{2,10}$.$0^{4,8}$]十六碳-2(10),3,5,8-四烯;

6-甲基-7-氧杂-5,14-二氮杂四环[10.3.1.$0^{2,10}$.$0^{4,8}$]十六碳-2(10),3,5,8-四烯;

6-乙基-7-氧杂-5,14-二氮杂四环[10.3.1.$0^{2,10}$.$0^{4,8}$]十六碳-2(10),3,5,8-四烯;

6-丙基-7-氧杂-5,14-二氮杂四环[10.3.1.$0^{2,10}$.$0^{4,8}$]十六碳-2(10),3,5,8-四烯;

5-甲基-7-氧杂-6,14-二氮杂四环[10.3.1.$0^{2,10}$.$0^{4,8}$]十六碳-2(10),3,5,8-四烯;

5-氧杂-7,14-二氮杂四环[10.3.1.$0^{2,10}$.$0^{4,8}$]十六碳-2(10),3,6,8-四烯;

6-甲基-5-氧杂-7,14-二氮杂四环[10.3.1.$0^{2,10}$.$0^{4,8}$]十六碳-2(10),3,6,8-四烯;

6-乙基-5-氧杂-7,14-二氮杂四环[10.3.1.$0^{2,10}$.$0^{4,8}$]十六碳-2(10),3,6,8-四烯;

6-丙基-5-氧杂-7,14-二氮杂四环[10.3.1.$0^{2,10}$.$0^{4,8}$]十六碳-2(10),3,6,8-四烯;

7-甲基-5-氧杂-6,14-二氮杂四环[10.3.1.$0^{2,10}$.$0^{4,8}$]十六碳-2(10),3,6,8-四烯;

4,5-二氟-11-氮杂三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯-4-氯-5-氟-11-氮杂三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯;

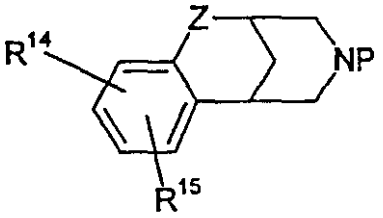
5-氯-4-氟-11-氮杂三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯;

4-(1-乙炔基)-5-氟-11-氮杂三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯;

5-(1-乙炔基)-4-氟-11-氮杂三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯;和

4,5-二氯-11-氮杂三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯;

本发明还涉及下式的化合物:



(I)

其中Z是CH_2、C(=O)或CF_2;P是氢,甲基,$COOR^{16}$,其中R^{16}是烯丙基、2,2,2-三氯乙基或(C_1-C_6)烷基;-C(=O)NR^5R^6,其中R^5和R^6如上述式I定义;-C(=O)H、-C(=O)(C_1-C_6)烷基,其中烷基部分可以被1-3个卤素原子,优选1-3个氟原子或氯原子任选取代;苄基或叔丁氧基羰基(t-Boc);和R^{14}和R^{15}独立地选自氢、羟基、硝基、氨基、-O(C_1-C_6)烷基或卤素;条件是当P是氢或甲基时,R^{14}和R^{15}不同时为氢。所述化合物在式I化合物的合成中用作中间体。

除非另外指出,此处所用的术语"卤素"包括氟、氯、溴和碘。

除非另外指出,此处所用的术语"烷基"包括直链、支链或环状烷基,并且可以包括直链和环状烷基部分以及支链和环状部分。

此处所用术语"烷氧基"是指"烷基-O";其中"烷基"定义如上。

此处所用的术语"亚烷基"是指具有两个有效键合位点的烷基(即-烷基-),其中"烷基"定义如上。

除非另外指出,此处所用术语"一个或多个取代基"是指基于有效键合位点数量的1个-最大数目的可能的取代基。

此处所用的术语"治疗"是指逆转、缓解、抑制该术语所针对的病症或疾病的恶化,或预防所述病症或疾病,或所述病症或疾病的一种或多种症状。此处所用的术语"治疗"是指治疗行为,如同上文刚才的定义。

式 I 的化合物可以具有旋光中心且因此存在不同的对映构型。本发明包括所有对映异构体、非对映异构体，和所述式 I 化合物的其它立体异构体，以及外消旋体或其其它混合物。

本发明还涉及式 I 化合物的所有放射性标记形式，优选的式 I 的放射性标记化合物是其中放射标记选自 ^{3}H、^{11}C、^{14}C、^{18}F、^{123}I 和 ^{125} 的那些。所述放射标记化合物在药代动力学研究和动物与人的结合试验中用作科研和诊断工具。

本发明涉及一种适用于在哺乳动物（包括人）中减轻烟瘾（nicotine addiction）或有助于停止或减少烟草使用的药物组合物，该组合物含有有效减轻烟瘾或有助于停止或减少烟草使用的量的式 I 化合物或其药学上可接受的盐以及药学上可接受的载体。

本发明还涉及一种用于在哺乳动物(包括人)中减轻烟瘾或有助于停止或减少烟草使用的方法，该方法包括给该哺乳动物施用可以有效减轻烟瘾或有助于停止或减少烟草使用的量的式 I 化合物或其药学上可接受的盐。

本发明还涉及选自如下病症或疾病的治疗方法，所述疾病选自：炎性肠病(包括但不限于溃疡性结肠炎、坏疽性脓皮病和局限性回肠炎)、过敏性肠综合征、痉挛性张力障碍、慢性疼痛、急性疼痛、腹腔口炎性腹泻、囊炎、血管收缩、焦虑、恐慌症、抑郁症、双相性精神障碍、孤独症、睡眠障碍、时差综合征、肌萎缩性脊髓侧索硬化症(ALS)、认知机能障碍、高血压、食欲过盛、厌食、肥胖、心律失常、胃酸分泌过多、溃疡病、嗜铬细胞瘤、进行性肌肉上部麻痹、化学品依赖性和癖嗜(例如对烟碱(和/或烟草产品)、醇、苯并二氮䓬类、巴比妥类、阿片样物质类或可卡因依赖或成瘾)，头痛、中风、创伤性脑损伤(TBI)、精神病、杭廷顿氏舞蹈病、迟发性运动障碍、运动机能亢进、诵读困难、精神分裂症、多梗塞性痴呆、衰老相关性认知衰退、癫痫(包括癫痫失神小发作)、阿耳茨海默氏型的老年性痴呆(AD)、帕金森氏病(PD)、注意力缺乏活动过强症(ADHD)和图雷特氏病；所述方法包括给需此治疗的哺乳动物施用可以有效治疗所述病症或疾病量的式 I 的化合物或

其药学上可接受的盐。

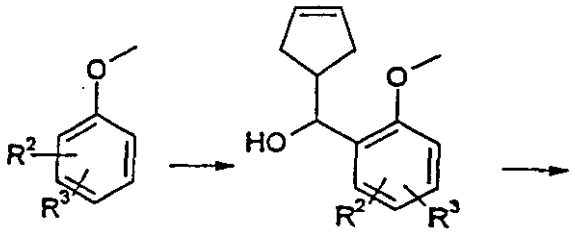
本发明还涉及用于治疗选自如下疾病或病症的药物组合物，所述疾病选自炎性肠病(包括但不限于溃疡性结肠炎、坏疽性脓皮病和局限性回肠炎)、过敏性肠综合征、痉挛性张力障碍、慢性疼痛、急性疼痛、腹腔口炎性腹泻、囊炎、血管收缩、焦虑、恐慌症、抑郁症、双相性精神障碍、孤独症、睡眠障碍、时差综合征、肌萎缩性脊髓侧索硬化症(ALS)、认知机能障碍、高血压、食欲过盛、厌食、肥胖、心律失常、胃酸分泌过多、溃疡病、嗜铬细胞瘤、进行性肌肉上部麻痹、化学品依赖性和癖嗜(例如对烟碱(和/或烟草产品)、醇、苯并二氮䓬类、巴比妥类、阿片样物质类或可卡因依赖或成瘾)，头痛、休克、创伤性脑损伤(TBI)、精神病、杭廷顿氏舞蹈病、迟发性运动障碍、运动机能亢进、诵读困难、精神分裂症、多梗塞性痴呆、衰老相关性认知衰退、癫痫(包括癫痫失神小发作)、阿耳茨海默氏型的老年性痴呆(AD)、帕金森氏病(PD)、注意力缺乏活动过强症(ADHD)和图雷特氏病；所述药物组合物含有一定量的式 I 的化合物或其药学上可接受的盐以及药学上可接受载体。

本发明还涉及式 I 化合物的药学上可接受的酸加成盐。式 I 化合物的药学上可接受酸加成盐的实例是盐酸、对-甲苯磺酸、富马酸、柠檬酸、琥珀酸、水杨酸、草酸、氢溴酸、磷酸、甲磺酸、酒石酸、苹果酸、二-对-甲苯甲酰基酒石酸和苦杏仁酸的盐。

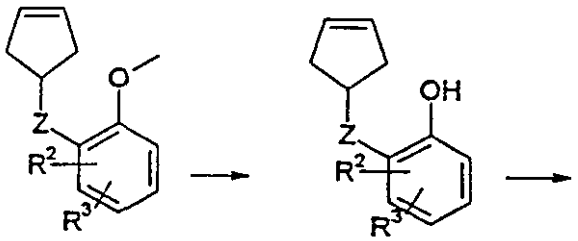
发明详述

除非另外说明，下文反应路线和讨论中的 R^1 至 R^{18}，m 和 P，和结构式 I 如上述定义。

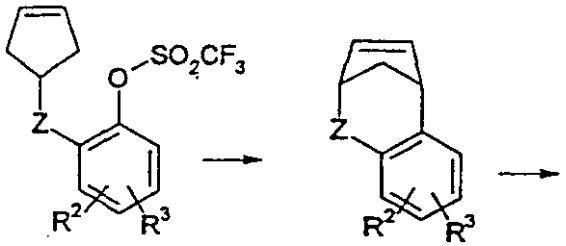
反应路线 1



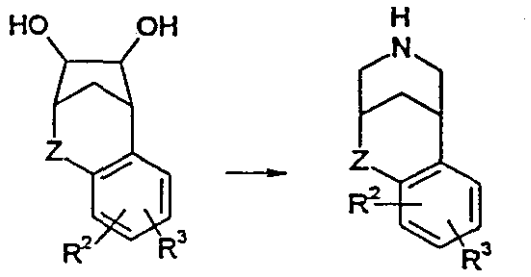
II III



IV V

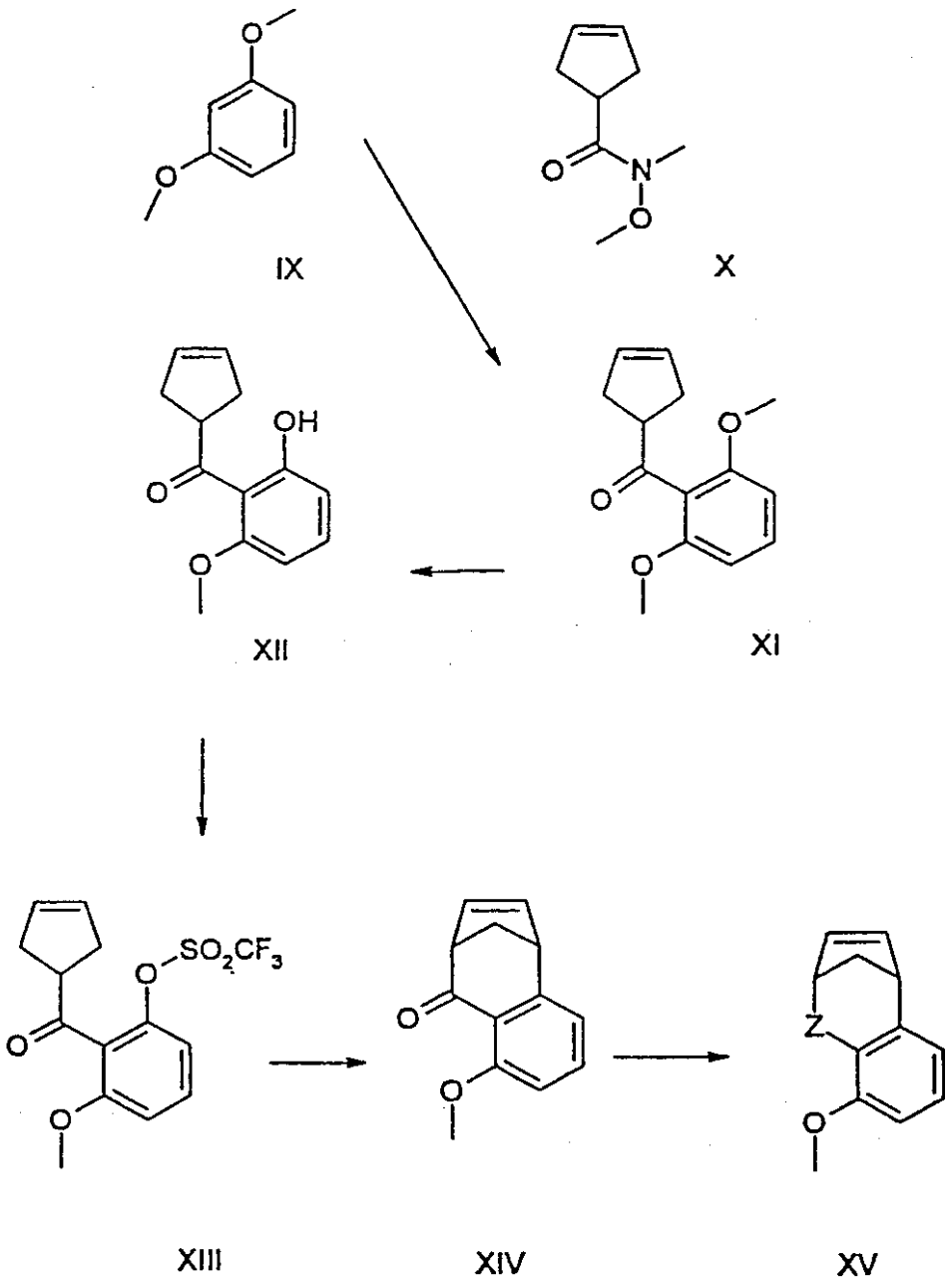


VI VII

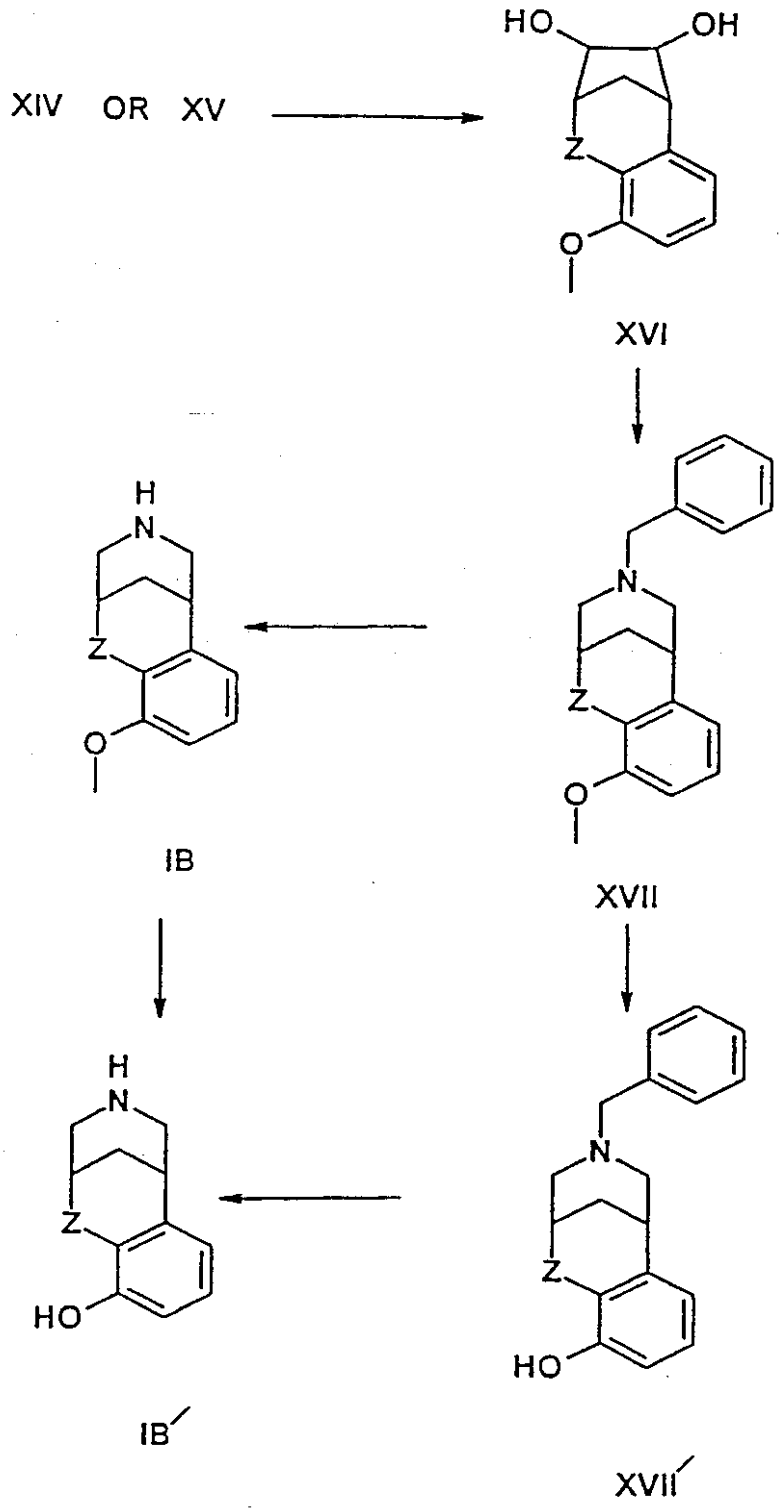


VIII IA

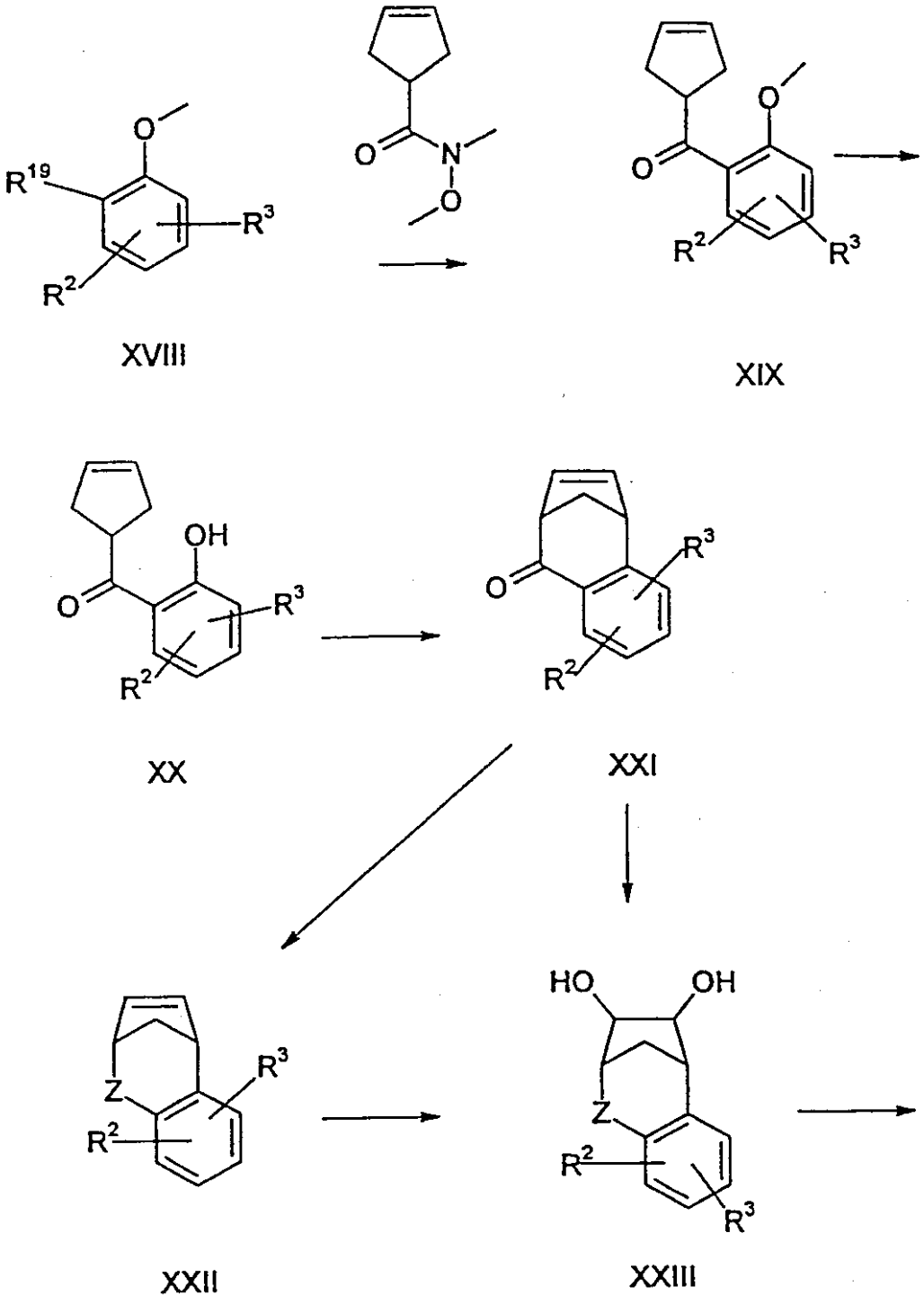
反应路线 2



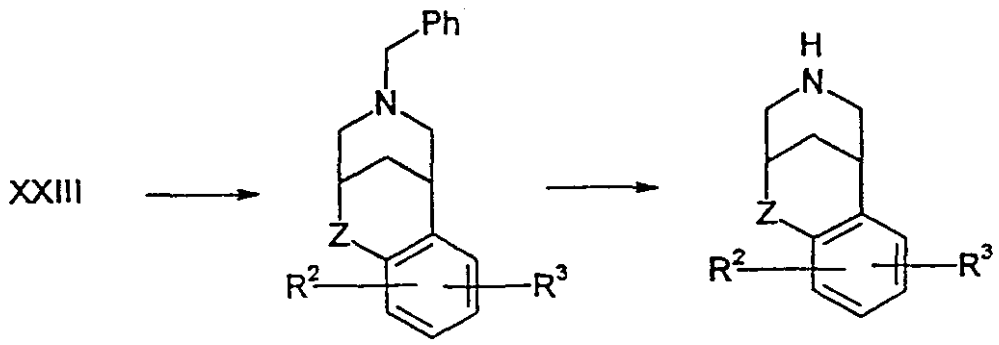
反应路线 2 续



反应路线 3


R19
O
R3
R2
XVIII
O
N
O
O
O
R2
R3
XIX
OH
O
R3
R2
XX
O
R3
R2
XXI
Z
R3
R2
XXII
HO
OH
Z
R2
R3
XXIII

反应路线 3 续

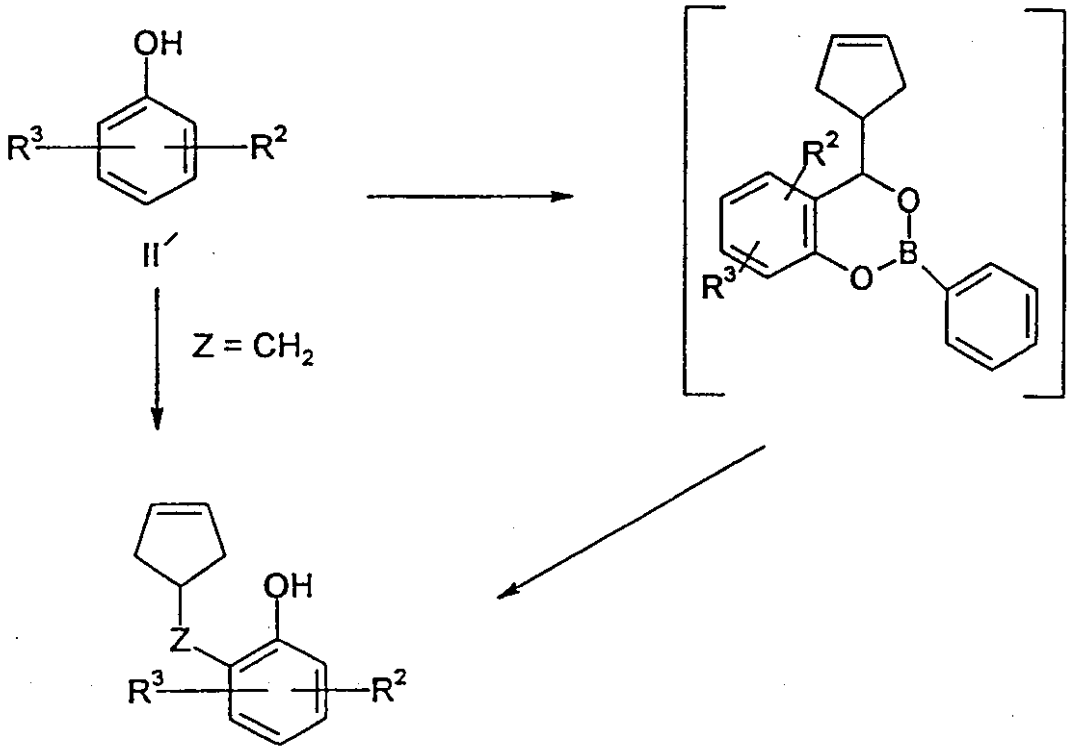


(Ph= 苯基)

XXIV

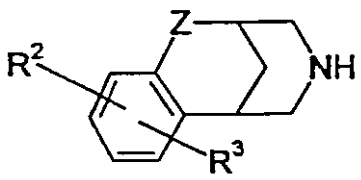
IC

反应路线 4



(Z = (C=O)或 CH_2或 CF_2)

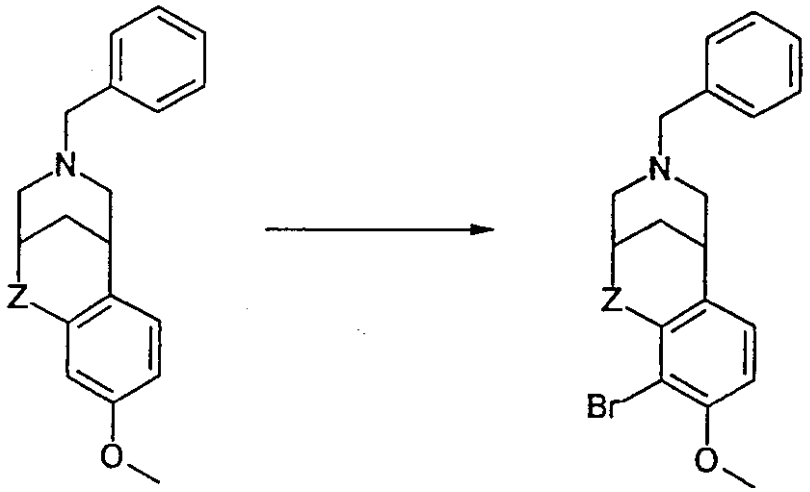
IV′



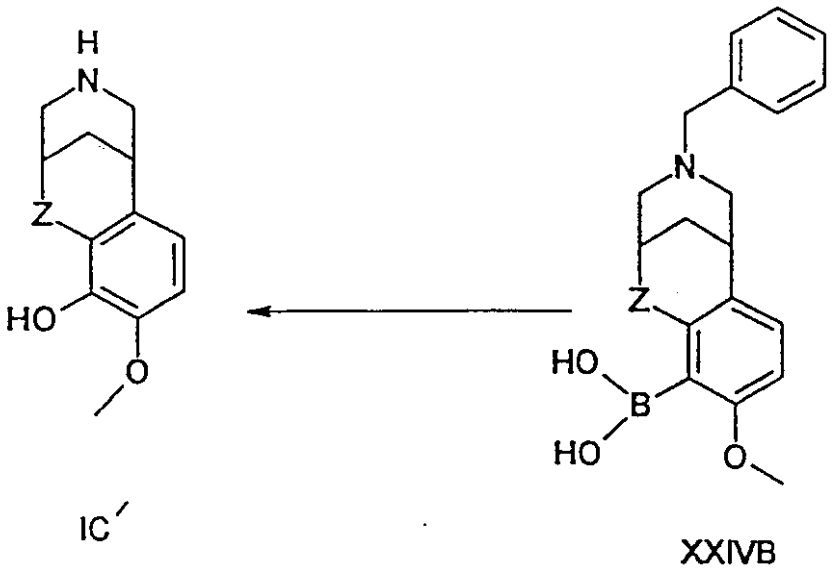
(Z = (C=O), CH_2或 CF_2)

IA′

反应路线 5

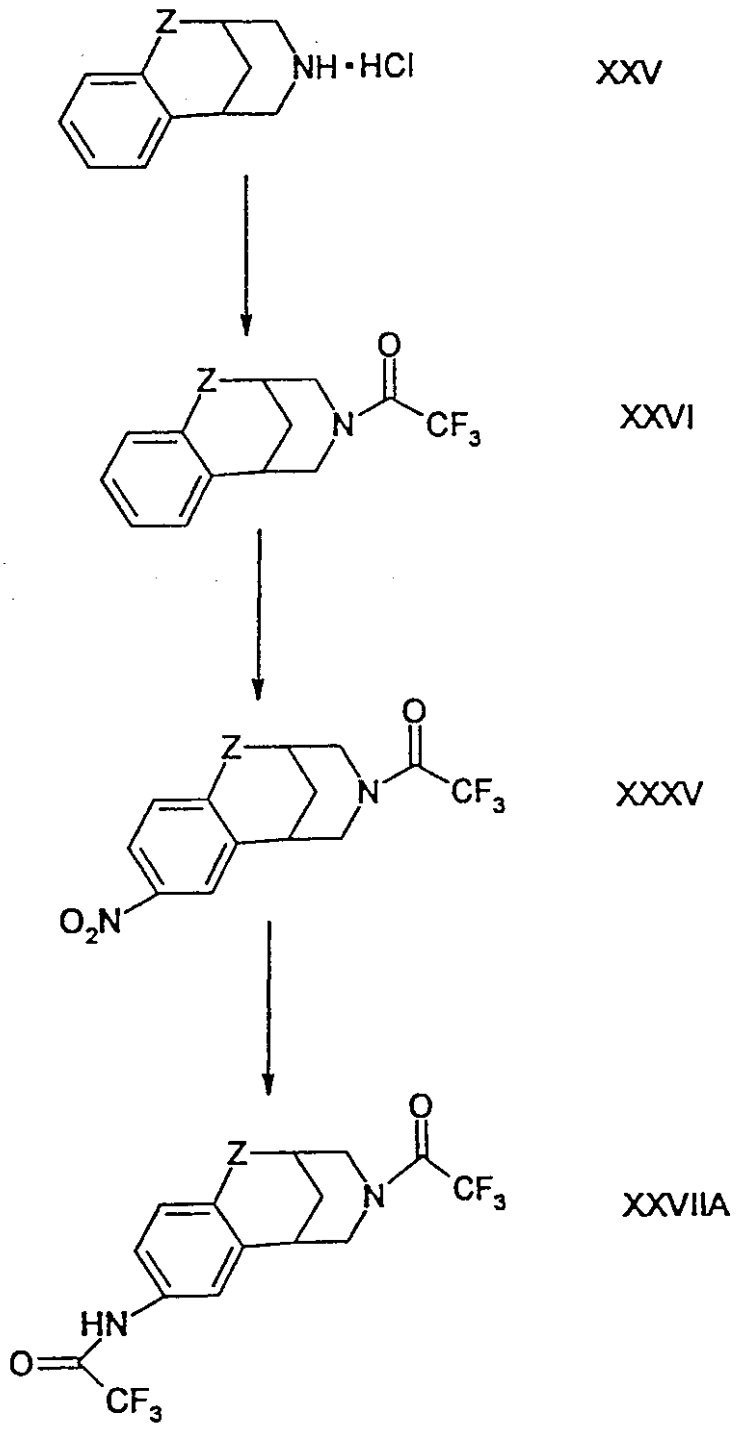


XXIV　　XXIVA

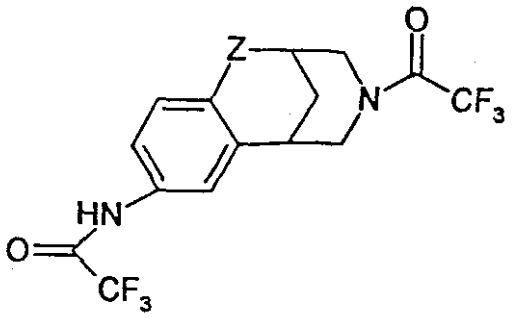


IC′　　XXIVB

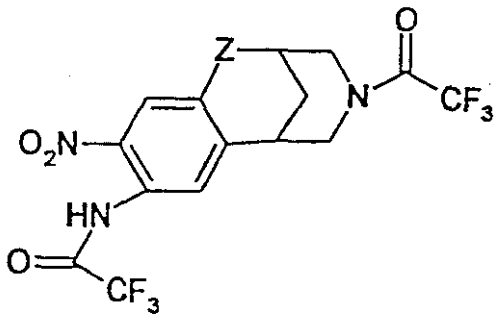
反应路线 6


Z
NH·HCl
XXV
O
Z
N
CF3
XXVI
O
Z
N
CF3
O2N
XXXV
O
Z
N
CF3
HN
O
CF3
XXVIIA

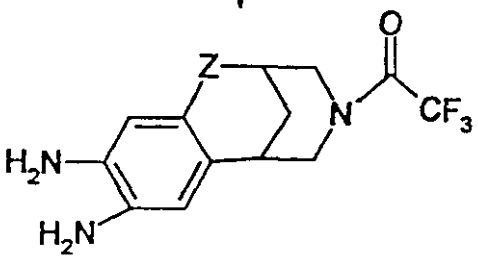
反应路线 6 续



XXVIIA

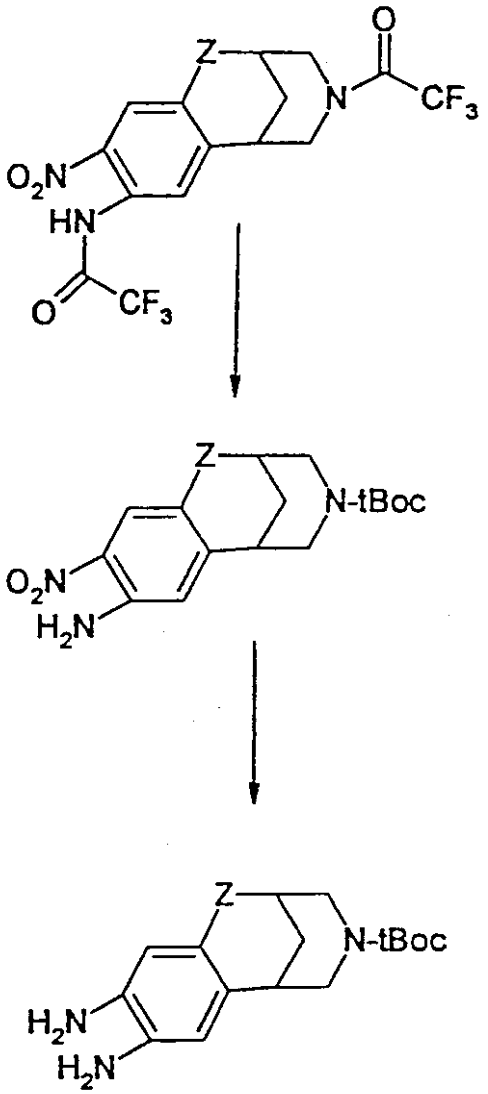


XXVIIA´

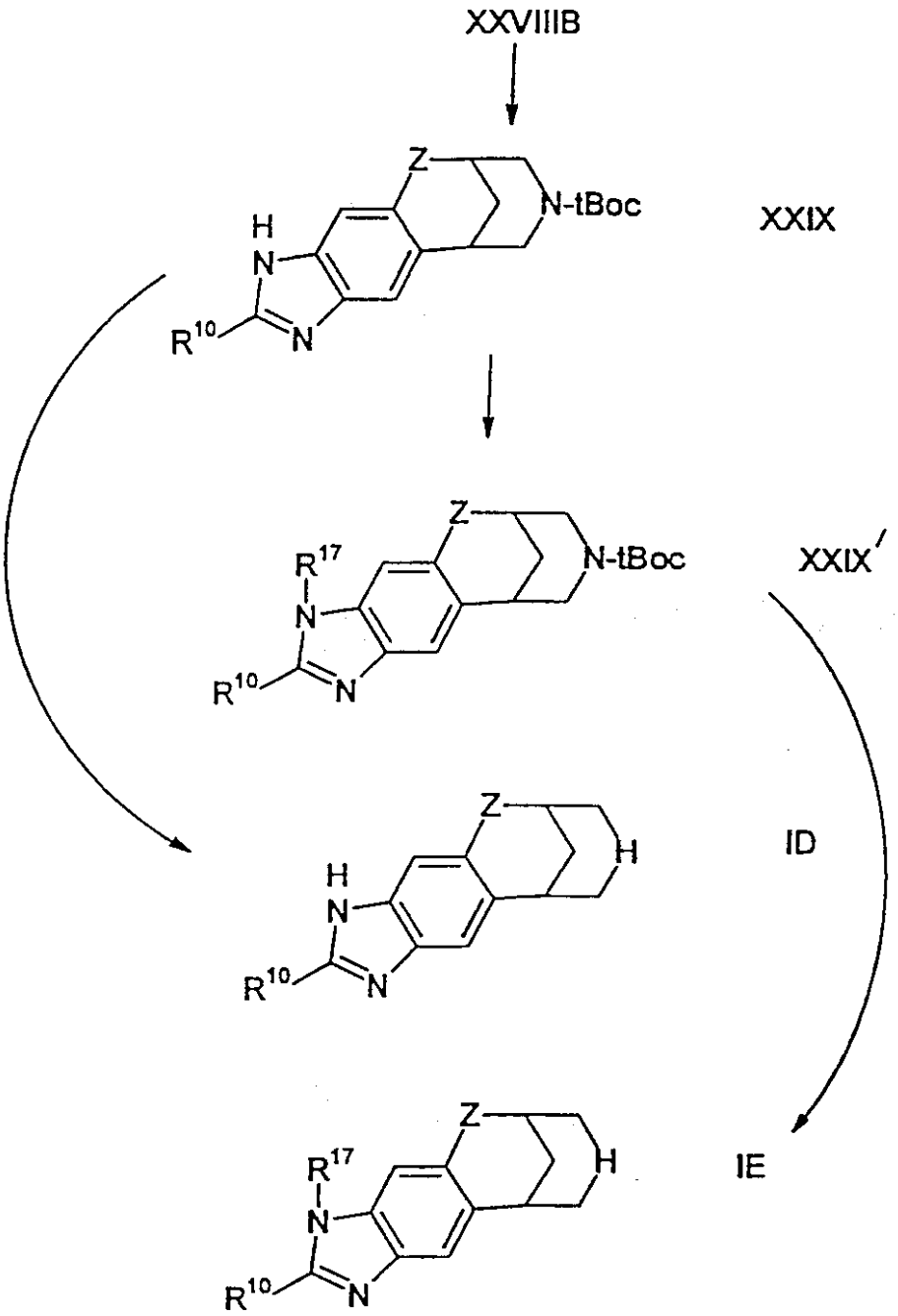


XXVIIB

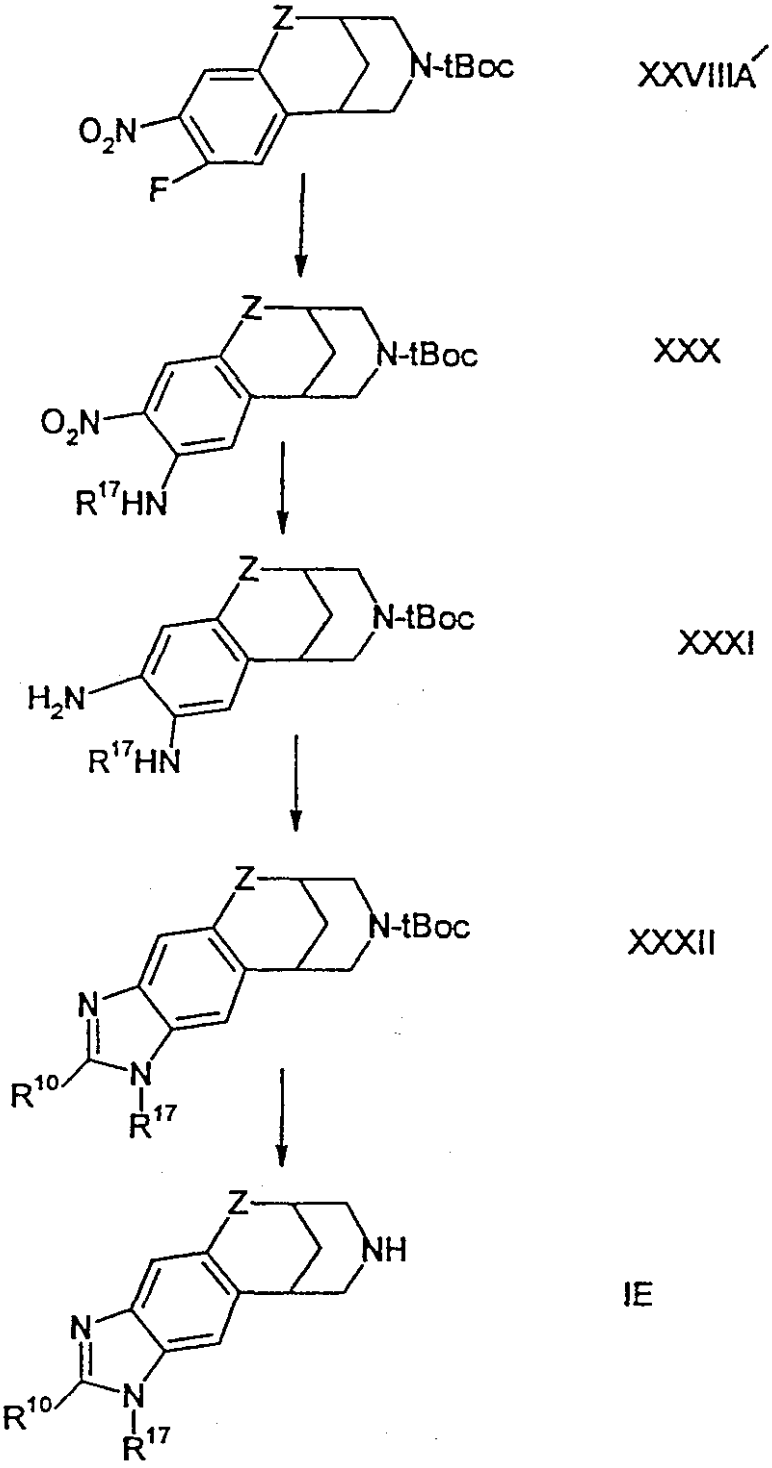
反应路线 7


Z
O
N
CF3
O2N
HN
O
CF3
XXVIIA
Z
N-tBoc
O2N
H2N
XXVIIIA
Z
N-tBoc
H2N
H2N
XXVIIIB

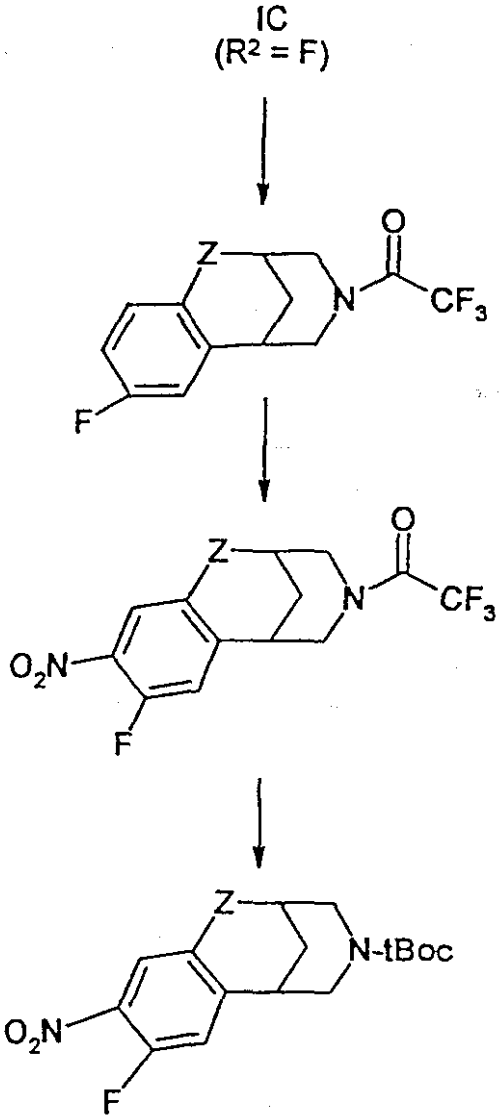
反应路线 7 续



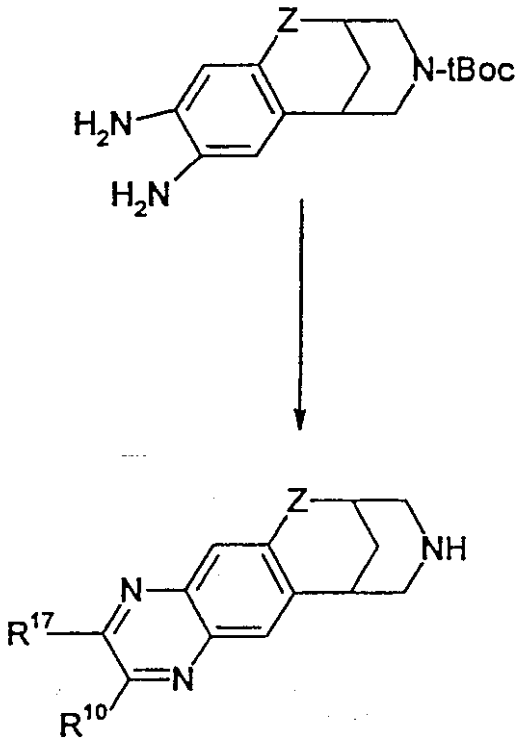
反应路线 8


Z
N-tBoc
O_2N
F
XXVIIIA
Z
N-tBoc
O_2N
$R^{17}HN$
XXX
Z
N-tBoc
H_2N
$R^{17}HN$
XXXI
Z
N-tBoc
N
R^{10}
N
R^{17}
XXXII
Z
NH
N
R^{10}
N
R^{17}
IE

反应路线 8A



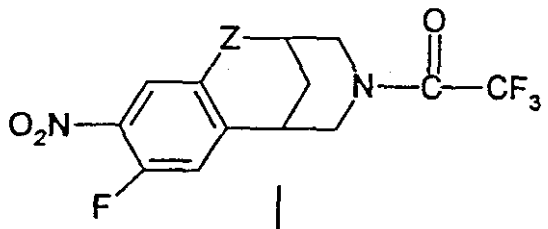
反应路线 9



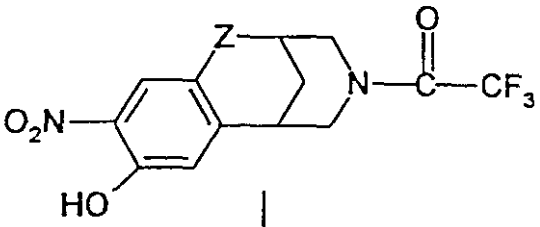
XXVIIIB

IF

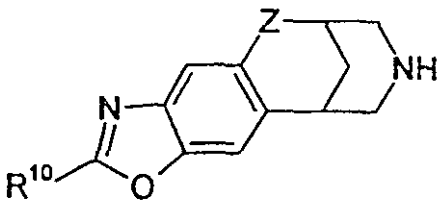
反应路线 10



ICTFA

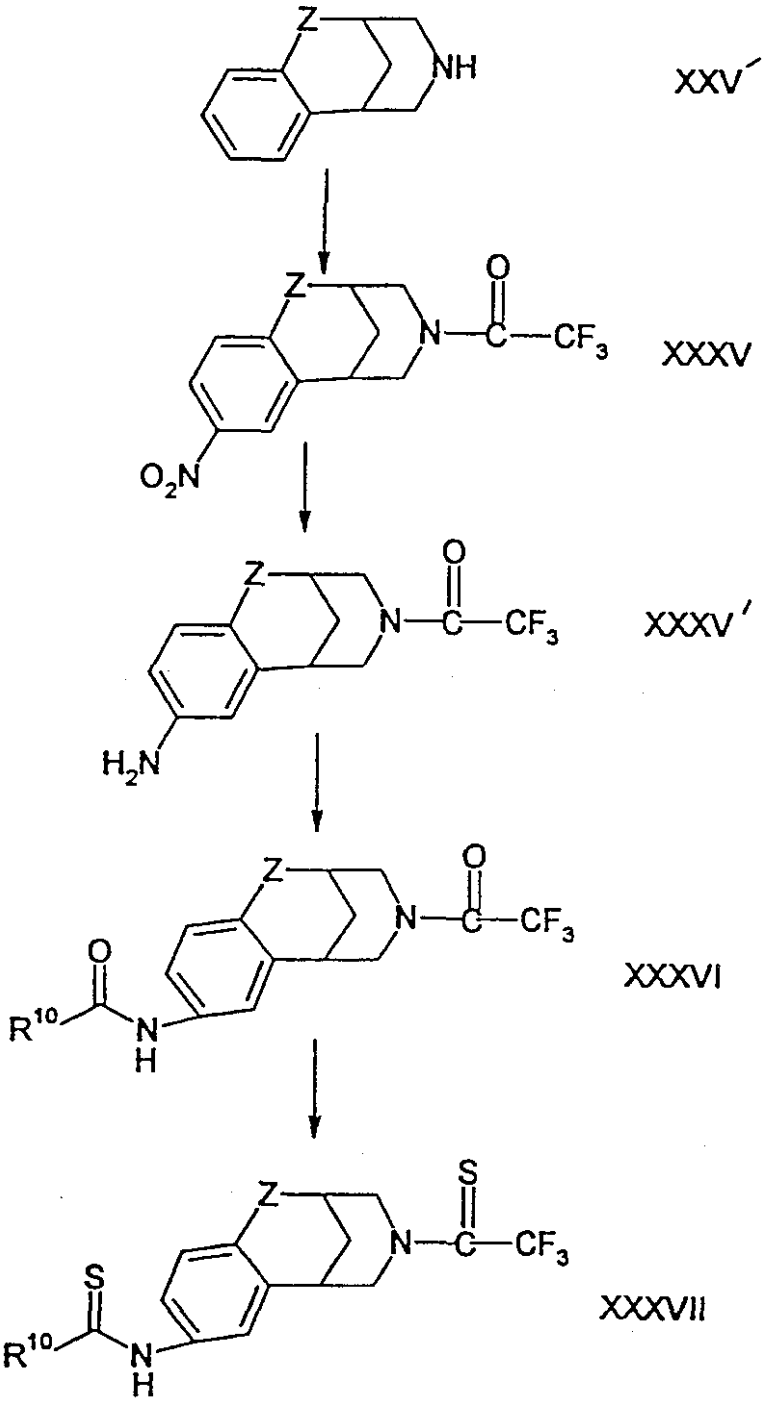


XXXIV

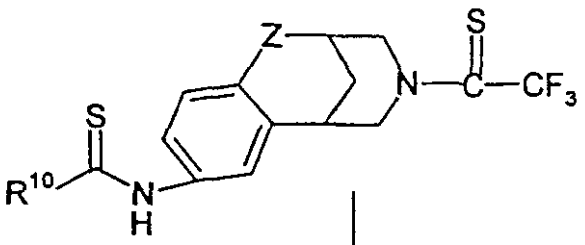


IG

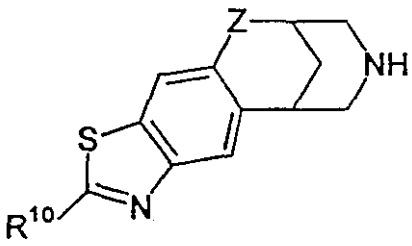
反应路线 11



反应路线 11 续

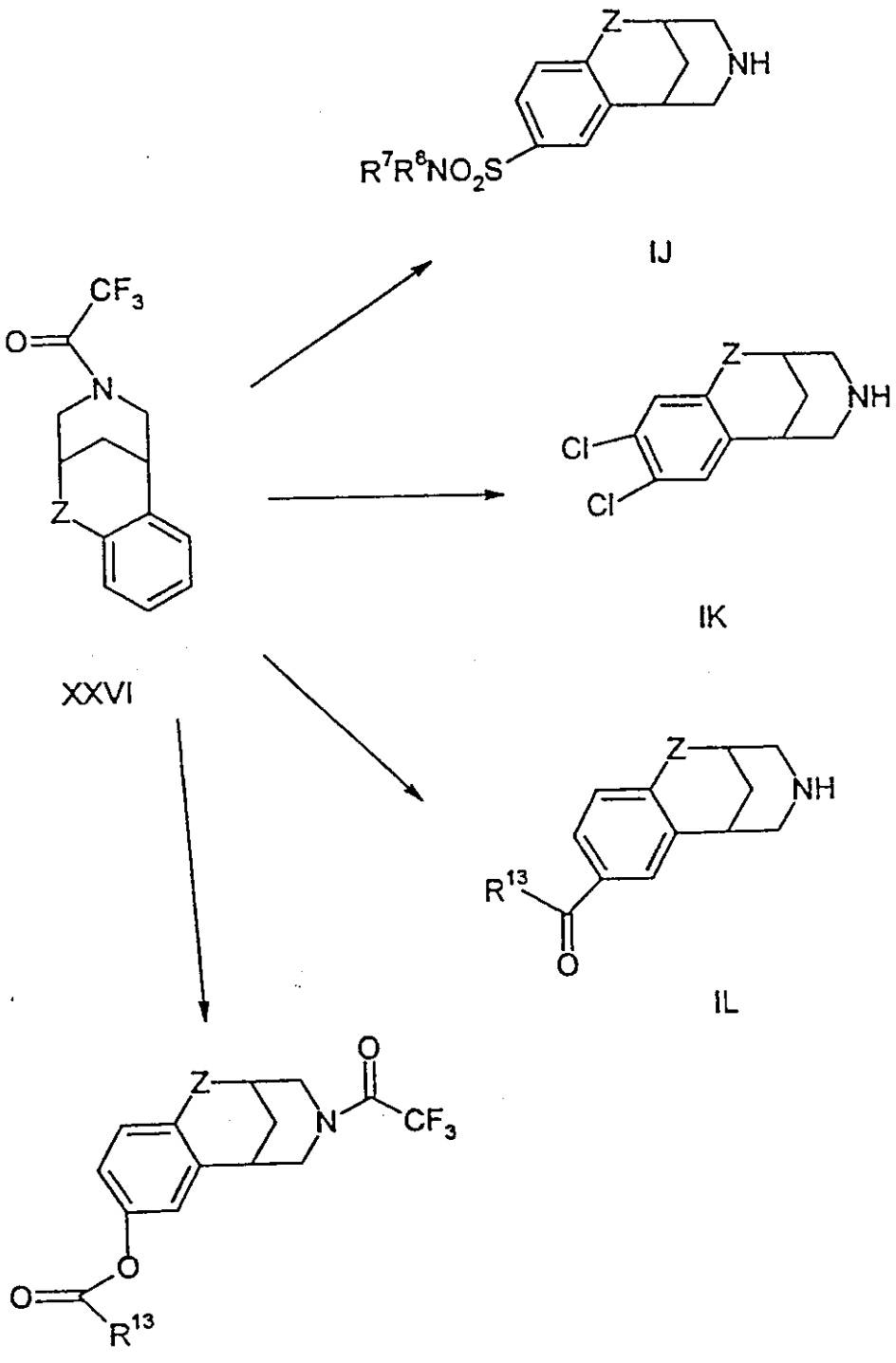


XXXVII

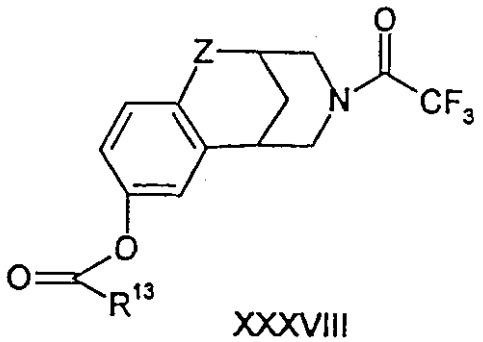


IH

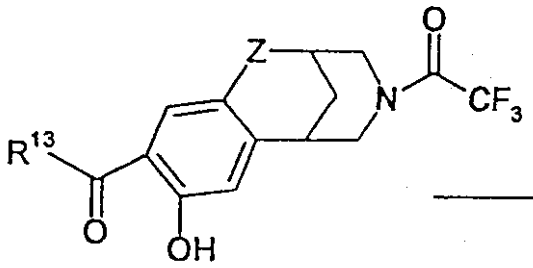
反应路线 12


Z
NH
R7R8NO2S
IJ
CF3
O
N
Z
XXVI
Z
NH
Cl
Cl
IK
Z
NH
R13
O
IL
O
Z
N
CF3
O
O
R13
XXXVIII

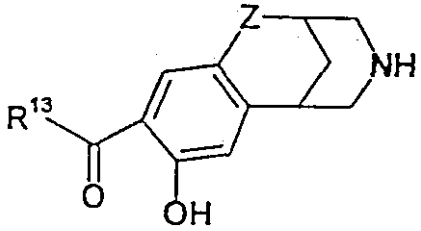
反应路线 12 续



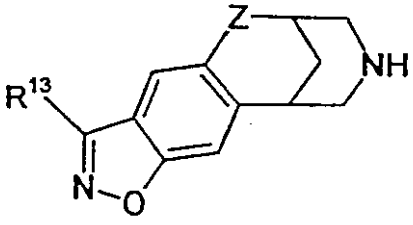
XXXVIII



XXXIX

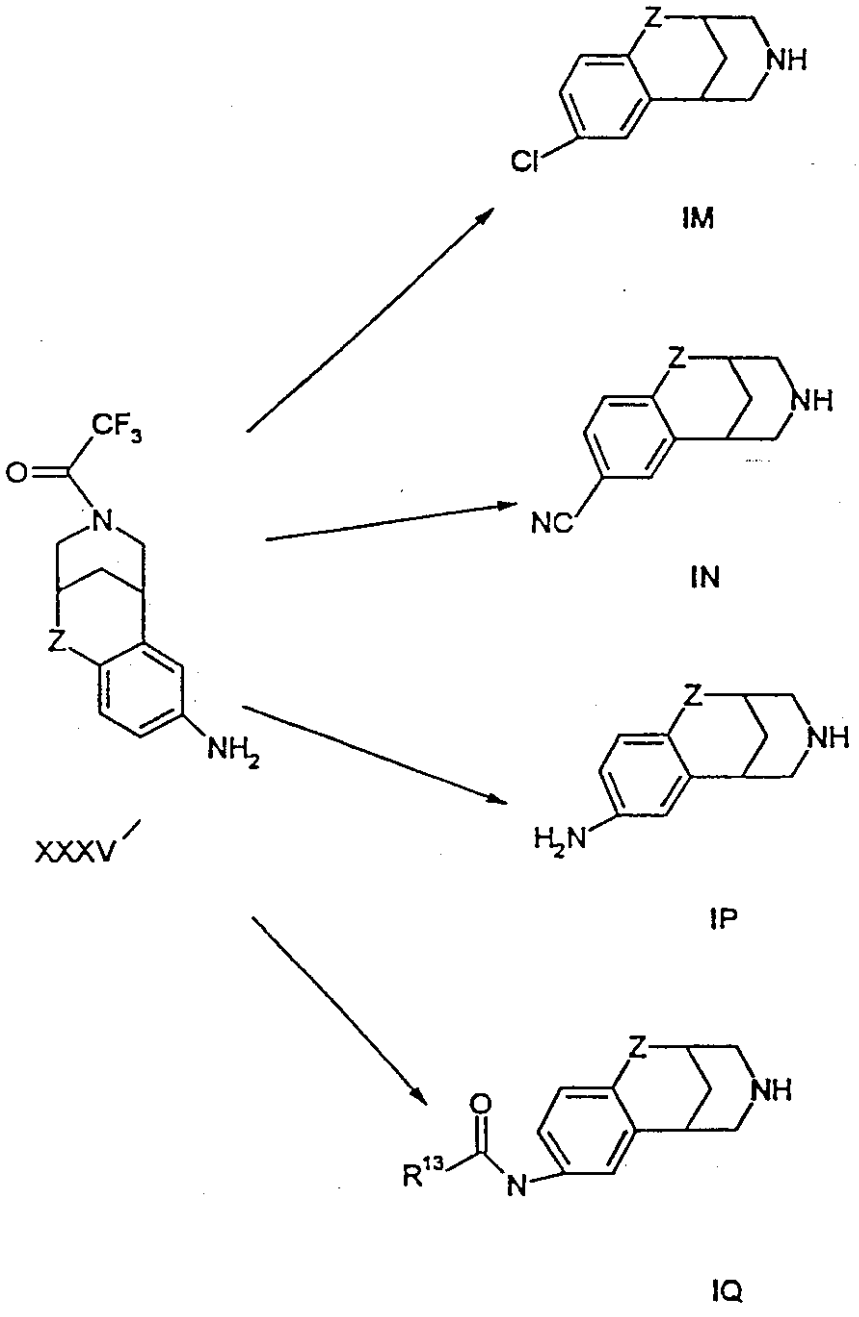


IS



IT

反应路线 13



反应路线 1-13 举例说明式 I 化合物的合成方法。反应路线 1-4 举例说明了其中取代基 R^2 和 R^3 在环化生成式 I 的三环核心之前相连的合成方法，这用其中 R^2 和 R^3 是氢的结构式 IA(反应路线 1)或 IC(反应路线 3)的游离碱表示。反应路线 5-13 举例说明了由含有上述核心的起始原料来制备式 I 的化合物的方法。

如反应路线 1 所示，式 II 的起始原料通过以下过程可以转化为式 III 的化合物。将式 II 的起始原料和约 1 当量的强碱如正丁基锂在溶剂如无水 THF、醚或甲基叔丁基醚中在约-78℃至约-65℃下反应。该金属化作用在约 10 分钟至 5 小时内发生，当维持在低于-65℃的温度下时通常约在 2 小时内发生。随后用环戊-3-烯甲醛在同样的溶剂中以维持温度低于-65℃的速率处理由此制得的阴离子。此后通过将反应混合物加入含水酸性介质中来终止该反应且后处理。

随后，由此制得的式 III 的化合物在三氟乙酸和还原剂如三甲基硅烷的作用下在苄基位置还原，生成具有式 IV 的相应化合物。该反应一般是在氯代烃溶剂如氯仿、二氯乙烷(DCE)或二氯甲烷中在室温下进行约 6 至 24 小时，优选约 18 小时内。

通过用等量的四丁基碘化铵和三氯化硼在氯代烃溶剂，例如氯仿、二氯乙烷(DCE)或二氯甲烷中处理式 IV 的化合物，该化合物被转化为相应的式 V 化合物。该反应一般是在温度为-78℃下起始，并且随后在室温下反应约 2 小时。

所得的式 V 的化合物随后与三氟甲磺酸酐在氯代烃类溶剂如氯仿、二氯乙烷(DCE)或二氯甲烷中在碱如吡啶或 3-甲基吡啶的存在下反应，生成相应的式 VI 的三氟甲磺酸酯。通常，起始反应温度约为-78℃并且令该反应升至室温以完成该反应。

式 VI 的三氟甲磺酸酯随后在 Heck 环化条件下反应生成相应的式 VII 的化合物。可以应用或不应用溶剂来完成该反应。适用的溶剂包括 N,N-二甲基甲酰胺(DMF)、N-甲基吡咯烷酮(NMP)和甲苯。约 60℃至约 130℃的温度范围是适宜的，并且该反应一般进行约 1 至 48 小时。优选该反应在约 100℃的温度下进行约 2-18 小时。通过用钯类原料处

理可以就地生成该反应中的催化剂，所述钯类原料例如醋酸钯($Pd(OAc)_2$)、二氯化钯($PdCl_2$)或还原的零氧化态的钯如炭载钯(Pd/C)或三(二亚苄基丙酮)二钯(0)($Pd_2(dba)_3$)。也可以采用类似的镍类催化剂。催化剂的用量是化学计量量的约 0.1mol%。优选应用约 2-10mol%的钯或镍催化剂。这些反应中经常应用的条件包括：配体，如三苯基膦或三甲苯基膦；或双齿配体，如 DPPF、DPPE、DPPB、DPPP(DPP=双-二苯基膦，F=二茂铁，E=乙基，P=丙烷，B=丁烷)；或任何不同的手性配体，如 BINAP(2,2'-双(二苯基膦)-1,1'-联萘)或砷酸盐配体；或上述具有手性取向基团的配体的双齿混合物，例如噁唑啉类；然而配体的包合并不是所有情况中所必需的。如果将配体与钯或镍类原料联合使用，配体的用量一般是钯或镍类催化剂的约 0.5 至约 4 摩尔当量。

上述反应是在碱的存在下进行，通常是叔胺碱，例如三乙基胺或二异丙基乙基胺。其它碱例如碳酸盐或醋酸盐(例如碳酸钾、碳酸钠、醋酸钠或醋酸钾)也可以提供适当的或理想的结果。在某些情况中，如试验实施例中所举实例，适宜将如上所述叔胺碱以和膦配体等当量的量与催化性醋酸盐或碳酸盐如醋酸钾联合应用。可以采用的附加添加剂是烷基卤化铵盐，例如四丁基氯化铵。这些条件是常规，和基于 Jeffrey T.在《化学会志和化学通讯杂志》(J. Chem. Soc. Chem. Commun.)1984,1287 和《合成》1987,70 所述内容。这些反应一般是在氮气或氩气的气氛下进行，但或可或不可地需要氧的存在。

式 VII 的化合物与四氧化锇和再氧化剂如 N-甲基吗啉-N-氧化物(NMO)在不同和水中在室温下反应，生成相应的式 VIII 的化合物。

利用以下方法可以将具有式 VIII 的化合物随后转化为预期相应的式 IA 的化合物。首先，在约 0℃至约室温下，令式 VIII 的化合物与高碘酸钠在氯化烃(优选二氯乙烷(DCE))和水的混合物中反应，或与四醋酸铅在氯化烃类溶剂中反应，生成二醛或烯糖中间体。此后，该反应的产物与苄胺(或氨)和三乙酰氧基硼氢化钠反应。脱去 N-苄基生成预期的式 IA 混合物。苄基的脱除可以利用所属领域技术人员熟知的

方法来完成，例如，通过首先令游离碱任选地与 1 当量的酸如盐酸反应(形成相应的酸加成盐)，并且随后用氢和氢氧化钯在甲醇中约室温下反应。

另外，还原性胺化作用可以如下列方式就地进行。在含水 THF 或醇中用高碘酸钠完成对式 VIII 所示二醇的氧化裂解，生成如上所述的二醛/烯糖中间体。用过量的苄胺(或氨)、氢氧化钯和氢在室温至约 70℃的温度下处理该中间体，生成预期的式 IA 的化合物。

如果所用的上述方法在化合物上残留下苄基，应脱除苄基生成预期的式 IA 的化合物。苄基的脱除可以利用所属领域技术人员熟知的方法来完成，例如，通过首先令游离碱任选地与 1 当量的酸如盐酸反应(形成相应的酸加成盐)，并且随后用氢和氢氧化钯在甲醇中约室温下反应。

在上述还原性胺化步骤和本文全文中，除了苄胺，还可以采用例如氨、羟胺、烷氧基胺、甲胺、烯丙基胺和取代苄胺(例如二苯基甲基胺和 2-和 4-烷氧基取代苄胺)。它们可以作为游离碱或其盐使用，优选其醋酸盐，并且随后可以利用 T.W.Greene 和 G.M.分别在“有机合成中的保护基”，1991，John Wiley & Sons，New York，NY 中所述的方法来脱除。

上述和反应路线 1 中举例说明的方法是制备式 I 化合物的优选方法，其中 R^2 或 R^3 易于反应生成芳炔或另一类型的副反应。

上述方法生成其中 Z 是 CH_2 的式 IA 的化合物。其中 Z 是(C=O)的式 IA 化合物可以利用上述反应路线 1 例举的方法来生成，但除了将式 III 的化合物在苄基位置氧化而不是还原，形成其中 Z 是(C=O)的式 IV 的化合物。这可以通过所属领域技术人员熟知的方法来完成，例如通过用 Jones 试剂(铬酸溶液)在醚或丙酮中于约 0℃至约室温下处理。其中 Z 是 CH_2 的式 IA 的化合物可以以类似方式通过将其中 Z 是(C=O)的式 IV 的氧化化合物转化为其中 Z 是 CF_2 的式 IV 的相应化合物，和随后继续采用反应路线 1 的反应顺序。上述转化作用可以利用所属领域技术人员熟知的方法来完成，例如，通过用 Lawesson 氏试剂来处理。

应用 Lawesson 氏试剂的反应一般是在反应惰性溶剂如苯或甲苯(优选甲苯)中在约室温至约反应混合物的回流温度(优选约回流温度)下进行。

反应路线 2 举例说明式 I 化合物的另一种制备方法。该方法是制备所述化合物的优选方法，其中 R^2 和 R^3 皆不易发生不利副反应。如反应路线 2 所示，用强碱如正丁基锂在约室温至约反应混合物的回流温度下、于溶剂如醚或正丁基甲基醚中处理式 IX 的化合物。该金属化作用在约 1 至 5 小时内发生，当该反应在回流温度下和醚中进行时一般是在约 4 小时内发生，随后在同样的溶剂中或在溶剂混合物(如含有四氢呋喃(THF))中将所得阴离子冷却至约-78℃。此后令该阴离子与环戊-3-烯甲酸甲氧基-甲基-酰胺(X)在约-78℃下反应约半小时，加热至室温令该反应达到完全。此反应生成式 XI 的化合物。随后，将式 XI 的化合物溶解在二氯甲烷中并且用三氯化硼于约-78℃下处理。约 20 分钟后，将反应升至约 0℃且后处理。此后，将所得式 XII 的酚通过上述制备式 XIII 化合物的方法转化为三氟聚合物酯。所得酯可以在上述的 Heck 条件下转化为式 XIV 的化合物。

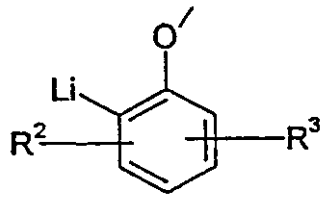
利用标准 Wolff-Kishner 条件还原式 XIV 的化合物，生成式 XV 的化合物。这些条件是所属领域技术人员熟知的条件，并且包括式 IV 的化合物与肼和氢氧化钾反应，该反应首先在约 100℃下在溶剂(通常为乙二醇或二甘醇)中进行，并且随后升温至约 180-200℃。也可以采用所属领域技术人员已知的与标准 Wolff-Kishner 还原作用等效的还原反应。通过类似于反应路线 1 中将式 VII 的化合物转化成为式 IA 的方法，可以将式 XV 的化合物转化为式 IB 的化合物。

与其将式 XIV 中的酮还原，不如通过 Lawesson 氏试剂处理，或利用所属领域技术人员所熟知的能够有效完成该转化作用的其它方法，可以形成其中氧代基团被 CF_2 所代替的相应化合物。

通过所属领域技术人员熟知的方法可以将甲醚转化为其相应酚。这可以通过将式 IB 或 XVII 的化合物暴露在氢溴酸下且将所得混合物加热至回流温度约 1 小时来完成。这种反应分别生成相应的式 IB'或

XVII'的酚。

另一种不同于反应路线 1 和 2 中所述方法的用于制备芳基阴离子的方法是应用卤素-金属交换条件。例如，如反应路线 3 所示，可以用烷基锂碱如正丁基锂，在约-78℃至 20℃，通常为约-78℃下处理其中 R^{19} 是溴或碘的式 XVIII 的化合物，生成下式的芳基阴离子:



XVIII'

该反应制得的阴离子随后和醛，例如反应路线 1 所述的醛反应，或与适当的二取代酰胺，例如反应路线 2 中所述的二取代酰胺反应，生成式 XIX 的化合物。(与其按照上文所述将式 XVIII 的化合物与烷基锂碱反应，不如首先利用标准方法将该化合物任选地转化为格氏试剂 (R^{19}—⊢⊣ MgR^{19})，并且按照上文所述方法令式 XVIII'反应用于制备式 XIX 的化合物)。

随即，可以利用上述式 XI 的化合物转化为那些式 IB 的化合物(反应路线 2)的方法和式 IV 的化合物转化为那些式 IA 化合物(反应路线 1)的方法将所得式 XIX 的化合物转化为式 IC 的化合物(反应路线 3)。

本申请合成过程中所应用的芳香体系的邻位上阴离子的生成是在所属领域技术人员称作定向邻位金属化(DOM)的已知常规合成策略下完成。业已为此目的研究了多个被称作定向金属化基团(DMG 类)的官能团，并且一些公开在 Snieckus, V.《化学评论》(Chem. Rev.)，1990，879 中。只要适用，除该文献中的那些 DMG 以外的 DMG 也同样适合用来制备本发明的化合物和中间体。

另一种用于制备与式 V、XII 或 XX 的化合物相类似的化合物的方

法如反应路线 4所示。在这种方法中，环戊-3-烯甲醛和酚与芳基硼酸和酸性催化剂如醋酸混合(在α位被卤素取代基任选取代以便调节该反应的酸度)，或与根据其性质可以在该反应的条件下生成无机酸的芳基二卤化物混合，混合是在溶剂如苯、甲苯、二噁烷或二氯甲烷中进行，优选苯。该反应的温度一般是回流温度，或是任何令该反应中所生成的水以确保该反应能够进行的速率被除去的标准方法的温度。常规方法是采用 Dean-Stark 分水器除去反应中生成的水。一般地，该反应进行 3-48 小时，常常为 10-24 小时，或直至收集到理论量的水分。此时，该反应无溶剂，随后处于上述用于还原苄羟基或醚的条件下，例如用三氟乙酸和还原剂如三乙基硅烷处理该中间体。该反应是在氯代烃类溶剂如氯仿、二氯乙烷(DCE)或二氯甲烷中在约室温下进行 6-24 小时，优选 18 小时。

上述反应生成其中 Z 是 CH_2 的式 IV'的化合物。可以利用上述制备其中 Z 是(C=O)或 CF_2 的式 IV 化合物的方法(反应路线 1)来制备其中 Z 是(C=O)和 CF_2 的式 IV'的相应化合物。

利用上述方法和反应路线 1 中用于制备式 IA 化合物的方法可以将所得的式 IV'的化合物(Z 是(C=O)、CH_2 或 CF_2)转化为相应的式 IA'化合物。

反应路线 5 举例说明向本发明的化合物中引入取代基如溴和氧的方法。在所属领域技术人员已知的标准条件下，例如在氯代烃溶剂(如氯仿、二氯乙烷(DCE)或二氯甲烷)中于约 0℃至约室温下(优选在室温下)在碱如醋酸钠的存在下用溴处理式 XXIV 的化合物，生成式 XXIVA 的相应化合物。由此所得的溴化物(XXIVA)随后可以通过上述卤素-金属交换法转化成为锂阴离子衍生物，该衍生物随即可以用多种亲电试剂如三烷基硼酸酯处理，一般是在-78℃至 0℃下处理生成相应的式 XXIVB 的硼酸衍生物。

此后，利用 Suzuki 偶联化学在所属领域技术人员熟知的标准条件下将该化合物转化为多种衍生物。另外，通过与过氧化氢或 N-甲基吗啉在溶剂如 THF 中反应，或通过其它所属领域技术人员已知的标准方

法，可以将这些硼酸化合物转化为相应的酚类衍生物。通过上述方法脱去苄基保护基，生成预期的式 IC'化合物。

如上制备的酚和试验部分中的酚可以被转化为相应的三氟甲磺酸酯。通过所属领域技术人员熟知的钯和镍催化法，例如 Heck、Suzuki 和 Stille 偶联反应以及 Heck 羰基化作用，这些衍生物以及式 XXIVA 的溴化物可以用来提供多种其它取代基(即其它形式的 R^2 和 R^3)如芳基、乙炔和乙烯基取代基，以及相应的羰基酯和酰胺。此外，利用不同的常规醚制备方法可以将酚烷基化。而且，可以用亲核试剂如格氏试剂处理酯以制备相应的叔醇。这些转化作用的实例如试验实施例所述。

反应路线 6 举例说明了某些反应路线 7 中所用的中间体的制备方法。如反应路线 6 所示，式 XXV 的起始原料与三氟乙酸酐在吡啶的存在下反应，形成式 XXVI 的化合物。该反应通常是在二氯甲烷中在约 0 ℃至约室温下进行。

其中 Z 不是(C=O)的式 XXVI 化合物可以随后通过以下方法转化为式 XXXV 的硝基衍生物。将式 XXVI 的化合物加入 2 个或多个当量的三氟甲磺酸(CF_3SO_2OH)和 1 至 1.5 个当量硝酸在氯代烃溶剂如氯仿、二氯乙烷(DCE)或二氯甲烷中的混合物内。令所得混合物反应约 5 至 24 小时。上述反应均在约-78℃至约 0℃下进行约 2 小时，并且随后在剩余的时间内加热至室温。

其中 Z 是(C=O)的式 XXXV 的化合物可以按照 Kapur 等人在《加拿大化学杂志》66, 1988, 2888-2893 中所述方法将其中 Z 是 CH_2 的类似化合物氧化来制得。

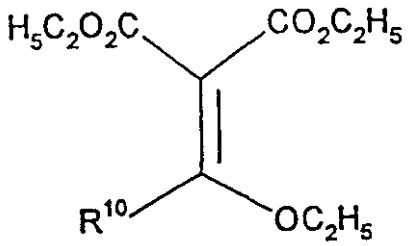
利用所属领域技术人员熟知的方法还原式 XXXV 的化合物，生成相应的苯胺。该还原反应可以在，例如应用氢和钯催化剂(如氢氧化钯)下完成，并且该反应是在甲醇或乙醇中在室温下进行。中间体苯胺随即通过上述式 XXVI 化合物的制备方法转化为式 XXVIA 的三氟乙酰胺。

按照上述制备式 XXXV 化合物的方法，将式 XXVIIA 的化合物一硝基化，生成相应的式 XXVIIA'的硝基衍生物。用含水碳酸氢盐在甲醇或

THF 中在约 20℃-至约 70℃下处理式 XXVIIA'的硝基衍生物，随后按照上述方法还原硝基，生成相应的式 XXVIIB 的化合物。

如反应路线 7 所示，式 XXVIIA'的化合物转化为其中三氟乙酰基保护基被 t-Boc 保护基取代的相应化合物(XXVIIIA)，这是通过首先令 XXVIIA'的化合物与碱金属或碱土金属(或铵)的氢氧化物或碳酸盐反应，并且随后将由上述反应中分离出的产物与二碳酸二叔丁基酯反应。采用碱金属或碱土金属(或铵)的氢氧化物或碳酸盐的反应通常是在含水醇、二噁烷或四氢呋喃(THF)中在约室温至约 70℃下，优选约 70℃下进行约 1 至约 24 小时。用二-叔丁基碳酸酯从上述反应中分离出非保护胺或所述胺的酸加成盐，反应的分离是适宜在溶剂如 THF、二噁烷或二氯甲烷中在约 0℃至约室温下进行。该反应可以在或可以不存在碱的存在下完成。当反应物是胺的盐时，优选应用碱。利用上述使式 XXVIIA'的化合物转化为相应的式 XXVIIB 二氨基化合物的方法，可以将所得式 XXVIIIA 的化合物转化为相应的式 XXVIIIB 的二氨基化合物。

通过令式 XXVIIIB 的化合物与下式的化合物反应可以完成式 XXVIIIB 的化合物向预期的式 XXIX 化合物的转化:



其中 R^{10} 是氢，被 1-7 个氟原子任选取代的(C_1-C_6)烷基，其中所述芳基选自苯基和萘基的芳基-(C_0-C_3)烷基，或杂芳基-(C_0-C_3)烷基，其中所述杂芳基选自含有 1-4 个杂原子且杂原子选自氧、氮和硫的 5-7 元芳香环，并且其中上述各个芳基和杂芳基可以被 1 个或多个取代基，优选被 0 个至 2 个取代基任选取代，所述取代基独立地选自：被 1-7 个氟原子任选取代的(C_1-C_6)烷基，被 1-7 个氟原子和氰基任选取代的

(C_1-C_6)烷氧基。-该反应优选的溶剂是乙醇:醋酸的 10:1 混合液。反应温度为约 40℃至约 100℃。优选约 60℃。其它适用的试剂包括醋酸、乙醇和异丙醇。

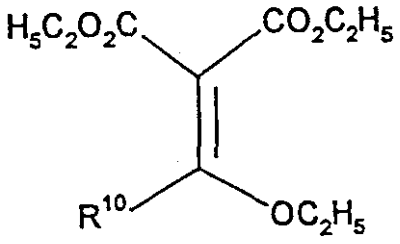
Segelstein 等人在《四面体通讯》, 1993, 34, 1897 中描述了由式 XXVIIIB 的化合物制备式 XXIX 的化合物的其它方法。

由式 XXIX 的化合物脱去 t-Boc 保护基生成相应的式 ID 的化合物。保护基可以利用所属领域技术人员熟知的方法脱除。例如，式 XXIX 的化合物可以用无水酸如盐酸、氢溴酸、甲磺酸或三氟乙酸，优选存在于乙酸乙酯中的盐酸，在约 0℃至约 100℃，优选约室温至约 70℃下处理约 1-24 小时。

式 XXIX 的化合物通过与式 $R^{17}Z$ 的化合物反应可以转化为相应的式 IE 的化合物，其中 R^{17} 如上述 R^{10} 的定义，同时 Z 是离去基团，例如卤素或磺酸盐(例如氯、溴、碘、甲磺酸盐或甲苯磺酸盐)，该反应是在碱如碱金属的氢化物、氢氧化物或碳酸盐(优选氢氧化钾)的存在下在极性溶剂如水、二甲基亚砜(DMSO)、THF 或 DMF(优选 DMSO 和水的混合物)中进行，和随后按照上述方法脱去保护基。与 $R^{17}Z$ 的反应一般是在约室温至约 100℃的温度下进行，优选约 50℃下进行约 5 小时。随后按照上述方法脱去保护基，生成预期的式 IE 的化合物。

反应路线 8 举例说明另一种由式 XXVIIIA'的化合物制备式 IE 的化合物的方法。当其中 R^{17} 是例如含芳基或杂芳基的基团时，或当 R^{17} 无法按照反应路线 7 中所示通过烷基化或芳基取代法相连时，该方法是制备式 IE 的化合物的优选方法。如反应路线 8 所示，式 XXVIIIA'的化合物与适当的式 $R^{17}NH_2$ 的化合物在极性溶剂如 THF、DMF 或 DMSO(优选 THF)中在约室温或约 100℃(优选回流温度)下反应约 4-18 小时。该反应生成式 XXX 的化合物。随后利用所属领域技术人员熟知的方法，通过将硝基还原为氨基可以使所得式 XXX 的化合物转化为相应的式 XXXI 的化合物。所示方法可以参见上述反应路线 6 中将式 XXVIIA'的化合物转化为式 XXVIIB 的化合物的方法。此后，上述反应所得的式 XXXI 的化合物通过与下式的化合物按照式 XXVIIIB 的化合物转化为式

XXIX 的化合物的方法反应可以关闭咪唑环，由此形成相应的式 XXXII 的化合物:

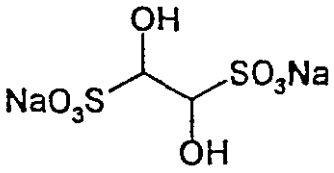


(其中 R^{10} 定义如上)。

脱去式 XXXII 化合物的保护基，生成相应的式 IE 的化合物。利用所属领域的已知方法可以完成该反应，例如按照上述由相应式 XXIX 的化合物形成式 ID 化合物的方法。

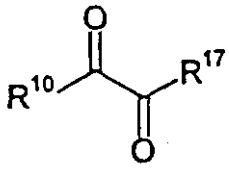
在反应路线的过程中用作起始原料的式 XXVIIIA'化合物可以按照反应路线 8A 和下述方法来合成。利用上述方法，将其中 R^2 是氟的适当式 IC 的化合物(反应路线 3)转化为式 ICTFA 的三氟乙酰胺衍生物。随后按照上述方法或利用其它所属领域技术人员熟知的方法硝化该衍生物，生成式 ICTFA'的相应硝基衍生物。用碱金属碳酸盐或碳酸氢盐在甲醇或 THF 中脱去三氟乙酰氨基，随后按照上述方法用二碳酸二叔丁基酯保护，生成相应的式 XXVIIIA'的化合物。

反应路线 9 举例说明一种式 IF 化合物的制备方法，其中 R^{10} 和 R^{17} 如上述定义。如反应路线 9 所示，式 XXVIIIB 的化合物与下述的化合物



(亚硫酸氢钠乙二酮加成物)在水或另一极性溶剂如 THF，DMF 或 DMSO，优选水和水可溶混的溶剂如 THF 的混合物中反应 1－4 小时。反应温度从约 40℃到约 100℃，优选在大约回流温度。

或者，式 XXVIIIB 化合物可与下式化合物在极性溶剂如 THF、水或乙酸(优选水和 THF 的化合物)中反应:



(双缩合反应)。该反应一般是在约 40℃至约 100℃，优选在回流温度下进行约 2-4 小时。

上述两种方法也可以用来将其中 t-Boc 保护基被另一种保护基如 TFA 代替的相应化合物(即式 XXVIIB 的化合物)转化为喹喔啉(quinoxoline)。

随后，利用上述令式 XXIX 的化合物转化为一种式 ID 的化合物的方法或上述脱去式 XXVIIA'的化合物的 TFA 基团的方法，通过将上述反应中形成的化合物脱保护可以生成式 IF 的喹喔啉。

反应路线 10 举例说明了式 I 化合物的制备方法，其中 R^2和 R^3一起与其相连的苯并环构成苯并噁唑环系。其中 R^1是氢的化合物在反应路线 10 中表示为化学式 IG。如反应路线 10 所示，其中 Y 是硝基或氟的式 ICTFA'的化合物与醋酸钾或另一种碱金属或碱土金属的羧酸盐在溶剂如二甲基亚砜(DMSO)、DMF 或乙腈(优选 DMSO)中反应。该反应一般进行约 12-24 小时。适用的反应温度是约 70℃至约 140℃。优选约 100℃。

上述反应生成式 XXXIV 的化合物，该化合物随后可以通过以下方法转化为具有式 IG 的预期化合物。首先，用氢和钯或铂催化剂如氢氧化钯在加成中约 0℃至约 70℃下，优选在室温下还原式 XXXIV 的化合物，形成相应的氨基衍生物。该反应的产物随后与其中 R^{10}是(C_1-C_6)烷基的式 $R^{10}COCl$ 的酰氯或式$(R^{10}CO)_2O$ 的酸酐，或与式 $R^{10}C(OC_2H_5)_3$的化合物，在适当的惰性溶剂如十氢萘、氯苯或二甲苯中反应。优选二甲苯的混合物。该反应一般在约 120-150℃，优选约 140℃下进行。当用 $R^{10}COCl$ 作为反应物时，优选向反应混合物中加入化学计量量的三乙

胺(TEA)或另一种有机叔胺碱和催化量的吡啶鎓对甲苯磺酸或对甲苯磺酸吡啶鎓盐(PPTS)。当用 $R^{10}C(OC_2H_5)_3$ 作为反应物时，优选向反应混合物中加入催化量的 PPTS。

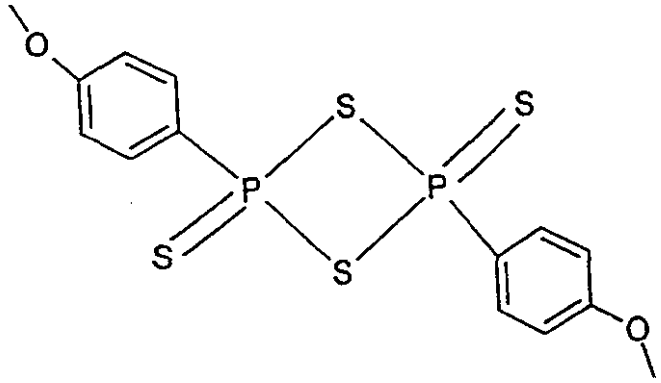
脱去三氟乙酰基氮保护基，生成预期的式 IG 的化合物。这可以利用所属领域技术人员熟知的方法实现，例如将被保护化合物与低级烷醇和碱金属或碱土金属(或铵)的氢氧化物或碳酸盐水溶液(碳酸钠水溶液)在约 50℃至约 100℃，优选约 70℃下反应约 2-6 小时。

反应路线 11 举例说明式 I 化合物的制备方法，其中 R^1 是氢并且 R^2 和 R^3 与其相连的苯并环一起构成苯并噻唑环系。这些化合物如反应路线 11 所示且此后称作"式 IH 的化合物"。参见反应路线 11，式 XXV' 的化合物与三氟乙酸酐反应，形成其中环氮被三氟乙酰基保护的相应化合物，所得氮保护化合物随后与 2 当量的三氟甲磺酸和 1 当量的硝酸反应，形成式 XXXV 的相应化合物。其中苯并环上存在一个硝基取代基。该采用三氟乙酸的该反应一般是在吡啶的存在下进行。上述两个反应通常是在反应惰性溶剂如氯代烃溶剂(优选二氯甲烷)中在约 0℃至约室温下(优选约室温)进行。

也可以利用其它所属领域技术人员熟知的硝化方法来实现上述转化。

可以按照上文所述方法将硝基还原为氨基，生成式 XXXV'的化合物。

式 XXXV'的化合物随后与其中 X 是卤素的式 $R^{10}COX$ 或 $(R^{10}CO)_2O$ 的羧酸卤化物或羧酸酐，和吡啶、TEA 或另一种叔胺碱反应，形成式 XXXVI 的化合物，该化合物此后可以通过与 Lawesson 氏试剂反应转化为具有式 XXXVII 的目标化合物，如下所示：



与其中 X 是卤素的 $R^{10}COX$ 或 $(R^{10}CO)_2O$ 的反应通常在约 0℃至约室温，优选约室温下进行。使用 Lawesson 氏试剂的反应一般在反应惰性溶剂如苯或甲苯(优选甲苯)中在约室温至约反应混合物的回流温度下(优选约回流温度)进行。

式 XXXVII 的化合物通过与铁氰化钾和氢氧化钠在水和甲醇的混合物($NaOH/H_2O/CH_3OH$)中在约 50℃至约 70℃下(优选约 60℃)反应约 1.5 小时，可以完成苯并噻唑环的闭环和氮的脱保护，由此生成预期的式 IH 的化合物。

反应路线 12 和 13 举例说明了式 I 化合物的制备方法，其中 R^1 是氢，和 R^2 和 R^3 表示上述多种不同的取代基，但不形成环。

反应路线 12 举例说明式 I 的化合物的制备方法，其中：(a)R^1 是氢和 R^2 是 $R^7R^8NO_2S-$；(b)R^1 和 R^2 同时为氯；和(c)R^1 是氢和 R^2 是 $R^{13}C(=O)$。这些化合物如反应路线 12 所示，分别为式 IJ、IK 和 IL 的化合物。

如反应路线 12 所示，式 XXVI 的化合物通过与两个或多个当量的卤代磺酸，优选氯代磺酸，在约 0℃至约室温下反应可以制备式 IJ 的化合物。由此形成的氯磺酸衍生物与具有式 R^7R^8NH 的胺反应，其中 R^7 和 R^8 如上述定义，催化脱去氮保护基，生成具有 IJ 的预期化合物。

式 IK 的化合物可以通过式 XXVI 的化合物与三氯化碘在氯代烃溶剂中反应，随后脱去氮保护基来制备。采用三氯化碘的反应一般是在约室温下进行。在以类似方式，相似的单-或二溴化或单-或二碘化化合物可以通过式 XXVI 化合物和 N-碘代琥珀酰亚胺或 N-溴琥珀酰亚胺在三氟甲磺酸溶剂中反应，随后按照上述方法脱去氮保护基来制备。

XXVI 的化合物与式 $R^{13}COCl$ 的酰卤或式 $(R^{13}CO)_2O$ 的酸酐在可有可无的反应惰性溶剂如氯代烃溶剂(优选二氯甲烷)中在路易斯酸如氯化铝的存在下反应，反应温度是约 0℃至约 100℃，随后氮脱保护，生成式 IL 的化合物。采用酰卤或酐的反应可以利用所属领域已知的其它路易斯酸或其它 Friedel-Crafts 酰化方法来完成。

如反应路线 12 所示和上文所述，此处所述的在式 XXVI 的化合物

上引入 NO_2、$-SO_2NR^7R^8$、$-COR_{13}$、I、Br 或 Cl 的反应可以在任何其中 R^2 是氢、(C_1-C_6)烷基、卤素、(C_1-C_6)烷氧基或$-NHCONR^7R^8$ 的类似化合物上完成，生成其中 R^2和 R^3如上述式 I 化合物中定义的式 I 化合物。

利用所属领域技术人员熟知的 Baeyer-Villiger 法可以将与那些式 IL 化合物相同但保留了氮保护基的化合物可以转化为相应的 O-酰基取代化合物，即其中式 IL 的$-C(=O)R^{13}$被$-O-C(=O)R^{13}$基团代替的那些化合物。所得化合物可以部分水解生成相应的羟基取代化合物，并且随后烷基化形成相应的烷氧基取代化合物。而且，所述 O-酰基取代化合物可以用来制备易变取代的苯并异噁唑，这可以利用所属领域技术人员熟知的方法，例如依次弗里斯重排、肟的形成、酰化和用碱处理。所述方法包括用纯净的路易斯酸如氯化铝($AlCl_3$)或在溶剂如氯苯中处理式 XXXIII 的化合物以进行弗里斯重排，重排是在约 100℃至约 200℃下，优选约 170℃下进行约 1-2 小时，优选约 2 小时，生成式 XXXIX 的化合物。令保护基断裂，生成相应的式 IS 的化合物。另外，利用所属领域技术人员熟知的标准方法可以将式 XXXIX 的化合物转化为其肟，例如用羟胺盐酸盐在醇(如甲醇)中在碱如乙酸钠的存在下于约 20℃至约 70℃(优选 50℃)下处理约 5-20 小时。采用该利用熟知的方法酰化所述肟，例如用乙酸酐和吡啶处理，随后用碱如氢化钠处理分离出的酰基肟，在溶剂如 DMF、NMP 或 DMSO 中，生成相应的闭合苯并异噁唑。在如上所述的标准条件下裂解保护基，生成预期的式 IT 的化合物。

反应路线 13 举例说明了式 I 化合物的制备方法，其中：(a)R^1是氢和 R^2是氯；(b)R^1是氢和 R^2是氰基；(c)R^1氢和 R^2是氨基；和(d)R^1是氢和 R^2是 $R^{13}C(=O)N(H)-$。这些化合物如反应路线 13 所示，分别为式 IM、IN、IP 和 IQ 的化合物。

由式 XXXV'的化合物通过和例如碱金属亚硝酸盐和无机强酸(例如盐酸、硫酸、氢溴酸)在水中生成重氮盐，随后与卤化铜盐如氯化亚铜(I)反应可以制备式 IM 的化合物。利用上述方法脱除氮保护，生成预期的式 IM 的化合物。还可以采用其它为所属领域已知和应用的重氮盐制备方法。上述反应通常是在约 0℃至约 60℃的温度下，优选约 60℃

下反应约 15 分钟至 1 小时。

上述方法制备的重氮盐和碘化钾在水介质中反应，生成类似的碘化物衍生物。该反应一般是在约 0℃至约室温下，优选约室温下进行。所得化合物或其类似的碳酸N-叔丁基酯保护体可以用来制备相应的氰基衍生物，这可以通过与氰化亚铜(I)和氰化钠在 DMF、N-甲基吡咯烷酮(NMP)、N,N-二甲基丙基脲(DMPU)或 DMSO(优选 NMP)中在约 50℃至约 180℃(优选约 175℃)反应。按照上述方法脱去氮保护基，生成相应的式 IN 的目标化合物。

通过所属领域技术人员熟知的钯和镍催化方法，例如 Heck、Suzuki 和 Stille 偶联反应以及 Heck 羰基化作用，上述碘化物、溴化物或重氮盐衍生物还可以用来提供多种其它取代基，如芳基、乙炔和乙烯基取代基，以及相应的羰基酯和酰胺。

脱除式 XXXV'化合物的氮保护，得到式 IP 的化合物。

利用上述方法，式 XXXV'的化合物可以和具有式 $R^{13}COCl$ 或 $(R^{13}CO)_2O$ 的酰基反应，随后脱除氮保护，生成式 IQ 的化合物。以类似方式，用具有式 $R^{13}SO_2X$ 的化合物处理保护的胺，其中 X 是氯或溴，随后脱去氮保护，生成相应的磺酰胺衍生物。

可用于本文其它方法的其它适当胺保护基包括$-COCF_3$、$-COCCl_3$、$-COOCH_2CCl_3$、-COO(C_1-C_6)烷基和$-COOCH_2C_6H_5$。这些基团在本文所述条件下稳定，并且可以通过上文的 Greene 在“有机化学中的保护基”中所述的方法脱除。

其中 R^1 不是氢的式 I 的化合物可以按照上述方法制备，例如还原性氨化环形成法，通过该方法生成了反应路线 3 中的化合物 XXIV(R^1=苄基)，和通过下文所述方法制备。其中 R^1 是氢的式 I 的化合物通过用当量量的醛(R^1CHO)或酮(R^1R^1CO，其中两个 R^1 相同或不同)和还原剂处理可以被转化为 R^1 不是氢的相应化合物，所述还原剂优选是氢化物试剂，例如三乙酰氧基硼氢化钠或氰基硼氢化钠，该处理是在溶剂如二氯甲烷、四氢呋喃或二噁烷中进行。在某些情况中需要在处理反应时加入酸，并且通常采用醋酸。该反应的温度一般是约 0.5 至 24 小时的

室温。常用方法如《有机化学杂志》1996，61，3849所述。

还可以通过所属领域技术人员熟知的方法令其中 R^1 是氢的相应化合物烷基化反应来制备其中 R^1 不是氢的式 I 的化合物。例如，用当量量或过量的 R^1X 或 R^1OH 的 O-硫酸酯处理其中 R^1 是氢的化合物，其中 R^1 不是氢且 X 是卤素，优选溴或碘。该反应一般是在纯净条件下或在极性溶剂如水、二甲基甲酰胺或二甲基亚砜中进行，该反应也常常在碱的存在下进行，所述碱例如但不限于碱金属碳酸盐。该反应的温度一般是长达约 0.1 至 24 小时的约 20-120℃(优选约 100℃)。

利用所属领域技术人员熟知的方法，通过 R^1 是氢的相应化合物与式 $R^1C(=O)X$（其中 X 定义如上）的化合物反应转化为酰胺，随后用硼烷或氢化锂铝还原所得酰胺，也可以制得其中 R^1 不是氢的式 I 化合物。该还原步骤常常是在醚溶剂如乙醚或 THF 中在约 20℃至约 70℃下进行约 1-20 小时，生成预期的胺。

在上文讨论的各个反应中，或在反应路线 1-13 的举例说明中，对压力没有严格规定，除非另外指出。约 0.5 至约 5 个大气压的压力一般是可接受的，通常优选常压，即约 1 个大气压。

式 I 的化合物及其药学上可接受的盐(此后称作“活性化合物”)可以经口服、经皮(例如应用贴剂)、鼻内、舌下、直肠、非肠道或局部途径给药。优选经皮和口服给药。虽然需要根据被治疗对象的体重和情况以及所选择的具体给药途径来变化，最理想的是，这些化合物以约 0.25mg 至约 1500mg/天的剂量，优选以约 0.25 至约 300mg/天的剂量给药，每天给药 1 次或分次给药。但是，首先采用约 0.01mg 至约 10mg/kg 体重/天的剂量水平。但是，剂量的变化取决于被治疗个体的体重和情况，他们对该药物的个体反应，以及所选择的药物制剂类型和给药时间和间隔时间。在某些情况中，低于上述剂量范围下限的剂量水平可以很适当，但在其它情况中柔软可以应用较大剂量而不会引起任何有害副作用，条件是这种大剂量首先在全天中被分成若干小的给药剂量。

活性化合物可以单独给药，或与药学上可接受载体或稀释剂一起

通过任何上述若干途径联合给药。更具体地说，活性化合物可以以多种不同的剂型给药，例如，它们可以和不同的药学上可接受的惰性载体混合成为片剂、胶囊、透皮贴剂、锭剂、糖锭、硬糖、粉末、喷雾剂、霜剂、油膏、栓剂、凝胶、明胶、糊剂、洗剂、软膏、水悬浮液、可注射溶液、酏剂、添加剂等的形式。所述载体包括固体稀释剂或填充剂、灭菌含水介质和多种无毒有机溶剂。此外，口服药物组合物可以适当地增甜和/或矫味。通常，活性化合物是以浓度水平为约 5.0% 至约 70% (重量)的剂型存在。

为了口服给药，含有多种赋形剂如微晶纤维素、柠檬酸钠、碳酸钙、磷酸二钙和甘氨酸的片剂可以与不同的崩解剂如淀粉(优选玉米淀粉、土豆淀粉或木薯淀粉)、海藻酸和某些复合硅酸盐，酏剂制粒粘合剂如聚乙烯吡咯烷酮、蔗糖、灭菌和阿拉伯胶联合使用。另外，片剂可以采用乳化剂，例如硬脂酸镁、十二烷基硫酸钠和滑石。类似类型的固体组合物还可以在明胶胶囊中用作填充剂；此时优选的材料还包括乳糖或奶糖酏剂高分子量聚乙二醇。当口服给药需要含水悬浮液和/或酏剂时，活性组分可以和多种甜味剂或矫味剂、着色物质混合，如果需要，还可以联合应用乳化剂和/或助悬剂和稀释剂如水、乙醇、丙二醇、甘油及其混合物。

为了非肠道给药，可以采用活性化合物存在于芝麻油或花生油中或存在于含水丙二醇中的溶液。如果必要，水溶液应被适当缓冲(优选 pH 大于 8)，液体稀释剂首先提供等渗。这些含水溶液适合静脉内注射的目的。油溶液适用于关节内、肌肉内和皮下注射。提供所属领域技术人员熟知的标准药学技术易于在灭菌条件下完成所有上述溶液的制备。

也可以将活性化合物局部给药，并且这可以提供霜剂、贴剂、凝胶剂、冻胶、糊剂、软膏等的途径按照标准药学实践实现。

生物学实验

所述活性化合物在抑制烟碱与特定受体位点结合中的有效性是通过以下方法来测定的，这方法是对 Lippiello, P.M.和 Femandes,

K.G.(在L-[^{3}H]-烟碱与一类大鼠脑膜的高亲和性位点的结合,《分子药理学》(Molecular Pharm.),29,448-54(1966)中)和 Anderson, D.J. 和 Americ,S.P.(在大鼠脑中烟碱受体结合的^{3}H-金雀花碱、^{3}H-烟碱和^{3}H-甲基氨基甲酰基胆碱,《欧洲药理学杂志》253, 261-67(1994))所述方法的改进。

方法

将得自 Charles River 的雄性 Sprague-Dawley 大鼠(200-300g)分组圈养在悬挂的不锈钢丝笼中并且维持 12 小时光照/黑暗循环(7a.m.-7p.m.光照期)。动物随意接受标准 Purina 大鼠饲料和水。

断头处死大鼠。斩首后立刻取出大脑。对 Lippiello&Femandez(分子药理学 29,448-454,1986)所述方法进行某些改进,利用改进的方法由脑组织制备膜。取出全脑,用冰冷缓冲液漂洗,在 0℃下于 10 个体积的缓冲液(w/v)中用设定在6档的 Brinkmann Polytron™匀浆30秒。所述缓冲液是由 50mM Tris 组成,其室温下的 pH 为 7.5。通过离心沉降该匀浆(10 分钟; 50,000xg; 0-4℃)。倾出上清液且用 Polytron 轻轻令膜重新悬浮丙在此离心(10 分钟; 50,000xg; 0-4℃)。再次离心后,将膜重新悬浮在试验缓冲液中,浓度为 1.0g/100ml。标准试验缓冲液的组成是 50mM Tris HCl、120mM NaCl、5mM KCl、2mM $MgCl_2$、2mM $CaCl_2$,并且其室温下的 pH 为 7.4。

常规实验是在硼硅酸盐玻璃试管中进行。试验混合物一般在 1.0mL 的培养终体积中由 0.9mg 膜蛋白组成。制备三组试管,其中各组试管内分别含有 50μL 载体、空白或试验化合物溶液。向各个试管中加入 200μL 存在于试验缓冲液中的[^{3}H]-烟碱,随后加入 750μL 的膜悬浮液。各个试管中的烟碱终浓度为 0.9nM。空白试管中的金雀花碱的终浓度为 1μM。所述载体是由含有每 50ml 水中 30μL 的 1N 醋酸的去离子水组成。将试验化合物和金雀花碱溶解在载体中。在向试管中加入膜悬浮液后通过涡旋启动实验。将样本在 0-4℃的振摇冰水浴中温育。通过在真空下经 Whatman GF/B™玻璃纤维滤膜、利用 Brandel™多支管组织收集器进行快速过滤以终止上述温育。在初次过滤试验化合物

后，滤膜用冰冷的缓冲液(每次 5mL)洗涤 2 次。随后将滤膜置于计数瓶中且与 20ml 的 ready Safy™(Beckman)剧烈混合，随后定量分析放射性。在效率为 40-50％的 LKB Wallach Rackbeta™液体闪烁计数器中对样本计数。所有分析均一式三份。

计算

对膜的特异性结合(C)是指只含有载体和膜的样本的总结合(A)与含有膜和金雀花碱的样本的非特异结合(B)之差，即:

特异性结合=(C)=(A)-(B)

试验化合物存在下的特异性结合(E)是试验化合物存在下的总结合(D)和非特性结合(B)之差，即(E)=(D)-(B)。

抑制率％=(1-((E)/(C))×100

被测定的本发明化合物在上述试验中表现出的 IC_{50} 小于 10μM。

下列试验实施例举例说明本发明，但不限制本发明的保护范围。

实施例 1

5,6-二氟-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2,4,6-三烯盐酸盐

A)环戊-3-烯基-(2,3-二氟-6-甲氧基-苯基)-甲醇(对于在先金属化反应可以参见实施例 6A。环戊-3-烯甲醛衍生自用氢化锂铝还原的环戊-3-烯甲酸甲氧基-甲基-酰胺，其制备如实施例 2A 所述。对于还原条件，参见 Garigipati,R.S.; Tschaen, D.M.; Weinreb, S.M.; 美国化学会志杂志.1990, 112, 3475-3482)。

在-78℃的氮气氛下，将 1,2-二氟-4-甲氧基-苯(10g, 69.4mmol)在含有无水(anh.)THF(80ml)的干燥三颈圆底烧瓶(3NRB 烧瓶)中搅拌。在 5 分钟内向其中加入正丁基锂(n-BuLi)(28ml, 2.5M/己烷的溶液, 70mmol)。在-70℃下搅拌 4.5 小时(h)后，在保持瓶内温度低于-70℃的同时，经滴液漏斗沿反应容器侧壁加入环戊-3-烯甲醛(5.7g, 69.4mmol)在无水 THF(30ml)中的溶液。搅拌半小时后，将反应混合物倾入饱和氯化铵水溶液(饱和 NH_4Cl 水溶液)(100ml)中，将该混合物搅拌并用乙酸乙酯(Et_2O)(2 ×50ml)提取。有机层用盐水(50ml)洗涤，干燥(Na_2SO_4)，过滤浓缩和在硅胶上层析，得到油状物(6.64g, 40%)。(薄

层层析(TLC) 20% 乙酸乙酯/己烷, R_f 0.16)。 ^{1}H NMR ($CDCl_3$) δ 7.01 (ddd, J=9.0Hz, 1H), 6.58 (m, 1H), 5.72 (ddd, J=5.8,4.5,2.2 Hz, 1H), 5.62 (ddd, J=5.8,4.5,2.2 Hz, 1H), 4.79 (br d, J=9.5 Hz, 1H), 3.85 (s, 3H), 3.20 (br s, OH), 2.87 (m, 1H), 2.52 (AB m, 2H), 1.99 (AB m, 2H). GCMS m/e 240 (M^+).

B)2-环戊-3-烯甲基-3,4-二氟-1-甲氧基-苯(有关实例参见: Leeson, P.D.; Emmett, J.C.; Shah, V.P.; Showell, G.A.; Novelli, R.《医学化学杂志》1989, 32, 320-336)。

0℃下, 环戊-3-烯基-(2,3-二氟-6-甲氧基-苯基)-甲醇(6.64g, 27.7mmol)和三乙基硅烷(3.38g, 29mmol)在二氯甲烷(40ml)中搅拌。向该溶液中加入三氟乙酸(17.3ml, 29mmol)。室温下将混合物搅拌18小时。将混合物浓缩成油状物, 将其溶解在己烷(100ml)中, 用水(H_2O)(2 ×50ml)和饱和碳酸氢钠水溶液(饱和 $NaHCO_3$ 水溶液)(50ml)洗涤, 随后干燥(硫酸钠(Na_2SO_4)), 过滤, 浓缩和在硅胶上层析, 得到油状物(3.67g, 59%)。(TLC 己烷 R_f 0.38)。

^{1}H NMR ($CDCl_3$) δ 6.92 (ddd, J=9.3 Hz, 1H), 6.49 (br d, J=9.3 Hz, 1H), 5.66 (br s, 2H), 3.78 (s, 3H), 2.72 (dd, J=7.5,2.0 Hz, 2H), 2.57 (m, 1H), 2.36 (AB m, 2H), 2.06 (AB dd, J=14.2,5.5 Hz, 2H). GCMS m/e 224 (M^+).

C)2-环戊-3-烯基甲基-3,4-二氟-苯酚

在-78℃的氮气(N_2)氛下, 将2-环戊-3-烯基甲基-3,4-二氟-1-甲氧基-苯(3.67g, 16.38mmol)和 n-Bu_4NI(7.17g, 19.4mmol)在干燥二氯甲烷(50ml)中搅拌。在2分钟内向其中加入三氯化硼(BCl_3)(22ml, 1M 二氯甲烷溶液, 22mmol)。5 分钟后, 将该溶液加热至室温(rt)且搅拌2小时。用水(100ml)终止该反应并搅拌1小时。分离各层, 水层用二氯甲烷(CH_2Cl_2)(2 ×30ml)提取。合并的有机层用水(2 ×50ml)和饱和碳酸氢钠水溶液(50ml)洗涤, 经棉塞干燥, 浓缩和在硅胶上层析, 得到油状物(3.30g, 96%)。(TLC 50% 乙酸乙酯(EtOAc)/己烷 R_f 0.70)。

^{1}H NMR ($CDCl_3$) δ 6.85 (ddd, J=9.0 Hz, 1H), 6.46 (m, 1H), 5.68 (br s, 2H), 4.76 (br s, 1H), 2.71 (d, J=8.0 Hz, 2H), 2.61 (m, 1H), 2.39 (AB m, 2H), 2.09 (AB dd, J=14.0,5.4 Hz, 2H). GSMS m/e 210 (M^+).

D)三氟-甲磺酸 2-环戊-3-烯基甲基-3,4-二氟-苯基酯

(在先参考文献可参见: Su, T.M.; Sliwinski, W.F.; Schleyer, P.v.R. 《美国化学会志杂志》1969,91,5386)。

在-78℃的 N_2 下, 将 2-环戊-3-烯基甲基-3,4-二氟-苯酚(3.30g, 15.7mmol)和吡啶(2.49g, 31.5mmol)在二氯甲烷(50ml)中搅拌并且用在 20 分钟内滴加的三氟甲磺酸酐(6.20g, 22.0mmol)处理。将混合物在室温下加热 1/2 小时, 随后倾入 1N 盐酸水溶液中并且振摇。分离各层, 水层用二氯甲烷(2 ×30ml)提取。合并的有机层用水(50ml)和饱和碳酸氢钠水溶液(50ml)洗涤, 经棉塞干燥, 浓缩和在硅胶上层析, 得到油状物(4.34g, 81%)。(TLC 30%EtOAc/己烷 R_f 0.60)

^{1}H NMR ($CDCl_3$) δ 7.13-7.03 (2H), 5.67 (br s, 2H), 2.82 (dd, J=7.5,2.0 Hz, 2H), 2.58 (m, 1H), 2.40 (dd, J=14.0,8.0 Hz, 2H), 2.05 (dd, J=14.0,5.5 Hz, 2H). GCMS *m/e* 342 (M^+).

E)5,6-二氟三环[7.2.1.$0^{2,7}$]十二碳-2(7),3,5,10-四烯

在氮气氛下, 将三氟-甲磺酸 2-环戊-3-烯基甲基-3,4-二氟-苯基酯(340mg, 0.99mmol)溶解在 DMF(5ml)中并用二异丙基乙基胺(0.26mL, 1.5mmol), 醋酸钾(981mg, 10.0mmol)和三-邻-甲苯基膦(12mg, 0.04mmol)处理。将混合物搅拌并脱气(3 个真空度/氮气净化循环)。随后用醋酸钯(5mg, 0.02mmol)处理。20 分钟后, 将混合物在 100℃下加热 18 小时, 冷却并倾入盐水(50ml)中。所得混合物用己烷(4 ×25ml)提取, 合并的有机层用饱和碳酸氢钠水溶液(10ml)、水(H_2O)(10ml)、盐水(10ml)洗涤, 干燥(硫酸镁($MgSO_4$)), 过滤和在硅胶上层析, 得到油状物(110mg, 60%)。(TLC 己烷, R_f 0.58)。

^{1}H NMR ($CDCl_3$) δ 6.80-(ddd, J=6.6,8.1,8.3 Hz, 1H), 6.68 (m, 1H), 6.17 (dd, J=5.5,2.8 Hz, 1H), 5.77 (dd, J=5.5,2.8 Hz, 1H), 3.29 (br s, 1H), 2.96 (br s, 1H), 2.84 (AB dd, J=17.9,5.0 Hz, 1H), 2.54 (AB d, J=17.9 Hz, 1H), 2.19 (m, 1H), 1.77 (d, J=10.5 Hz, 1H). GCMS m/e 192 (M^+).

F)5,6-二氟-10,11-二羟基三环[7.2.1.$0^{2,7}$]十二碳-2(7),3,5-三烯

将 5,6-二氟三环[7.2.1.$0^{2,7}$]十二碳-2(7),3,5,10-四烯(714mg, 3.72mmol)和 N-甲基吗啉 N-氧化物(553mg, 4.10mmol)在丙酮(20ml)和水(3ml)中搅拌。向其中加入四氧化锇(OsO_4)(0.2ml, 2.5(重量)%的叔丁醇(t-BuOH)溶液, 0.02mmol)。18 小时后, 将混合物浓缩为油状物, 用最少量的二氯甲烷溶解, 经硅胶垫(3 ×3mm)过滤, 用 20%乙酸乙酯/己烷洗脱。浓缩含产物的馏分, 得到油状物(850mg, 100%)。)TLC 20%乙酸乙酯/己烷 R_f 0.37)。

^{1}H NMR ($CDCl_3$) δ 6.88 (ddd, J=9.3,8.5,7.6 Hz, 1H), 6.78 (m, 1H), 4.01 (AB d, 2H), 3.06 (br s, 1H), 2.92 (AB dd, J=17.9,5.0 Hz, 1H), 2.75 (br AB, J=17.9 Hz, 1H), 2.44 (br s, 1H), 2.32 (2-OH), 2.26 (m, 1H), 1.50 (d, J=7.8 Hz, 1H). GCMS m/e 226 (M^+).

G)5,6-二氟-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯盐酸盐

在帕尔氏瓶中, 将 5,6-二氟-10,11-二羟基三环[7.2.1.$0^{2,7}$]十二碳-2(7),3,5-三烯(840mg, 3.72mmol)在乙醇(EtOH)(30ml)和水(10ml)中搅拌。向该溶液中加入存在于水(5ml)中的高碘酸钠($NaIO_4$)(810mg, 3.72mmol)。将所得乳白色分散体搅拌 15 分钟, 随后用 37%氢氧化铵(NH_4OH)水溶液(25ml)和氢氧化钯($Pd(OH)_2$)(360mg, 20%重量/C)处理并且在 45psi 的氢气下振摇。18 小时后, 经硅藻土垫过滤该混合物, 用乙醇和 3:1 的乙醇:水混合液漂洗。将滤液浓缩为油状固体, 将该固体溶解在乙酸乙酯(50ml)中, 用饱和碳酸钠(Na_2CO_3)水溶液(2 ×2ml)洗涤。有机层用硫酸钠(Na_2SO_4)干燥, 过滤, 浓缩和在硅胶上层析, 得到油状物(330mg, 42%)。(TLC 5%甲醇/二氯甲烷 R_f 0.36)。

^{1}H NMR ($CDCl_3$) δ 6.92 (ddd, J=8.1,8.5,10.0 Hz, 1H), 6.74 (m, 1H), 3.02-2.93 (4H), 2.83-2.71 (3H), 2.09 (br s, 1H), 1.98 (br d, J=12.5 Hz, 1H), 1.82 (br d, J=12.5 Hz, 1H). GSMS m/e 209 (M^+). APCI MS m/e 209.8 [$(M+1)^+$].

将产物溶解在甲醇(CH_3OH)中并用 3M 盐酸(HCl)/EtOAc 溶液(3ml)处理。浓缩所得浆液，溶解在最少量的甲醇中，用乙酸乙酯饱和，搅拌 18 小时。过滤出固体，得到白色固体(335mg, 86%)，熔点：290-305℃。

实施例 2

11-苄基-6-甲氧基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯盐酸盐

A)环戊-3-烯甲酸甲氧基-甲基酰胺(为了制备环戊-3-系甲酸，参见 Depres, J-P.；Greene, A.E.《有机化学杂志》1984, 49, 928-931, 和最新的合成途径参见：a)Nugent, W.A.；Feldman, J.；Calabrese, J. C.《美国化学学会杂志》1995, 117, 8992-8998, 和 b)Marinez, L.E.；Nugent, W.A.；Jacobsen, E.N.《有机化学杂志》1996, 61, 7963-7966。对于酰胺形成的有关方法，参见：Nitz, T.J.；Volkots, D.L.；Alous, D.J.；Oglesby, R.C.《有机化学杂志》1994, 59, 5828-5832)。

分次用羰基二咪唑(100g, 617mmol)处理存在于二氯甲烷(1L)中的环戊-3-烯甲酸(65.6g, 586mmol)。约 45 分钟后，所得溶液用 N,O-二甲基羟胺(60.8g, 623mmol)处理，将该混合物搅拌 40 小时。用 1N 盐酸水溶液(600ml)终止该反应，振摇并分离各层。用二氯甲烷(2 × 100ml)提取水层。合并的有机层用 1N 盐酸水溶液(100ml)、水(2 × 150ml)、50%饱和碳酸钠水溶液/盐水(200ml)洗涤，经棉垫干燥。滤液用乙酸乙酯稀释至~10%乙酸乙酯/二氯甲烷，经硅胶垫(10 ×10mm)过滤，用 10%乙酸乙酯/二氯甲烷洗脱，除去基质颜色。浓缩得到液体(86g, 95%)。(TLC 10%乙酸乙酯/二氯甲烷 R_f 0.56)。

^{1}H NMR ($CDCl_3$) δ 5.64 (br s, 2H), 3.69 (s, 3H), 3.47 (m,

1H), 3.19 (s, 3H), 2.61 (m, 4H). GSMS m/e 155 (M^+).

B)环戊-3-烯基-(2,6-二甲氧基-苯基)-甲酮(对于在先参考文献可以参见: Koft, E.R.; Smith, A.B. III.《美国化学学会杂志》1982, 104, 2659)

在0℃和氮气氛下，将1,3-二甲氧基苯(31.9g, 231mmol)在无水乙醚(200ml)中搅拌并且用正丁基锂(n-BuLi)(92.5ml, 2.5M/己烷溶液, 231mmol)处理5分钟。将该溶液回流4小时，随后冷却至-78℃。用在约 1 小时内滴加至该浆液中的环戊-3-烯甲酸甲氧基-甲基酰胺(35.9g, 231mmol)进行处理，随后将混合物搅拌18小时(冷却裕蒸发过夜)。将混合物倾入1N盐酸水溶液(200ml)并振摇。过滤各层，用乙醚(2 ×100ml)提取水层。有机层用水(50ml)和饱和碳酸氢钠水溶液(100ml)洗涤，干燥(Na_2SO_4)，经硅胶塞过滤，浓缩成油状物(52.6g, 98%)。(TLC 10% 乙酸乙酯/己烷 R_f 0.25)。

^1H NMR ($CDCl_3$) δ 7.24 (t, J=8.4 Hz, 1H), 6.24 (d, J=8.4 Hz, 2H), 5.63 (br s, 2H), 3.76 (s, 6H), 3.68 (m, 1H), 2.75 (m, 2H), 2.48 (m, 2H). GSMS m/e 232 (M^+).

C)环戊-3-烯基-(2-羟基-6-甲氧基-苯基)-甲酮(对于在先参考文献参见: Nagaoka, H.; Schmid, g.; Lio, H.; Kishi, Y. 《四面体通讯》1981, 22, 899)

在-78℃和氮气氛下，将环戊-3-烯基-(2,6-二甲氧基-苯基)-甲酮(52.6g, 226mmol)在二氯甲烷(200ml)中搅拌并且用三氯化硼(BCl_3)(273ml, 1M 二氯甲烷溶液, 273mmol)处理30分钟。令混合物升至室温，用另外的BCl_3(41.0ml, 1M二氯甲烷溶液, 41.0mmol)处理。在将混合物搅拌 20 分钟后，将其缓慢倾入水(300ml)中并且搅拌 30 分钟。分离各层，用二氯甲烷(2 ×50ml)提取水层。合并的有机层用水(3 ×100ml)、饱和碳酸氢钠水溶液(100ml)洗涤，经棉塞干燥，经硅胶垫过滤以除去基质颜色。浓缩得到琥珀色油(46.0g, 93%)。(TLC 10% 乙酸乙酯/己烷 R_f 0.50)。

^{1}H NMR ($CDCl_3$) δ 7.32 (t, J=8.5 Hz, 1H), 6.57 (dd, J=8.5,1.0 Hz, 1H), 6.38 (dd, J=8.5,1.0 Hz, 1H), 5.66 (br s, 2H), 4.31 (m, 1H), 3.89 (s, 3H), 2.80-2.63 (4H). GSMS m/e 218 (M^+).

D)三氟-甲磺酸 2-(环戊-3-系羰基)-3-甲氧基-苯基酯

在-78℃氮气氛下，将环戊-3-烯基-(2-羟基-6-甲氧基-苯基)-甲酮(45.0g, 206mmol)和吡啶(36.0g, 453mmol)在二氯甲烷(250ml)中搅拌。在半小时内向其中滴加三氟甲磺酸酐(75.7g, 268mmol)在二氯甲烷(100ml)中的溶液。将混合物加热至室温，搅拌 1 小时， 随后倾入 1N 盐酸水溶液(250ml)中。振摇混合物，分离各层，有机层用 1N 盐酸水溶液(3 ×150ml)、水(2 ×100ml)、饱和碳酸氢钠水溶液(100ml)，最后用盐水(100ml)洗涤。有机层经棉塞干燥，浓缩得到油状物，经硅胶塞侧线，用 10% 乙酸乙酯己烷洗脱，随后浓缩得到油状物(62.5g, 87%)。(TLC 10% 乙酸乙酯/己烷 R_f 0.14) ^{1}H NMR ($CDCl_3$) δ 7.41 (t, J=8.5 Hz, 1H), 6.95 (dd, J=8.5,1.0 Hz, 2H), 5.64 (br s, 2H), 3.86 (s, 3H), 3.73 (m, 1H), 2.70 (m, 2H), 2.57 (m, 2H). GSMS m/e 350 (M^+).

E)6-甲氧基三环[7.2.1.$0^{2,7}$]十二碳-2(7),3,5,10-四烯-8-酮(对于在先参考文献可以参见: Heck, R. F.《有机反应》(N. Y.)1982, 27, 345; 和 Cabri, W.; Candiani, I. Acc. Chem. Res. 1995, 28, 2-7)。

在氮气氛下将三氟-甲磺酸 2-(环戊-3-烯羰基)-3-甲氧基-苯基酯(45.0g, 129mmol)溶解在 DMF(100ml)中并且用三乙胺(19.5g, 193mmol)、醋酸钾(1.89g, 19.0mmol)和 1,3-双(联苯基膦)丙烷(5.30g, 12.9mmol)处理。搅拌该混合物并且脱气(3 个真空度/N_2 净化循环)，随后用醋酸钯(1.16g, 5.14mmol)处理。20 分钟后，将混合物在 130℃下加热 1 小时，冷却，倾入盐水(300ml)中。所得混合物用乙酸乙酯(4 ×100ml)提取，合并的有机层用饱和碳酸氢钠水溶液(100ml)、水(100ml)和盐水(100ml)洗涤，干燥($MgSO_4$)，过滤和蒸发，得到油状物(55g)。在硅胶上层析该油状物，得到产物，其为白色固体(12.0g,

47%)。(TLC 25% 乙酸乙酯/己烷 R_f 0.27)。^1H

NMR ($CDCl_3$) δ 7.29 (t, J=8.0 Hz, 1H), 6.84 (d, J=8.0 Hz, 1H), 6.73 (d, J=8.0 Hz, 1H), 6.63 (dd, J=5.0,3.0 Hz, 1H), 6.15 (dd, J=5.0,3.0 Hz, 1H), 3.87 (s, 3H), 3.60 (br s, 1H), 3.39 (br s, 1H), 2.56 (AB m, 2H). ^{13}C NMR 195.38, 161.61, 149.82, 143.47, 133.77, 131.84, 131.80, 117.51, 111.46, 57.63, 55.96, 47.63, 47.51. GSMS m/e 200 (M^+). mp 135-136 °C.

F)6-甲氧基三环[7.2.1.$0^{2,7}$]十二碳-2(7),3,5,10-四烯(作为探讨可以参见: Fieser & fieser, 《有机合成的试剂》(N.Y.)1967,I,第435页)

将 6-甲氧基三环[7.2.1.$0^{2,7}$]十二碳-2(7),3,5,10-四烯-8-酮(3.0g,15mmol)和粉碎的氢氧化钾(5.05g, 90mmol)在乙二醇(40ml)中加热直至生成溶液。将混合物冷却至室温,用水合肼(3.0g, 60mmol)处理并加热回流 2 小时。用蒸馏头取代回流冷凝器,收集 120-190℃的馏出液。用水(100ml)稀释这些馏出液并且用所有水(4 ×40ml)稀释,用乙酸乙酯(4 ×40ml)提取。有机层用水(4 ×30ml)和盐水(25ml)洗涤,干燥($MgSO_4$),过滤并浓缩至油状物(2.68g, 96%)。(TLC 50% 乙酸乙酯/己烷 R_f 0.67)。 ^1H NMR ($CDCl_3$) δ 7.18 (t, J=8.0 Hz, 1H), 6.82 (d, J=8.0 Hz, 1H), 6.77 (d, J=8.0 Hz, 1H), 6.32 (dd, J=5.0,3.0 Hz, 1H), 5.93 (dd, J=5.0,3.0 Hz, 1H), 3.91 (s, 3H), 3.45 (dd, J=5.0,1.5 Hz, 1H), 3.11 (br s, 1H), 2.88 (AB dd, J=17.0,5.0 Hz, 1H), 2.58 (AB d, J=17.0 Hz, 1H), 2.31 (m, 1H), 1.96 (d, J=9.5 Hz, 1H).

G)6-甲氧基-10,11-二羟基三环[7.2.1.$0^{2,7}$]十二碳-2(7),3,5,10-三烯

在丙酮(20ml)和水(0.16ml)中搅拌 6-甲氧基三环[7.2.1.$0^{2,7}$]十二碳-2(7),3,5,10-四烯(1.5g, 8.19mmol)和 N-甲基吗啉 N-氧化物(1.06g, 9.03mmol)。向其中加入四氧化锇溶液(OsO_4)(0.2ml, 2.5(重量)%的叔丁醇(t-BuOH)溶液,0.02mmol)。2 小时后,用乙酸乙酯(50ml)稀释该混合物并且用 10%硫酸氢钠水溶液(30ml)、水(2 ×30ml)、饱和碳酸氢钠水溶液(30ml)和盐水(30ml)洗涤。有机层用干燥($MgSO_4$),过滤并且蒸发成为油状物(1.79g, 99%)。(TLC 50% 乙酸乙酯/己烷 R_f 0.20)。

H)11-苄基-6-甲氧基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯盐酸盐(对于用 Pb(OAc$_4$)氧化裂解的探讨可以参见: fieser & Fieser, 《有机合成试剂》(N,Y.)1967,I,549。对于还原性胺化条件和参考文献参见 Abdel-Megid 等人《有机化学杂志》1996,61,3849; 和 Mazzocchi 等人《医学化学杂志》1979, 22, 455)。

0℃下, 在二氯甲烷(70ml)中搅拌 1-甲氧基-6,7,8,9-四氢-5H-5,8-甲烷-苯并环庚-6,7-二醇 (2.40g, 11.0mmol) 并用 Pb(OAc$_4$) (5.08g, 11.5mmol)处理。2小时后, 经硅藻土垫过滤该混合物且用二氯甲烷(10ml)漂洗。向搅拌的滤液中加入醋酸(AcOH) (1.97g, 33.0mmol)和苄胺(1.23g, 11.5mmol)。15分钟后, 用三乙酰氧基硼氢化钠(NaBH(OAc)$_3$) (6.94g, 33.0mmol)处理该混合物且搅拌18小时。将混合物倾入饱和碳酸氢钠水溶液(100ml)中, 搅拌半小时。过滤各层并且用二氯甲烷(2 ×50ml)提取。用饱和碳酸氢钠($NaHCO_3$)水溶液(2 × 50ml)、水(50ml)、盐水(50ml)洗涤有机层, 经棉塞干燥, 浓缩, 在硅胶上层析纯化, 用 10% 乙酸乙酯/己烷洗脱, 得到产物, 该产物为油状物(1.45g, 45%)。(TLC 25% 乙酸乙酯/己烷 R_f 0.76)。

^{1}H NMR ($CDCl_3$) δ 7.12 (m, 4H), 6.89 (m, 2H), 6.74 (d, J=8.0 Hz, 1H), 6.64 (d, J=8.0 Hz, 1H), 3.87 (s, 3H), 3.41 (AB d, J=14.2 Hz, 1H), 3.38 (AB d, J=14.2 Hz, 1H), 2.87-2.70 (m, 5H), 2.36-2.23 (m, 3H), 1.85 (br AB d, J=12.1 Hz, 1H), 1.77 (br AB d, J=12.1 Hz, 1H).

将该油状物溶解在最少量甲醇(MeOH)中, 搅拌, 用乙醚饱和。18小时后, 过滤出白色固体。^{1}H

NMR (CD_3OD) δ 7.44 (m, 5H), 7.15 (t, J=8.0 Hz, 1H), 6.85 (d, J=8.0 Hz, 1H), 6.68 (d, J=8.0 Hz, 1H), 4.27 (AB d, J=13.0 Hz, 1H), 4.15 (AB d, J=13.0 Hz, 1H), 3.84 (s, 3H), 3.47 (br d, J=12.3 Hz, 1H), 3.36-3.19 (m, 4H), 2.98 (AB dd, J=18.7,7.2 Hz, 1H), 2.85 (AB d, J=18.7 Hz, 1H), 2.60 (br s, 1H), 2.00 (AB d, J=13.0 Hz, 1H), 1.87 (AB d, J= 13.0 Hz, 1H). mp 210-212 °C

实施例 3

6-甲氧基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯盐酸盐

将 11-苄基-6-甲氧基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳

-2(7),3,5-三烯(525mg, 1.64mmol)、甲酸铵(2.07g, 32.0mmol)和10%碳载氢氧化钯($Pd(OH)_2/C$)(200mg)在甲醇(30ml)中混合和回流2小时。经硅藻土热过滤该混合物，浓缩滤液，随后由甲醇(5 ×50ml)共沸，生成固体。自甲醇/乙醚中重结晶，得到白色固体(306mg , 81%)。

^1H NMR(游离碱, $CDCl_3$) δ 7.15 (t, J=8.0 Hz, 1H), 6.74 (d, J=8.0 Hz, 1H), 6.63 (d, J=8.0 Hz, 1H), 3.82 (s, 3H), 3.34 (br d, J=13.0 Hz, 1H), 3.11-3.02 (m, 4H), 2.94 (AB d, J=18.3 Hz, 1H), 2.87 (AB dd, J=18.3,6.5 Hz, 1H), 2.41 (br s, 1H), 1.91 (AB q, 2H). GSMS m/e 203 (M^+). mp 272-274 °C.

实施例4

11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯-6-醇

在48%氢溴酸(HBr)水溶液(5ml)中回流6-甲氧基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯盐酸盐(55mg, 0.23mmol)。1小时后，将溶液冷却并且倾入1N氢氧化钠水溶液中调至pH 10，用乙酸乙酯(3 ×40ml)提取产物。有机层用盐水(50ml)洗涤，干燥($MgSO_4$)和浓缩成为白色固体，由乙酸乙酯/己烷中重结晶(20mg, 46%)。

^1H NMR ($CDCl_3$) δ 6.95 (t, J=8.0 Hz, 1H), 6.68 (d, J=8.0 Hz, 1H), 6.53 (d, J=8.0 Hz, 1H), 3.27 (m, 1H), 3.11 (m, 2H), 3.02 (m, 2H), 2.77 (m, 1H), 2.57 (m,1H), 2.33 (br s, 1H), 1.90 (m, 2H). mp 106-108 °C.

实施例5

6-氟-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯盐酸盐

在-78℃下，将3-氟甲氧基苯(15.8g, 125mmol)在无水THF(100ml)中搅拌并且用n-BuLi(50mL, 2.5M己烷溶液, 125mmol)处理5分钟。在-70℃以下搅拌4小时后，在~1/4小时内滴加环戊-3-烯甲酸甲氧基-甲基酰胺(18.4g, 119mmol)用于处理该混合物。在-70℃下将该混合物搅拌1小时，随后在~1小时内升至室温。将混合物倾入1N盐酸水溶液(200ml)中并且振摇。过滤各层，水层用乙酸乙酯(3 ×100ml)提取。有机层用水(50ml)、饱和碳酸氢钠水溶液(100ml)和盐水(50ml)洗涤，干燥(Na_2SO_4)，经硅胶塞过滤，浓缩得到油状物(21.0g, 76%)。(TLC 30%乙酸乙酯/己烷 R_f 0.43)。GCMS m/e 220(M^+)。通过实施例2C-G和实施例1G的方法将该原料转化为标题化合物。(TLC 10% 甲

醇/二氯甲烷(NH_3)R_f 0.20)。^1H NMR (CD_3OD) δ 7.24 (m, 1H), 7.01 (m, 2H), 3.36 (d, J=13.0 Hz, 1H), 3.33-3.10 (m, 5H), 2.90 (d, J=18.5 Hz, 1H), 2.60 (m, 1H), 2.13 (AB d, J=13.0 Hz, 1H), 1.97 (AB d, J= 13.0 Hz, 1H). mp 240-241 °C.

实施例 6

11-苄基-5-甲氧基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯盐酸盐

A)环戊-3-烯基-(2,5-二甲氧基-苯基)-甲酮(对于卤素-金属交换的讨论,参见: Parham, W.E.; Bradsher, C.K. Acc. Chem. Res. 1982, 15, 300)

在氮气和-78℃下,将 2-溴-1,4-二甲氧基-苯(42.2g, 195mmol)在乙醚(Et_2O)(200ml)中搅拌。加入 THF(50ml)溶解所得沉淀。在 10 分钟内向所得溶液中加入 n-BuLi(78mL, 2.5M 的己烷溶液, 195mmol)。搅拌 10 分钟后,该黄色溶液用存在于乙醚(50ml)中的环戊-3-烯甲酸甲氧基-甲基-酰胺(29.15g, 188mmol)处理 10 分钟,随后将该混合物搅拌 18 小时(冷却裕蒸发过夜)。将混合物倾入 10% 盐酸水溶液(400ml)中并且振摇。过滤各层,水层用乙醚(3 ×50ml)提取。有机层用水(50ml)、饱和碳酸氢钠水溶液(100ml)洗涤,干燥(Na_2SO_4),经硅胶塞过滤,浓缩得到油状物(43.0g, 99%)。(在分离试验中,适宜用 THF 代替上述反应的乙醚)。(TLC 10% 乙酸乙酯/己烷 R_f 0.39)。^1H NMR ($CDCl_3$) δ 7.16 (d, J=3.0 Hz, 1H), 6.98 (dd, J=9.0,3.0 Hz, 1H), 6.88 (d, J=9.0 Hz, 1H), 5.64 (br s, 2H), 4.11 (m, 1H), 3.84 (s, 3H), 3.77 (s, 3H), 2.66 (m, 4H).

B)环戊-3-烯基-(2-羟基-5-甲氧基-苯基)-甲酮

按照实施例 2C 所述方法将环戊-3-烯基-(2,5-二甲氧基-苯基)-甲酮(40.0g, 172mmol)转化为标题混合物,产物为油状物(39.5g, 粗品)。(TLC 10% 乙酸乙酯/己烷 R_f 0.50)。

^1H NMR ($CDCl_3$) δ 7.21 (m, 1H), 7.10 (m, 1H), 6.93 (br d,

J=9.0 Hz, 1H), 5.69 (br s, 2H), 4.06 m, 1H), 3.79 (s, 3H), 2.76 (m, 4H). GCMS *m/e* 218 (M^+).

C) 三氟-甲磺酸-2-(环戊-3-烯羰基)-4-甲氧基-苯基酯

在-78℃氮气氛下，将环戊-3-烯基-(2-羟基-5-甲氧基-苯基)-甲酮(39.5g, 172mmol)和吡啶(28.7g, 362mmol)在二氯甲烷(300ml)中搅拌。在半小时内向其中滴加三氟甲磺酸酐(63.8g, 226mmol)在二氯甲烷(100ml)中的溶液。令混合物加热至室温并且搅拌 1 小时，倾入 1N 盐酸水溶液(250ml)。振摇该混合物，过滤各层，有机层用 1N 盐水水溶液(3 ×150ml)、水(2 ×100ml)、饱和碳酸氢钠水溶液(100ml)洗涤，并且最后用盐水(100ml)洗涤。有机层经棉塞干燥，浓缩得到油状物，经硅胶塞层析，用 10% 乙酸乙酯/己烷洗脱，浓缩后得到油状物(55.7g, 2 步的收率 93%)。GCMS m/e 350(M^+).

D) 5-甲氧基三环[7.2.1.$0^{2,7}$]十二碳-2(7),3,5,10-四烯-8-酮

在氮气下，将三氟-甲磺酸 2-(环戊-3-烯羰基)-4-甲氧基-苯基酯(19.09g, 54.5mmol)溶解在 DMF(100ml)中并且用二异丙基乙基胺(10.6g, 82.0mmol)、醋酸钾(1.07g, 11.0mmol)和 1,3-双(联苯基膦)丙烷(2.25g, 5.46mmol)处理。搅拌该混合物并且脱气(3 个真空度/N_2 净化循环)，随后用醋酸钯(0.49g, 2.18mmol)处理。20 分钟后，将混合物在 120℃下加热 18 小时，冷却，倾入盐水(300ml)中。所得混合物用乙酸乙酯(4 ×100ml)提取，合并的有机层用饱和碳酸氢钠水溶液(100ml)、水(100ml)和盐水(100ml)洗涤，干燥($MgSO_4$)，过滤，浓缩和在硅胶上层析，得到油状物(10.4g, 95%)。(洗脱 W/7% 乙酸乙酯/己烷)。^{1}H NMR ($CDCl_3$) δ

7.41 (d, J=2.8 Hz, 1H), 7.03 (d, J=8.0 Hz, 1H), 6.88 (dd, J=8.0,2.8 Hz, 1H), 6.72 (dd, J=5.2,3.0 Hz,1H), 6.06 (dd, J=5.2,3.2 Hz, 1H), 3.77 (s, 3H), 3.60 (dd, J=4.3,3.2 Hz, 1H), 3.44 (dd, J=5.0,3.4 Hz, 1H), 2.65 (AB m, 1H), 2.58 (br AB d, J=10.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) 196.11, 158.87, 145.90, 140.34, 130.295, 129.94, 126.14, 119.42, 111.90, 55.61, 55.48, 49.08, 45.97. GCMS *m/e* 200 (M^+).

E) 5-甲氧基三环[7.2.1.$0^{2,7}$]十二碳-2(7),3,5,10-四烯

将 5-甲氧基三环[7.2.1.$0^{2,7}$]十二碳-2(7),3,5,10-四烯-8-酮(6.41g,47mmol)和粉碎的氢氧化钾(KOH)(6.17g, 110mmol)在乙二醇(50ml)中加热直至生成溶液。将混合物冷却至室温，用水合肼(6ml, 190mmol)处理且加热回流 2 小时。用蒸馏头代替回流冷凝器，收集120-190℃的馏出液。用水(100ml)稀释这些馏出液并且用所有水(4 ×40ml)稀释，用乙酸乙酯(4 ×40ml)提取。有机层用水(4 ×30ml)和盐水(25ml)洗涤，干燥($MgSO_4$)，过滤并浓缩得到油状物(8.2g, 94%)。(TLC 25% 乙酸乙酯/己烷 R_f 0.68)。^{1}H NMR ($CDCl_3$) δ 6.92 (d, J=8.0 Hz, 1H), 6.88 (m, 2H), 6.25 (dd, J=5.1,2.5 Hz, 1H), 5.79 (dd, J=5.1,2.4 Hz, 1H), 3.77 (s, 3H), 3.31 (br s, 1H), 3.01-2.94 (2H), 2.56 (d, J=16.5 Hz, 1H), 2.22 (m, 1H), 1.85 (d, J=10.0 Hz, 1H). GCMS *m/e* 186 (M^+).

F)5-甲氧基-10,11-二羟基三环[7.2.1.$0^{2,7}$]十二碳-2(7),3,5,10-三烯

按照实施例 2G 所述方法，将 5-甲氧基三环[7.2.1.$0^{2,7}$]十二碳-2(7),3,5,10-四烯(6.66g, 35.7mmol)转化为标题化合物，该产物为油状物(7.86g, 100%)。(TLC 10% 甲醇/二氯甲烷 R_f 0.44)。

^{1}H NMR ($CDCl_3$) δ 6.95 (d, J=8.0 Hz, 1H), 6.63 (dd, J=8.0,2.5 Hz, 1H), 6.56 (br s, 1H), 4.00 (s, 3H), 3.77 (m, 3H), 3.04-2.99 (m, 2H), 2.69 (d, J=13.0 Hz, 1H), 2.41 (br s, 1H), 2.33 (br s, 1H), 2.22 (m, 1H), 1.52 (d, J=11.5 Hz, 1H).

G)11-苄基-5-甲氧基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯盐酸盐

0℃下，用 5-甲氧基-10,11-二羟基三环[7.2.1.$0^{2,7}$]十二碳-2(7),3,5,10-三烯(18.0g, 79.0mmol)在二氯甲烷中搅拌并且用四醋酸铅($Pb(OAc)_4$)(35.0g, 79.0mmol)处理。30 分钟后，经硅藻土垫过滤该混合物，用二氯甲烷(50ml)漂洗。向搅拌的滤液中加热AcOH(23.7g, 395mmol)和苄胺(8.50g, 79.0mmol)。15 分钟后，用

$NaBH(OAc)_3$(50.2g, 237mmol)处理该混合物并且搅拌 18 小时。将混合物倾入饱和碳酸钠水溶液(100ml)中搅拌 1/2 小时。分离各层并且用二氯甲烷(2 ×100ml)提取。有机层用饱和碳酸钠水溶液(2 ×50ml)、水(50ml)和盐水(50ml)洗涤，经棉塞干燥，浓缩，得到油状物。在硅胶上层析，用 5% 乙酸乙酯/己烷洗脱，得到产物，该产物为油状物(9.48g, 41%)。(TLC 25% 乙酸乙酯/己烷 R_f 0.69)。

^{1}H NMR ($CDCl_3$) δ 7.15 (m, 3H), 6.92 (m, 3H), 6.71 (br s, 1H), 6.67 (dd, J=8.0,2.5 Hz, 1H), 3.83 (s, 3H), 3.99 (s, 2H), 3.07 (AB dd, J=17.5,7.0 Hz, 1H), 2.85 (br s, 1H), 2.83 (m, 1H), 2.79 (AB d, J=17.5 Hz, 1H), 2.70 (br d, J=10.5 Hz, 1H), 2.35 (dd, J=10.5,2.0 Hz, 1H), 2.27 (dd, J=10.2,2.0 Hz, 1H), 2.15 (br s, 1H), 1.86 (AB d, J=12.3 Hz, 1H), 1.78 (AB d, J=12.3 Hz, 1H). GCMS *m/e* 293 (M^+).

将该原料溶解在过量的 1N 盐酸甲醇溶液中，浓缩。将固体溶解在最少量甲醇中，搅拌，用乙醚饱和。搅拌 18 小时后，过滤出白色固体(900mg ，58%)。 ^{1}H NMR (CD_3OD) δ 7.40 (m, 5H), 7.00 (d, J=8.0 Hz, 1H), 6.73 (m, 2H), 4.28 (AB d, J=13.5 Hz, 1H), 4.16 (AB d, J=13.5 Hz, 1H), 3.76 (s, 3H), 3.48 (br d , J=12.0 Hz, 1H), 3.35-3.20 (m, 5H), 2.98 (AB d, J=18.4 Hz, 1H), 2.54 (br s, 1H), 2.01 (AB d, J=12.0 Hz, 1H), 1.89 (AB d, J= 12.0 Hz, 1H). mp 233-234 °C.

实施例 7

11-苄基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯-5-醇盐酸盐

在 48 % HBr(5ml) 回流 11-苄基-5-甲氧基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯(203mg, 0.62mmol)。1 小时后，冷却该溶液并且倾入氢氧化铵水溶液中，pH 调至~9。用乙酸乙酯(3 ×40ml)提取该产物。有机层用盐水(50ml)洗涤，干燥($MgSO_4$)，浓缩得到油状物。(TLC 25% 乙酸乙酯/己烷(NH_3)R_f 0.37)。将该原料溶解在过量的 1N 盐酸甲醇溶液，浓缩。由甲醇/乙醚重结晶，得到固体(154mg, 80%)。 ^{1}H NMR ($CDCl_3$) δ 7.42 (m, 5H), 6.90 (d, J=8.0 Hz, 1H), 6.60 (m, 2H), 4.27 (AB d, J=13.0 Hz, 1H), 4.15 (AB d, J=13.0 Hz, 1H), 3.47 (d, J=12.2 Hz, 1H), 3.33-3.15 (5H), 2.86 (d, J=18.0 Hz, 1H), 2.52 (br s, 1H), 1.99 (AB d, J=12.5 Hz, 1H), 1.88 (AB d, J=12.5 Hz, 1H). mp 251-253 °C.

实施例 8

5-甲氧基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯-5-醇盐酸盐

按照实施例 3 所述方法，将 11-苄基-5-甲氧基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯(206mg, 0.63mmol)转化为标题化合物，该产物为白色固体(122mg, 81%)。(TLC 10% 甲醇/二氯甲烷(NH_3) R_f 0.48)。

^{1}H NMR (CD_3OD) δ 7.08 (d, J=8.0 Hz, 1H), 6.77 (m, 2H), 3.76 (s, 3H), 3.31-3.12 (m, 6H), 2.98 (AB d, J=18.4 Hz, 1H), 2.43 (br s, 1H), 2.10 (AB d, J=13.0 Hz, 1H), 1.94 (AB d, J= 13.0 Hz, 1H). GSMS m/e 203 (M^+). mp 253.5-256 °C.

实施例 9

11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯-5-醇盐酸盐

在 48% HBr(5ml)回流 5-甲氧基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯盐酸盐(187mg, 0.78mmol)。1 小时后，冷却该溶液并且倾入氢氧化铵水溶液中，pH 调至~9。用乙酸乙酯(3 ×40ml)提取该产物。有机层用盐水(50ml)洗涤，干燥($MgSO_4$)，浓缩得到固体。(TLC 10% 甲醇/二氯甲烷(NH_3) R_f 0.13)。将该原料溶解在过量的 1N 盐酸甲醇溶液中，浓缩。由甲醇/乙醚重结晶，得到固体(70mg, 40%)。

^{1}H NMR (CD_3OD) δ 6.99 (d, J=8.0 Hz, 1H), 6.63 (m, 2H), 3.48-3.11 (6H), 2.83 (d, J=18.0 Hz, 1H), 2.42 (br s, 1H), 2.08 (AB d, J=12.5 Hz, 1H), 1.93 (AB d, J= 12.5 Hz, 1H). mp 295-298 °C.

实施例 10

11-苄基-5-二氟甲氧基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯

(参见在先参考文献: Langlois, B. R. J. Fluorine Chem. 1988, 41, 247-262.)

在一球形瓶氟利昂（HCF_2Cl）存在下，于 1,4-二氧六环（5ml）和水（1ml）中回流搅拌 11-苄基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯-5-醇（572mg，2.05mmol）。向其中滴加 3N KOH，以保持 pH～12。通过 TLC 监测原料消耗 2 小时。冷却反应，用 H_2O（40ml）稀释并用 EtOAc 萃取。有机层用饱和 Na_2CO_3 水溶液（25ml）和盐水（25ml）洗涤，干燥（$MgSO_4$）、过滤并浓缩，得到油状物（620mg，92%）。GCMS m/e 329（M^+）。

实施例 11

5-二氟甲氧基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯盐酸盐

将 11-苄基-5-二氟甲氧基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯（620mg，1.88mmol）转化为实施例 3 描述的标题化合物。按实施例 9 的方法制备 HCl 盐，得到白色粉末状产物（280mg，54%）。^1H

NMR ($CDCl_3$) δ 7.42 (m, 5H), 7.01 (d, J=9.0 Hz, 1H), 6.92 (m, 2H), 6.48 (t, J=74 Hz, 1H), 3.37 (d, J=13.0 Hz, 1H), 3.18-3.04 (6H), 2.39 (br s, 1H), 1.95 (br s, 2H). GCMS *m/e* 239 (M^+). *mp* 230-234 °C.

实施例 12

11-苄基-5-乙基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯盐酸盐（参见综述：Mitsunobu，O. Synthesis，1981，1.）

在 N_2 条件下，在 0℃，于 THF（2.5ml）中搅拌 11-苄基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯-5-醇（208mg，0.75mmol）、乙醇（69mg，1.49mmol）和三苯基膦（391mg，1.49mmol）。向其中滴加偶氮二羧酸二乙酯（259mg，1.49mmol）。18 小时后，浓缩反应，用 Et_2O（20ml）稀释并用 1% 的磷酸水溶液萃取（3 ×20ml）。用 Et_2O（10ml）萃取合并的水层，然后用 1N 的 NaOH 溶液进行碱化至 pH 为 10。产物用 EtOAc 萃取（3 ×20ml），合并的有机层用 1N 的 NaOH 溶液（20ml）

和盐水（20ml）洗涤。将溶液干燥（$MgSO_4$），过滤并蒸发，得到油状物（170mg，74%）。（TLC 17%EtOAc/己烷 (NH_3) R_f 0.76）^{1}H NMR ($CDCl_3$) δ 7.12 (m, 3H), 6.91 (m, 2H), 6.86 (d, J=8.0 Hz, 1H), 6.68 (br s, 1H), 6.63 (dd, J=8.0,2.5 Hz, 1H), 4.03 (q, 2H), 3.37 (br s, 2H), 3.03 (dd, J=17.0,7.0 Hz, 1H), 2.82-2.68 (4H), 2.18 (2H), 2.12 (br s, 1H), 1.83 (AB d, J=12.0 Hz, 1H), 1.75 (AB d, J=12.0 Hz, 1H), 1.43 (t, J=7.0 Hz, 3H). GCMS *m/e* 307 (M^+).

将该物料溶解在 1N 的过量 HCl MeOH 中并进行浓缩。从 CH_2Cl_2/Et_2O 中重结晶，得到固状物（185mg，97%）。mp 200-203℃。

实施例 13

5-乙基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯盐酸盐

在甲醇（MeOH）（5ml）中合并 11-苄基-5-乙基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯盐酸盐（160mg，mmol）、甲酸铵（220mg，3.49mmol）和 10%$Pd(OH)_2/C$（100mg），加热回流 15 分钟。将混合物冷却、过滤、浓缩、用饱和 Na_2CO_3 水溶液稀释，并用 EtOAc 萃取（3 ×20ml）。将萃取物干燥（$MgSO_4$），过滤并蒸发，得到油状物（94mg，83%）。（TLC 50%EtOAc/己烷 (NH_3) R_f 0.20）

^{1}H NMR ($CDCl_3$) δ 6.90 (d, J=9.0 Hz, 1H), 6.66 (2H), 3.97 (m, 2H), 3.08 (dd, J=18.0,6.0 Hz, 1H), 2.94 (m, 3H), 2.76-2.65 (3H), 1.96 (m, 2H), 1.88 (d, J=11.0 Hz, 1H), 1.38 (t, J=7.0 Hz, 3H).

将该物料溶解在过量 1N 的 HCl MeOH 中并进行浓缩。从 CH_2Cl_2/Et_2O 中重结晶，得到固体（74mg，68%）。mp 243-245℃。

实施例 14

5-异丙氧基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯盐酸盐

将 11-苄基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯-5-醇（208mg，0.75mmol）和异丙醇（90mg，1.49mmol）转化为实施

例 12 描述的标题化合物（中间体苄基化合物的 TLC，17% EtOAc/己烷 R_f 0.78）。GCMS m/e 321（M^+）。去保护并转化为实施例 13 描述的盐，得到固状产物（83mg，总计 42%）。（标题化合物的 TLC，TLC 50% EtOAc/己烷（NH_3）R_f 0.10）。

^{1}H NMR ($CDCl_3$) δ ^{1}H NMR ($CDCl_3$) δ 6.89 (d, J=9.0 Hz, 1H), 6.66 (2H), 4.51 (m, 1H), 3.08 (dd, J=18.0,6.5 Hz, 1H), 2.98 (m, 3H), 2.78-2.68 (3H), 1.96 (m, 2H), 1.87 (d, J=11.0 Hz, 1H), 1.32 (t, J=5.5 Hz, 6H). mp 211-213 °C.

实施例 15

11-苄基-4-甲氧基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯盐酸盐

A) 2-环戊-3-烯基甲基-5-甲氧基-苯酚（参见在先参考文献：a) Nagata, W.; Okada, K.; Aoki, T. Synthesis 1979, 365-368; b) Lau, C. K.; Williams, H. W. R.; Tardiff, S.; Dufresne, C.; Scheigetz, J.; Belanger, P, C. Can. J.Chem. 1989, 67, 1384-1387.）

将 3-甲氧基苯酚（5.12g，42.0mmol）、环戊-3-烯甲酰醛（8.00g，83.0mmol）、苯基硼酸（5.58g，46mmol）和 1,1,1-三氯乙酸（2.04g，12.5mmol）在苯（150ml）中回流 18 小时。（TLC 5% CH_2Cl_2/己烷 R_f 0.47）。将混合物浓缩至油状，将其在 0℃下在 CH_2Cl_2（100ml）中搅拌，依次用三乙硅烷（8.87g，76.0mmol）和三氟乙酸（36.3g，318mmol）处理。将混合物搅拌 1 小时，然后加热回流 24 小时。浓缩混合物，将其溶解在 CH_2Cl_2（200ml）中，用饱和 $NaHCO_3$ 水溶液（3 ×50ml）洗涤。经棉絮塞干燥合并后的有机层，浓缩并进行硅胶色谱分离，得到油状物（3.85g，45%）。（TLC 10% EtOAc/己烷 R_f 0.35）。

^{1}H NMR ($CDCl_3$) δ 6.99 (d, J=8.0 Hz, 1H), 6.42 (dd, J=8.0,2.5 Hz, 1H), 6.36 (d, J=2.5 Hz, 1H), 5.67 (br s, 2H), 3.75 (s, 3H), 2.58 (m, 3H), 2.40 (m, 2H), 2.08 (m, 2H). GCMS *m/e* 204 (M^+).

B) 三氟-甲磺酸 2-环戊-3-烯基甲基-5-甲氧基-苯酯

采用实施例 1D 的方法，将 2-环戊-3-烯基甲基-5-甲氧基-苯酚（3.85g，19.0mmol）转化为标题化合物（4.92g，77%）。（TLC 10% CH_2Cl_2/己烷 R_f 0.52）。^{1}H NMR ($CDCl_3$) δ 7.21 (d, J=8.0 Hz, 1H), 6.86 (dd, J=8.0,2.5 Hz, 1H), 6.79 (d, J=2.5 Hz, 1H), 5.67 (br s, 2H), 3.79 (s, 3H), 2.70 (d, J=7.5 Hz, 2H), 2.59 (m, 1H), 2.43 (m, 2H), 2.03 (m, 2H).

C) 4-甲氧基三环[7.2.1.$0^{2,7}$]十二碳-2(7),3,5,10-四烯

在氮气氛下，将三氟-甲磺酸 2-环戊-3-烯基甲基-5-甲氧基-苯酯（2.00g, 5.95mmol）溶解在 DMF（10ml）中，用三乙胺（0.91g, 8.92mmol）和 1,3-双(二苯基膦基)丙烷（0.37g，0.89mmol）处理。将该混合物搅拌并除气（真空/N_2吹洗循环 3 次），然后用乙酸钯（93mg, 0.42mmol）处理。搅拌 20 分钟后，将混合物加热至 100℃18 小时，冷却并注入盐水（30ml）中。用 EtOAc（4 ×10ml）萃取混合物，并用饱和 $NaHCO_3$ 水溶液（10ml）、H_2O（10ml）和盐水（10ml）洗涤合并的有机层，干燥（$MgSO_4$），过滤并蒸发，得到油状物。将油状物进行硅胶色谱分离（2% CH_2Cl_2/己烷），得到油状产物（1.05g，95%）。（TLC 10% EtOAc/己烷 R_f 0.52）。^{1}H NMR ($CDCl_3$) δ 6.94 (d, J=8.0 Hz, 1H), 6.68 (dd, J=8.0,2.8 Hz, 1H), 6.59 (d, J=2.8 Hz, 1H), 6.23 (dd, J=5.5,2.8 Hz,1H), 5.79 (dd, J=5.5,2.6 Hz, 1H), 3.77 (s, 3H), 3.28 (m, 1H), 2.96-2.89 (m, 2H), 2.49 (d, J=15.5 Hz, 1H), 2.19 (m, 1H), 1.85 (d, J=10.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) 156.94, 144.07, 138.95, 131.24, 131.21, 126.34, 111.73, 111.45, 55.22, 45.10, 40.18, 38.47, 29.49. GCMS *m/e* 186 (M^+).

D) 11-苄基-4-甲氧基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯盐酸盐

根据实施例 2G 中的方法，将 4-甲氧基三环[7.2.1.$0^{2,7}$]十二碳-2(7),3,5,10-四烯（1.0g，5.37mmol）转化为 4-甲氧基-10,11-二羟

基三环[7.2.1.$0^{2,7}$]十二碳-2(7),3,5,10-四烯(0.95g, 80%)(TLC 50% EtOAc/CH_2Cl_2 R_f 0.46)。采用实施例 2H 中的方法，最后从 Et_2O/己烷中重结晶，从而将所得物料转化为标题化合物（650mg, 46%）。(TLC 50%EtOAc/CH_2Cl_2 R_f 0.67). ^{1}H NMR (CD_3OD) δ 7.42 (m, 5H), 7.12 (d, J=8.0 Hz, 1H), 6.84 (dd, J=8.0,2.5 Hz, 1H), 6.67 (d, J=2.5 Hz, 1H), 4.27 (AB d, J=13.0 Hz, 1H), 4.17 (AB d, J=13.0 Hz, 1H), 3.72 (s, 3H), 3.48 (br d , J=12.5 Hz, 1H), 3.34-3.16 (m, 5H), 2.86 (AB d, J=18.0 Hz, 1H), 2.55 (br s, 1H), 2.00 (AB d, J=13.0 Hz, 1H), 1.90 (AB d, J= 13.0 Hz, 1H). mp 245-246 °C.

实施例 16

4-甲氧基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯盐酸盐

采用实施例 3 中的方法，将 11-苄基-4-甲氧基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯盐酸盐（525mg, 1.60mmol）转化为标题化合物，得到白色固体产物（336mg, 88%）。(TLC 40% EtOAc/CH_2Cl_2 (NH_3) R_f 0.22)。

^{1}H NMR (CD_3OD) δ 7.11 (d, J=8.5 Hz, 1H), 6.82 (dd, J=8.5,2.5 Hz, 1H), 6.75 (d, J=2.5 Hz, 1H), 3.76 (s, 3H), 3.34-3.16 (m, 6H), 2.86 (AB d, J=17.7Hz, 1H), 2.45 (m, 1H), 2.11 (AB d, J=13.5 Hz, 1H), 1.94 (AB d, J= 13.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) 158.47, 136.58, 130.15, 127.71, 114.11, 112.61, 54.32, 49.99, 49.47, 32.16, 31.97, 27.15, 25.70. mp 259-261 °C.

实施例 17

11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯-4-醇

在 48% HBr（2ml）中回流 4-甲氧基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯盐酸盐（120mg, 0.50mmol）。1 小时后，冷却溶液，将其注入 1N 的 NaOH 水溶液中，调节其 pH 值为 10。产物用 EtOAc 萃取（3 ×40ml）。用盐水（50ml）洗涤有机层，干燥（$MgSO_4$）并浓缩，从 Et_2O/己烷中重结晶，得到白色固体（40mg, 42%）。(TLC 50% EtOAc/CH_2Cl_2 R_f 0.15)。

^{1}H NMR ($CDCl_3$) δ 6.96 (d, J=8.0 Hz, 1H), 6.60 (dd, J=8.0,2.5 Hz, 1H), 6.46 (d, J=2.5 Hz, 1H), 3.31 (m, 1H), 3.03 (dd, J=17.0,6.0 Hz, 1H), 2.95 (m, 2H,NH), 2.73 (m, 3H), 1.99 (m, 2H), 1.87 (AB d, J= 12.5 Hz, 1H). mp 215-217 °C.

实施例 18

11-苄基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯盐酸盐

按实施例 15 的方法，由苯酚（525mg，1.60mmol）制得标题化合物。（TLC 10%EtOAc/己烷 (NH_3) R_f 0.76）。^{1}H NMR (CD_3OD) δ 7.42 (m, 5H), 7.22 (m, 2H), 7.15 (t, J=7.5 Hz, 1H), 7.10 (t, J=7.5 Hz, 1H), 4.28 (AB d, J=13.0 Hz, 1H), 4.18 (AB d, J=13.0 Hz, 1H), 3.51 (d, J=12.8 Hz, 1H), 3.36 (d, J=13.2 Hz, 1H), 3.34-3.23 (m, 4H), 2.95 (d, J=12.2 Hz, 1H), 2.58 (m, 1H), 2.03 (AB d, J=13.0 Hz, 1H), 1.92 (AB d, J=13.0 Hz, 1H). mp 125-127 °C.

实施例 19

11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯盐酸盐

按照实施例 3 的方法，将 11-苄基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯盐酸盐（150mg，0.50mmol）转化为标题化合物。（TLC 20%EtOAc/己烷 (NH_3) R_f 0.20）。

^{1}H NMR (CD_3OD) δ 7.26-7.17 (m, 4H), 3.37-3.18 (m, 6H), 2.92 (d, J=18.2 Hz, 1H), 2.48 (m, 1H), 2.13 (AB d, J=13.0 Hz, 1H), 1.97 (AB d, J= 13.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 136.08, 135.67, 129.43, 128.78, 127.30, 126.42, 49.90, 49.05, 32.67, 31.86, 27.15, 25.60. mp 227-228 °C.

实施例 20

4-硝基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯盐酸盐

A) 1-(11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯-11-基)-2,2,2-三氟乙酮

在 0℃下于 CH_2Cl_2（10ml）中搅拌 11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯（1.22g，7.08mmol），依次用三乙胺（0.94g，10.6mmol）和 TFAA（1.90ml，14.2mmol）处理。1 小时后，将溶液注入 0.5N 的 HCl（200ml）中，分层。水层用 CH_2Cl_2（3 ×50ml），合并的

有机层用 0.5N HCl（50ml）、H_2O（2×50ml）和饱和碳酸氢钠水溶液（50ml）洗涤。溶液经棉絮塞干燥，然后用～3%EtOAc 稀释，经 2 英寸的硅胶填充物过滤，用～3%EtOAc/CH_2Cl_2 洗脱。浓缩得到透明油状物（1.90g，99%）。 ^{1}H NMR ($CDCl_3$) δ 7.15-7.02 (4H), 4.67 (d, J=13.0 Hz, 1/2H), 4.42 (d, J=13.0 Hz, 1/2H), 4.03 (d, J=13.0 Hz, 1/2H), 3.81 (d, J=13.0 Hz, 1/2H), 3.44 (d, J=13.0 Hz, 1H), 3.29-2.99 (3H), (d, J=18.0 Hz, 1H), 2.37 (br s, 1/2H), 2.30 (br s, 1/2H), 2.04 (AB d, 2H). GCMS *m/e* 269 (M^+).

B) ～硝基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯盐酸盐

根据 Coon 等人在 J. Org. Chem.，1973，25，4243 中描述的方法，按如下步骤制备标题化合物。向在 0℃下搅拌的三氟甲磺酸（0.94ml，10.6mmol）的 CH_2Cl_2（10ml）溶液中缓慢加入硝酸（0.60 ml，14.1mmol），得到白色沉淀物。10 分钟后，将得到的混合物冷却至-78℃，用在 CH_2Cl_2（15ml）中的 1-(11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯-11-基)-2,2,2-三氟乙酮（1.9g，7.06mmol）滴加处理 5 分钟。在-78℃下搅拌反应 2 小时，然后升温至 0℃1/2 小时。将反应混合物注入搅拌的冰（50g）中。分层，用 CH_2Cl_2（3×30ml）反萃取水层。合并有机层，用水（3×30ml）洗涤。用饱和碳酸氢钠水溶液（20ml）和水（20ml）洗涤合并后的有机层，然后经棉絮塞干燥并浓缩，得到含有 4 种产物（TLC）的黄色固体（1.58g）。使固体在 Et_2O 中成为淤浆，过滤得到固体产物（900mg，41%）。（TLC 30%EtOAc/己烷 R_f 0.21）。滤液进行硅胶色谱分离，用 30%EtOAc/己烷洗脱，得到 3 种物料。R_f 0.32（50mg，2%），R_f 0.21（如上述固体）和 R_f 0.13（50mg，2%）。GCMS m/e 314(M^+)。

C) 4-硝基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯盐酸盐

通过 H-3 和 H-1 之间的 4%NOE，NOE（核欧沃豪斯效应）试验说明了主要产物（TLC 30%EtOAc/己烷 R_f 0.21）是 2,2,2-三氟-1-(4-

硝基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯-11-基)-乙酮。在 MeOH（20ml）中搅拌该固体产物（780mg，2.48mmol）并用碳酸钠（650mg，4.96mmol）的水（10ml）溶液处理。将搅拌的混合物加热升温至 70℃6 小时，浓缩至固态，用水稀释，用 CH_2Cl_2（3 ×40ml）萃取。将产物萃取到 1N 的盐酸水溶液（3 ×40ml）中，用乙酸乙酯洗涤，然后用饱和碳酸钠水溶液中和至 pH 值为～10。产物用 CH_2Cl_2（3 ×40ml）萃取，经棉絮塞干燥，浓缩，得到油状物。将该油状物溶解在甲醇中，用 3N 的 HCl EtOAc（4ml）处理并浓缩，然后溶解在最少量的 CH_2Cl_2 中，用己烷使溶液达到饱和，搅拌 18 小时。过滤收集产物（145mg，23％）。

^{1}H NMR ($DMSO_{d-6}$) d 8.12 (d, J=2.5 Hz, 1H), 8.09 (d, J=8.0 Hz, 1H), 7.50 (dd, J=8.0,2.5 Hz, 1H), 3.25 (m, 3H), 3.08 (m, 3H), 2.88 (m, 2H), 2.27 (m,1H), 1.99 (d, J=11.0 Hz, 1H). GCMS *m/e* 218 (M^+). mp 215-220 °C.

实施例 21

5-硝基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯盐酸盐

采用实施例 20C 的方法，将上文得到的另一个间位取代的异构体 2,2,2-三氟-1-(5-硝基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯-11-基)-乙酮（TLC 30％EtOAc/己烷 R_f 0.13）转化为标题化合物。^{1}H NMR 游离碱

($CDCl_3$) δ 8.01 (d, J=2.0 Hz, 1H), 7.95 (dd, J=8.0,2.0 Hz, 1H), 7.17 (d, J=8.0 Hz, 1H), 3.16 (dd, J=18.0,6.5 Hz, 1H), 3.10-2.97 (4H), 2.89 (d, J=18.0 Hz, 1H), 2.79 (d, J=12.0 Hz, 1H), 2.12 (m, 1H), 2.02 (d, J=12.5 Hz, 1H), 1.88 (d, J=12.5 Hz, 1H).

转化为实施例 20C 中描述的盐，得到固体产物，mp 245－255℃。

实施例 22

3-硝基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯盐酸盐

采用实施例 20C 的方法，将上文分离出的残余异构体产物 2,2,2-三氟-1-(3-硝基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯

-11-基)-乙酮 (TLC 30%EtOAc/己烷 R_f 0.32)(50mg)转化为标题化合物，得到 25mg 产物(64%)。通过 C-3 和 H-1 之间的 HMQC(异核多级相关性)确定该硝基异构体的区域化学。^{1}H NMR ($DMSO_{d-6}$) δ 7.80 (d, J=8.0 Hz, 1H), 7.53 (d, J=8.0 Hz, 1H), 7.45 (t, J=8.0 Hz, 1H), 3.71-3.15 (m, 6H), 2.95 (d, J=18.5 Hz, 1H), 2.40 (br s, 1H), 2.04 (d, J=12.5 Hz, 1H), 1.70 (d, J=12.5 Hz, 1H).

实施例 23

11-苄基-5-氟-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯盐酸盐

按实施例 6 描述的方法，由 2-溴-4-氟-1-甲氧基-苯制备标题化合物。^{1}H NMR (CD_3OD) δ 7.15 (m, 3H), 6.94-6.76 (m, 5H), 3.40 (AB d, 2H), 3.06 (dd, J=17.5,7.0 Hz, 1H), 2.87-2.73 (3H), 2.69 (d, J=10.5 Hz, 1H), 2.37 (d, J=10.5 Hz, 1H), 2.28 (d, J=10.5 Hz, 1H), 2.17 (br s, 1H), 1.83 (AB d, 2H). GCMS *m/e* 281 (M^+). mp 202-203 °C.

实施例 24

5-氟-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯盐酸盐

按实施例 3 描述的方法，将 11-苄基-5-氟-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯盐酸盐(310mg, 0.94mmol)转化为标题化合物，得到白色固体产物(140mg, 65%)。

^{1}H NMR (CD_3OD) δ 7.22 (m, 1H), 6.93 (m, 2H), 3.38-3.14 (6H), 2.93 (d, J=18.5 Hz, 1H), 2.45 (m, 1H), 2.17 (AB d, J=13.0 Hz, 1H), 1.94 (AB d, J=13.0 Hz, 1H). mp 286-287 °C.

实施例 25

5,7-二氧杂-14-氮杂-四环[10.3.1.$0^{2,10}$.$0^{4,8}$]十六碳-2(7),3,8-三烯盐酸盐

采用实施例 3 和 6 描述的方法，将 5-溴-6-甲氧基-苯并[1,3]间二氧杂环戊烯(制备方法参见: Getahun Z.; Jurd, L.; Chu, P. S.; Lin, C. M.; Hamel, E. J. Med. Chem. 1992, 35, 1058-1067)转

化为标题化合物，得到白色固体产物（110mg）。

^{1}H NMR (CD_3OD) δ 6.65 (s, 2H), 5.88 (s, 2H), 3.33-3.12 (6H), 2.81 (d, J=18.0 Hz, 1H), 2.42 (m, 1H), 2.09 (AB d, J=12.5 Hz, 1H), 1.90 (AB d, J= 12.5 Hz, 1H). GCMS *m/e* 217 (M^+). APCI MS *m/e* 218.1 [$(M + 1)^+$]. mp 241-243 °C.

实施例 26

11-苄基-6-溴-5-甲氧基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯

在 0℃下，在 CH_2Cl_2（10ml）和 AcOH（5ml）中搅拌 11-苄基-5-甲氧基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯（3.00g, 10.2mmol），用在 CH_2Cl_2（10ml）和 AcOH（5ml）中的溴（3.21g, 20mmol）处理。18 小时后，用 20%的碳酸氢钠水溶液（100ml）终止反应。产物用 CH_2Cl_2（3 ×40ml）萃取，并用饱和碳酸氢钠水溶液（3 ×50ml）洗涤。合并的有机层经棉絮塞干燥，浓缩，进行硅胶色谱分离，得到油状物（1.05g, 28%）。（TLC 30%EtOAc/己烷 R_f 0.48）。

^{1}H NMR ($CDCl_3$) δ 7.13 (m, 3H), 6.91 (m, 3H), 6.68 (d, J=8.0 Hz, 1H), 3.90 (s, 3H), 3.36 (s, 2H), 2.86-2.79 (4H), 2.67 (br d, J=9.0 Hz, 1H), 2.31 (br s, 1H), 2.28 (br s, 1H), 2.22 (br s, 1H), 1.78 (AB d, J=13.0 Hz, 2H). GCMS *m/e* 373,371 (M^+).

实施例 27

11-苄基-6-羟基-5-甲氧基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯

在-78℃下，在无水 THF（10ml）中搅拌 11-苄基-6-溴-5-甲氧基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯（1.05g, 2.70mmol），用正丁基锂（1.08ml, 2.5M 的己烷溶液, 2.70mmol）滴加处理 1 分钟。10 分钟后，加入硼酸三异丙酯（559g, 2.79mmol），将混合物升温至室温。用饱和碳酸氢钠水溶液（50ml）终止反应。产物用乙酸乙酯（3 ×20ml）萃取。将有机层干燥（硫酸镁），过滤并蒸发，得到油状物（640mg, 67%）。（TLC 30%EtOAc/己烷 R_f 0.18）。

将该物料（640mg，1.81mmol）在 THF（10ml）中与 30％的过氧化氢水溶液（205mg，1.81mmol）一起搅拌。18 小时后，用 20％的 $NaHSO_3$ 水溶液（10ml）终止反应。用饱和碳酸氢钠水溶液（50ml）稀释混合物，产物用 CH_2Cl_2（3 ×40ml）萃取。有机层用饱和碳酸氢钠水溶液（3 ×50ml）洗涤，经棉絮塞干燥，浓缩，进行硅胶色谱分离，得到油状物（36mg，64％）。（TLC 40％EtOAc/己烷 R_f 0.44）。^{1}H NMR ($CDCl_3$) δ 7.14 (3H), 6.95 (2H), 6.67 (d, J=8.0 Hz, 1H), 6.52 (d, J=8.0 Hz, 1H), 3.89 (s, 3H), 3.40 (AB d, 2H), 2.88-2.63 (5H), 2.34-2.22 (3H), 1.79 (AB d, 2H). GCMS *m/e* 309 (M^+).

实施例 28

6-羟基-5-甲氧基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯盐酸盐

采用实施例 3 描述的方法，将 11-苄基-6-羟基-5-甲氧基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯（58mg，0.18mmol）转化为标题化合物，然后，转化为实施例 9 中描述的盐，得到白色固体产物（15mg，32％）。（TLC 10％MeOH/CH_2Cl_2 (NH_3) R_f 0.26）。

^{1}H NMR (CD_3OD) δ 6.84 (d, J=8.0 Hz, 1H), 6.68 (d, J=8.0 Hz, 1H), 3.82 (s, 3H), 3.29 (3H), 3.13 (m, 2H), 3.00 (dd, J=18.0,6.0 Hz, 1H), 2.85 (d, J=18.0 Hz, 1H), 2.42 (m, 1H), 2.09 (AB d, J=12.5 Hz, 1H), 1.82 (AB d, J= 12.5 Hz, 1H). mp 285-290 °C.

实施例 29

三氟-甲磺酸-11-苄基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯-5-基酯

采用实施例 1D 的方法，将 11-苄基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯-5-醇（850mg，3.03mmol）转化为标题化合物（1.18g，94％）。（TLC 30％EtOAc/己烷 R_f 0.47）。

^{1}H NMR ($CDCl_3$) δ 7.10 (3H), 6.97 (3H), 6.78 (2H), 3.40 (AB d, J=14.0 Hz, 1H), 3.30 (AB d, J=14.0 Hz, 1H), 3.05 (AB dd, J=17.5,7.0 Hz, 1H), 2.89-2.79 (3H), 2.62 (d, J=10.0 Hz, 1H), 2.40 (d, J=10.5 Hz, 1H), 2.28 (d, J=12.0 Hz, 1H), 2.17 (br

s, 1H), 1.83 (AB d, 2H). APCI MS *m/e* 412.1 [(M + 1)$^+$].

实施例 30

5-(4-三氟甲基苯基)-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯盐酸盐

A) 11-苄基-5-(4-三氟甲基苯基)-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯（有关的论述可参见：Miyaura, N.; Suzuki, A. Chem. Rev. 1995, 95, 2457-2483.）

在 10/1 的乙醇/水（5ml）中合并三氟甲磺酸 11-苄基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯-5-基酯（258mg, 0.63mmol）、乙酸钾（493mg, 5.02mmol）和 4-三氟甲基苯基硼酸（141mg, 0.94mmol）。将混合物脱气（真空/N_2循环 3 次），用四(三苯基膦)合钯(0)（36.0mg, 0.032mmol）处理，升温至 90℃18 小时。冷却反应，用水稀释并用乙醚（3 ×50ml）萃取。有机层用盐水（50ml）洗涤，干燥（硫酸镁），过滤并浓缩，得到油状物（60mg, 23%）。（TLC 己烷 R_f 0.16）。

^{1}H NMR ($CDCl_3$) δ 7.73 (d, J=8.5 Hz, 2H), 7.68 (d, J=8.5 Hz, 2H), 7.38 (d, J=2.0 Hz, 1H), 7.32 (dd, J=8.0,2.0 Hz, 1H), 7.10 (4H), 6.88 (m, 2H), 3.40 (s, 2H), 3.14 (dd, J= 17.5, 7.0 Hz, 1H), 2.94-2.87 (3H), 2.76 (d, J=10.5 Hz, 1H), 2.40 (dd, J=10.5,2.0 Hz, 1H), 2.33 (dd, J=10.5,2.0 Hz, 1H), 2.22 (br s, 1H), 1.91 (AB d, J=12.5 Hz, 1H), 1.83 (AB d, J=12.5 Hz, 1H). GCMS *m/e* 407 (M)$^+$.

B) 5-(4-三氟甲基苯基)-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯盐酸盐

采用实施例 3 的方法，将 11-苄基-5-(4-三氟甲基苯基)-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯转化为标题化合物。（TLC 50 % EtOAc/己烷 R_f 0.81）。^{1}H NMR ($CDCl_3$) δ 7.62 (m, 4H), 7.15-6.98 (3H) 3.50-2.97 (6H), 2.92 (d, J=18.0 Hz, 1H), 2.38 (br s, 1H), 2.02 (AB d, 2H).

实施例 31

5-(4-甲氧基苯基)-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯盐酸盐

采用实施例 30 的方法，将三氟甲磺酸 11-苄基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯-5-基酯和 4-甲氧基苯基硼酸转化为标题化合物。 ^{1}H NMR (CD_3OD) δ 7.57 (d, J=8.0 Hz, 2H), 7.42 (d, J=2.0 Hz, 1H), 7.38 (dd, J=8.0,2.0 Hz, 1H), 7.16 (d, J=8.0 Hz, 1H), 6.97 (d, J=8.0 Hz, 2H), 3.81 (s, 3H), 3.48-3.08 (6H), 2.95 (d, J=18.0 Hz, 1H), 2.30 (br s, 1H), 2.10 (AB d, J=11.5 Hz, 1H), 1.97 (AB d, J=11.5 Hz, 1H).

实施例 32

11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯-5-羧酸甲酯盐酸盐（参见 Dolle, R. E.; Schmidt, S. J.; Kruse, L. I. J. Chem. Soc., Chem. Commun. 1987, 904-905）

将三氟甲磺酸 11-苄基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯-5-基酯（1.0g, 2.26mmol）溶解在 DMSO（15ml）和甲醇（2ml）中，用三乙胺（505mg, 4.99mmol）、乙酸钾（22.0mg, 0.23mmol）和 1,3-双(二苯基膦基)丙烷（94.0g, 0.23mmol）处理。将该混合物搅拌并除气(真空/N_2吹洗循环 3 次)，然后用乙酸钯(51mg, 0.23mmol）处理。在气球压力下，用一氧化碳气体（CO(g)）吹洗体系，搅拌 20 分钟，升温至 100℃3 小时，冷却，然后注入盐水（50ml）中。得到的混合物用乙酸乙酯（4 ×40ml）萃取，用饱和碳酸氢钠水溶液（100ml）、水（100ml）和盐水（100ml）洗涤合并的有机层，干燥（硫酸镁），过滤并蒸发，得到油状物 11-苄基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯-5-羧酸甲酯，将其进行硅胶色谱分离，得到油状物（280mg, 38%）。（TLC 10%EtOAc/己烷 R_f 0.21）。APCI MS m/e 322.2[$(M+1)^+$]。按实施例 3 的方法，将该油状物转化为标题化合物。（TLC 10% CH_2Cl_2/MeOH (NH_3) R_f 0.21）。^{1}H NMR (CD_3OD) δ 7.87 (d,

J=2.0 Hz, 1H), 7.83-(dd, J=8.0,2.0 Hz,1H), 7.35 (d, J=8.0 Hz, 1H), 3.87 (s, 3H), 3.49-3.12 (6H), 2.97 (d, J=18.5 Hz, 1H), 2.52 (br s, 1H), 2.18 (AB d, J=11.5 Hz, 1H), 1.97 (AB d, J=11.5 Hz, 1H). mp 255-256 °C.

实施例 33

2-(11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯-5-基)丙-2-醇盐酸盐

在氮气下，于-78℃，在无水 THF（15ml）中搅拌 11-苄基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯-5-羧酸甲酯（180g，0.62mmol），用过量的溴化甲基镁（~1ml，3M 的 THF 溶液）进行处理。将所得混合物升温至室温，用饱和氯化铵水溶液（25ml）终止反应。产物用乙酸乙酯（3 ×50ml）萃取，用盐水（50ml）洗涤，干燥（硫酸镁），过量并蒸发，得到油状物（100mg，50%）。GCMS m/e 321(M^+)。按实施例 3 的方法，将该物料转化为标题化合物。^{1}H

NMR (CD_3OD) δ 7.32 (OH), 7.24 (s, 1H), 7.16 (d, J=8.0 Hz, 1H), 7.08 (m, 1H), 3.50-3.12 (6H), 2.91 (d, J=18.5 Hz, 1H), 2.47 (br, s, 1H), 2.11 (AB d, J=11.5 Hz, 1H), 1.97 (AB d, J=11.5 Hz, 1H), 1.15 (s, 6H). mp 80-81°C.

实施例 34

5-吡啶-3-基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯盐酸盐

按实施例 30 的方法，将三氟甲磺酸 11-苄基-11-氮杂-三环[7.3.1.$0^{2,7}$]十三碳-2(7),3,5-三烯-5-基酯和二乙基-吡啶-3-基-硼烷转化为标题化合物。 ^{1}H NMR (CD_3OD) δ 9.14 (br s, 1H), 8.78 (m, 2H), 8.08 (m, 1H), 7.69 (d, J=2.0 Hz, 1H), 7.62 (dd, J=8.0,2.0 Hz,1H), 7.43 (d, J=8.0 Hz, 1H), 3.43-3.18 (6H), 3.05 (d, J=18.5 Hz, 1H), 2.56 (br s, 1H), 2.18 (AB d, J=11.5 Hz, 1H), 2.02 (AB d, J=11.5 Hz, 1H). GCMS *m/e* 250 (M^+). mp 240-242 °C.